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Content/Índice

Editorial

Alerta transcends language barriers

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The English language is spoken by millions of people in the world. Throughout history, it has become the language of science due to its role in the dissemination of scientific knowledge and globalization[1]. Publishing articles in English brings great advantages related to visibility and impact, as well as the possibility of acceptance in indexes such as Web of Science and Scopus[2]. That is why it was decided to invest in human talent that can translate our journal Alerta 100 % into this language.

Therefore, this new publication, volume 5, issue 2, is a dream come true because we delivered to the scientific community for the first time an issue translated entirely into English with each of the articles diagrammed in PDF, XML, HTML, e-Pub in both languages.

The content of this issue includes four case reports. The first one deals with the surgical approach of a brown tumor of the maxilla, in a patient with Sagliker syndrome; the second is about the diagnosis of four synchronous primary neoplasms in an adult; the third narrates the clinical manifestations of a fracture secondary to a mild trauma and the studies that confirmed an Ewing sarcoma. The three cases mentioned were treated in the radiology service of the Salvadoran Social Security Institute. The fourth and final case report of the Rosales National Hospital on Morris syndrome, characterized by complete insensitivity to androgens addressed by the endocrinology and urology specialties of the Rosales National Hospital.

Besides, an original article is included comparing the risk of SARS-CoV-2 infection after artificial and hybrid immunization in health personnel, sent by the Civil Hospital of Guadalajara in Mexico. Also, a dental article is published, entitled "Relationship between dental caries and body mass index in children". Moreover, a brief communication on the index and prevalence of dental caries in kindergarten children residing in an urban-marginal area presented by the Solidarity Fund for Health.

Three narrative reviews have been selected in this issue. One reports non-pharmacological strategies as adjuvants for the management of acute pain associated with puncture in pediatrics; the following shows the importance of knowing the factors that hinder the diagnosis of postural orthostatic tachycardia syndrome in adults. The latest deals with the impact of lifestyle factors on the immune system and how they modulate susceptibility to pathogens in adults. The three were prepared by doctors in process of graduating from the Dr. José Matías Delgado university.

We are pleased that with each issue the institutions and countries that seek to publish in Alerta increase. This, at the same time, becomes a commitment to continue the path of indexing and building the prestige of Alerta, which has already been accepted in databases and indices such as Latindex, LILACS, REDIB, AmeliCA, MIAR, recently in PERIÓDICA and BIBLAT of Mexico.

It is thanks to its indexing in BIBLAT that the Alerta articles already have Altmetric[3], Dimensions[4] and PlumX[5] indicators. This favors visibility and evidence the number of times work of researchers has been mentioned on the web. Not only do altime-

trics identify the number of citations, but they also consider other aspects such as how many data or knowledge bases refer to the article, the times a text has been commented or discussed, the number of views and downloads of documents and mentions in the media, press, social networks, blogs and other collaborative platforms; it even tracks their use in government policies[3-5].

All these advantages represent a benefit for our authors when showing the coverage and use that their publication has throughout the web and not only citations. For example, Dimensions allows to identify the impact of each article thanks to four metrics: total citations, recent citations (last two years), Field Citation Ratio (performance of an article compared to others of the same topic) and Relative Citation Ratio, which shows the performance of an article compared to others of the same line of research[3].

Every day we hope Alerta will be more recognized and useful for the entire scientific community, academy and clinical decision makers, managers and students in the health sciences of all levels.

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Case reports

Surgical approach of brown maxillary tumor in Sagliker syndrome

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Abordaje quirúrgico de tumor pardo de maxilar en síndrome de Sagliker

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Abstract
Case presentation. This is a 20-year-old female patient with stage 5 chronic kidney disease on hemodialysis who noticed progressive enlargement of the palatal region in the last seven months, which generated dyslalia and difficulty in chewing with expansion of the maxillary bone, separation of the upper teeth and changes in the facial configuration and profile compatible with a brown tumor. Laboratory results confirmed hyperparathyroidism and hypocalcemia secondary to renal disease. Ultrasound findings were compatible with left-sided parathyroid hyperplasia. **Treatment.** Calcium carbonate and paricalcitol were administered during the two weeks prior to surgery. The treatment consisted of subtotal parathyroidectomy and surgical resection of the tumor in the maxilla and oral calcium and vitamin D3 supplements. **Outcome.** Calcium and phosphorus levels normalized and parathyroid hormone levels decreased. After a follow-up of more than two years, no recurrences were identified.

Keywords
Chronic kidney disease, hyperparathyroidism, maxillofacial surgery, renal osteodystrophy.

Resumen
Presentación del caso. Se trata de una paciente femenina de 20 años de edad con enfermedad renal crónica estadio 5 en tratamiento de hemodiálisis que notó aumento progresivo de la región palatina en los últimos siete meses, que le generaba dislalia y dificultad para la masticación con expansión del hueso maxilar, separación de las piezas dentales superiores y cambios en la configuración y perfil facial compatibles con un tumor pardo. Los resultados de laboratorio confirmaron un hiperparatiroidismo e hipocalcemia secundarios a la enfermedad renal. Los hallazgos ecográficos fueron compatibles con hiperplasia de paratiroides del lado izquierdo. **Intervención terapéutica.** Se administró carbonato de calcio y paricalcitol durante las dos semanas previas a la cirugía. El tratamiento consistió en una paratiroidectomía subtotal y la resección quirúrgica de la tumoración en el maxilar y los suplementos de calcio y vitamina D3 por vía oral. **Evolución clínica.** Se obtuvo normalización de los niveles de calcio y de fósforo y disminuyeron los niveles de la paratohormona. Después de un seguimiento de más de dos años, no se identificaron recurrencias.

Palabras clave
Insuficiencia renal crónica, hiperparatiroidismo, cirugía maxilofacial, osteodistrofia renal.

Introduction

Sagliker syndrome is the set of craniofacial and skeletal alterations produced by the elevated level of parathyroid hormone and the alteration in calcium metabolism[1], secondary to chronic renal failure[2,3]. It consists of renal osteodystrophy[4] that manifests itself as a disfigured appearance of the face, among the most common, protrusion of the maxilla and jaw, hyperplasia of the soft tissues of the palate, loss of nasal anatomy, dental and finger deformity and short stature[1].This syndrome was described by Sagliker *et al.* in 2004[1]. An incidence of 0,5 % of patients on haemodialysis has been reported and most frequently occurs in females aged 18 to 39 years[5].

Damage to renal function results in a decrease in the levels of 1,25-dihydroxycholecalciferol, which causes hypocalcemia and hyperphosphatemia due to the decrease in calcium absorption at the intestinal level and, together, an increase in phosphorus retention[6,7]. In response to these metabolic alterations, the cells of the parathyroid glands develop a process of adaptive hyperplasia that directly stimulates the increase in the release of parathyroid hormone[2]. The state of secondary hyperparathyroidism (SHPT) in Sagliker syndrome produces changes throughout the body, especially the long, vertebral and cranial bones, and contributes to the formation of brown tumors[8]. Brown tumors are also caused by the decrease in calcium levels in the body, which increase bone resorption by stimulation of osteoclasts induced by parathyroid hormone, and produce alterations that can be described as intraosseous tissue lesions, unique or multifocal, and are usually located in the maxillary bones[9].

This case presents the management and treatment of a patient with brown maxillary tumor with Sagliker syndrome who attends the oral and maxillofacial surgery service of the Rosales National Hospital in El Salvador.

Case presentation

This is a 20-year-old female patient with a history of eight years of having been diagnosed with stage 5[10] chronic kidney disease, on hemodialysis treatment for the last four years. She consulted the oral and maxillofacial surgery service of the Rosales National Hospital to notice a progressive increase in the palatine region in the last seven months that generated dyslalia and difficulty chewing with expansion of the maxillary bone. Also, it causes separation of the upper teeth and changes in the configuration and facial profile (Figure 1).

The physical evaluation showed short stature (1,46 m), growth of the scapular bone in recent years of renal failure, abnormalities and shortening of the distal phalanges (Figure 1). Moreover, in the intraoral evaluation, a tumor was observed in the maxilla that affected the hard palate and the separation of the teeth was identified in the frontal dental region, which confirmed the alteration in the growth of the maxilla.

Laboratory test results confirmed hyperparathyroidism, hypocalcemia, hyperphosphatemia, and elevation of alkaline phosphatase (Table 1).

Figure 1. a. Intraoral clinical image of the palate. b. Frontal intraoral clinical imaging. c. Facial images with convex facial profile characteristics. d. Upward shortening and curvature of distal phalanges. e. Tendency to scapular growth in the sagittal direction

The CT scan showed hypodense images with osteolytic pattern that compromised the hard palate towards the bony part of the maxillary sinuses, the frontal bone, the sphenoid bone and a portion of the bilateral temporal bones, identifying irregularities in bone trabeculation at the aforementioned sites (Figure 2).

Ultrasound findings were described as compatible with left-sided parathyroid hyperplasia; moreover, parathyroid gammagraphy with Technetium 99-sestamibi (Tc99m) Technetium-99m-sestamibi parathyroid gammagraphy (Tc99m) combined with a monophoton emission computed tomography of the neck confirmed glandular tissue with excess cell activity in static images of the neck and mediastinum at 15 minutes and two hours (Figure 2).

Treatment

The case was analyzed with a multidisciplinary team (maxillofacial surgery, nephrology and endocrinology) for the choice of medical treatment, from the preoperative moment to the surgical management. Calcium carbonate 3600 mg daily orally and paricalcitol 15 µg were intravenously administered in three doses during the two weeks prior to surgery. The surgical treatment consisted of a subtotal parathyroidectomy without thymectomy, with the complete removal of three parathyroid glands and approximately two-thirds of the left lower parathyroid gland (Figure 3). Then, a surgical resection of the tumor in the maxilla was proceeded (Figure 3) and a sample of the palatine region was obtained, which measured approximately 4,5 × 4,3 × 1 cm. Finally, it was sent for histopathological study (Figure 3). In the immediate postoperative period, calcium gluconate 10 % was administered, one ampoule every eight hours intravenously In the immediate postoperative period and in the postoperative period, treatment with vitamin D3 0,25 µg daily and oral calcium supplement 3600 mg daily orally was initiated.

The histopathological study of the tumor of the maxillary palatine region reported the finding of moderately pleomorphic spindle cells intermingled with multinucleated giant cells of the osteoclast type, hemosiderin deposits and abundant osteoid of benign appearance of diffuse distribution, compatible with a brown maxillary tumor.

It was maintained in control and follow-up with the multidisciplinary team to monitor the evolution and continue the treatment of kidney disease.

Table 1. Comparison of laboratory results in the pre- and postoperative periods

Serology	Preoperative	Postoperative	Range
Parathyroid hormone	2870,5	650	12-88 pg/mL
Calcium	8,44	8,99	8,5-10,5 mg/dL
Phosphorus	6,74	4,40	3-5 mg/dL
Alkaline phosphatase	1807	322	30–125 UI/L

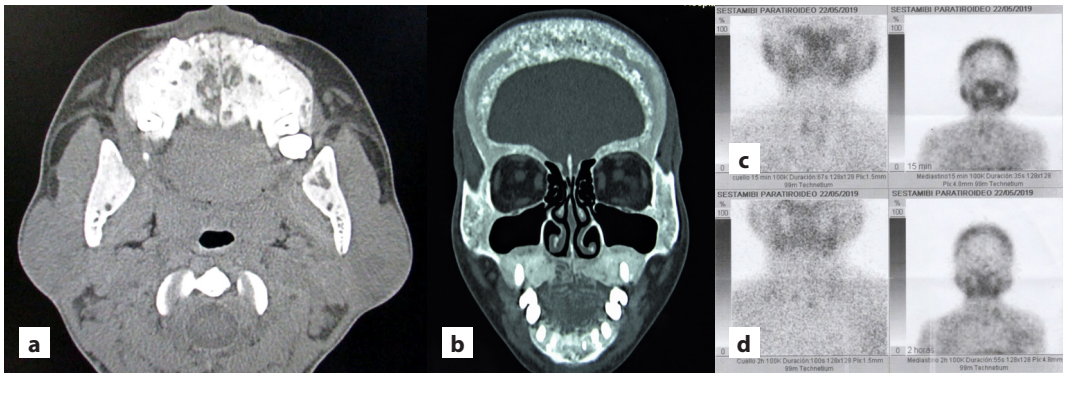

Figure 2. a. Tomographic image of axial cut with hypodense areas in palatine bones of the maxilla. b. Coronal tomographic image with salt and pepper-like lesions on the cranial bones. c. Parathyroid gammagraphy at 15 minutes at the level of the neck and mediastinum with diffuse uptake of radiotracers in the thyroid tissue. d. Parathyroid gammagraphy at two hours with capture of a small zone in the area corresponding to the lower pole of the left thyroid lobe

Outcome

The patient satisfactorily progressed in the immediate postoperative period; however, on the fifth postoperative day, she presented an area of necrosis in the mucosa of the palate in which hyaluronic acid was applied in 0,2 % bioadhesive gel every six hours and hygiene measures were included in the intervened area, which favorably developed. Moreover, control laboratory tests were performed, which reported normal levels of calcium, phosphorus and alkaline phosphatase; as well as decreased paratohormone levels (Table 1).

After two weeks post surgery, a granulation tissue with the secondary healing was presented on the palate, which favored the feeding ability and improved the quality of life of the patient. Also, the clinical evolution was monitored by controls every four months for more than two years. No recurrences were identified during this period (Figure 4).

Clinical diagnosis

A diagnosis of brown maxillary tumor was established in a patient with Sagliker syndrome since the clinical, radiographic, biochemical and histopathological findings.

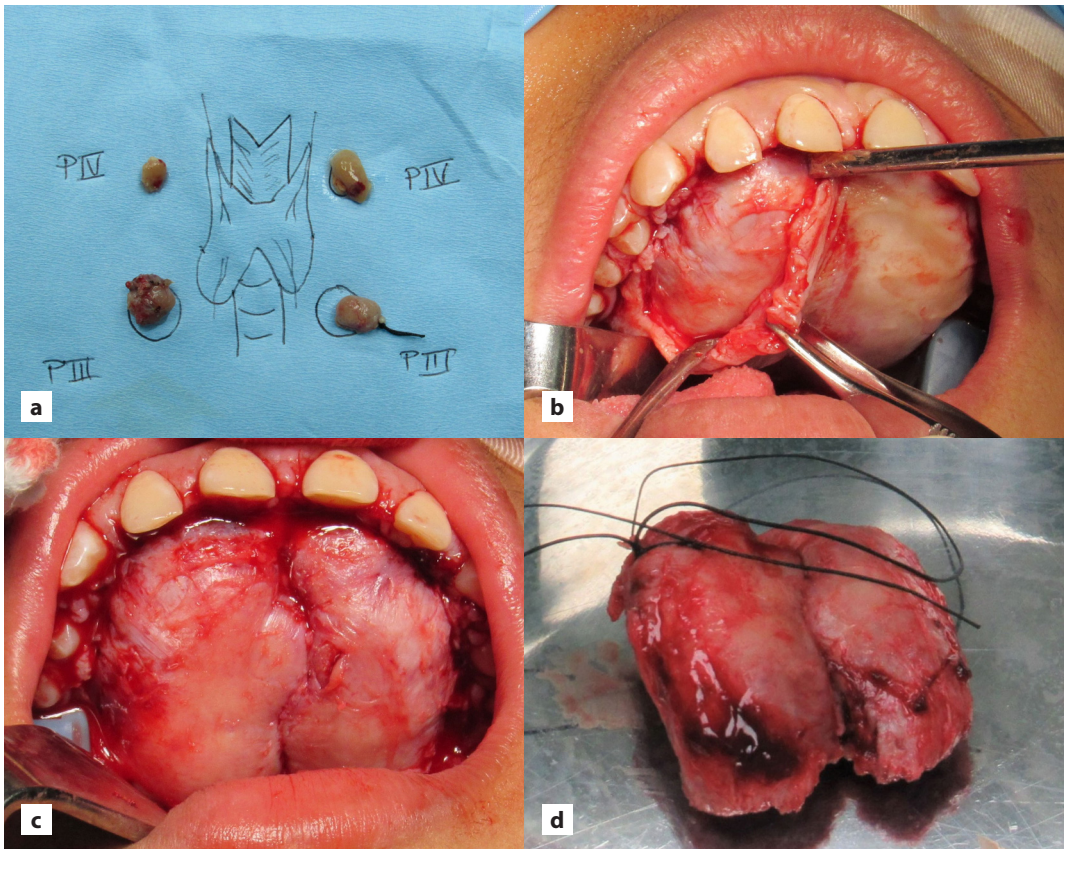

Figure 3. Transoperative imaging. a. Subtotal parathyroidectomy. b-c. Complete surgical resection of tumor. d. Sample obtained from the palatine bone of the maxilla

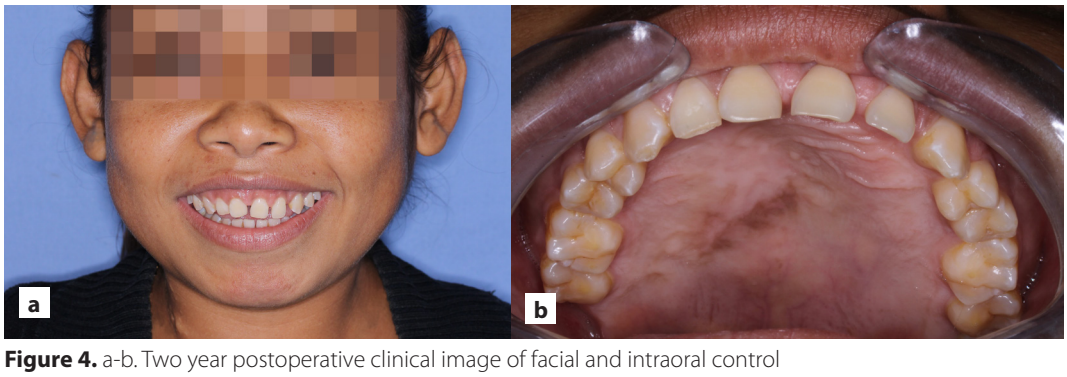

Figure 4. a-b. Two year postoperative clinical image of facial and intraoral control

Discussion

Brown tumors are intraosseous lesions that are produced by the action of osteoclasts[3]. These cells cause a replacement of bone tissue by fibrous tissue, multinucleated giant cells and hemosiderin deposits, mainly in the maxillary bones[9,11]. This is because the maxilla has a rapid rate of bone resorption and apposition. Some authors report an incidence of 1,5 % in patients with SHPT[12].

Clinical, biochemical, imaging and histopathological findings are the main tools to establish the diagnosis of brown tumors in SHPT in individuals with Sagliker syndrome[5,9]. Serum levels of calcium, phosphorus, alkaline phosphatase and parathyroid hormone in the initial assessment are of importance for proper management[13]. Likewise, imaging studies allow to identify bone alterations not only in the maxilla but also in other anatomical areas[13]. Salt-and-pepper-like lesions in the cranial bones are common to be observed in Sagliker syndrome[8].

The clinical manifestations detected in the patient are related to those described by other authors, including the characteristics of convex facial profile and malocclusions due to the protrusion of the maxillary angle in relation to the mandibular angle[14], the short stature, the growth of the scapular bone, the shortening with upward curvature of the distal phalanges, the deformity of the knees, scapulae and certain gait disturbances[1,15]. Furthermore, some authors mention other findings that are less frequent, such as moderate to severe neurological alterations, including headaches and auditory abnormalities[15].

Parathyroid gammagraphy with Technetium 99-sentamibi (Tc99m) combined with a monophotonic emission computed tomography of the neck are used as auxiliary methods of diagnostic imaging[5,9]. These allow to identify the increased cellular function of the parathyroid glands and are a guide tool for the surgeon in the surgical approach of the parathyroid glands[5].

The definitive diagnosis of brown tumor does not depend only on the histopathological result, since it presents histological characteristics similar to other giant cell tumors; therefore, this case required a combination of clinical, biochemical and imaging findings that corroborated the SHPT, and the identification of the specific signs and symptoms that determined the presence of Sagliker syndrome[12].

For many authors, the conservative therapeutic approach should encompass SHPT control and vitamin D administration to improve serum calcium levels; consequently, this improves parathyroid hormone levels and do not generate deformities in cases of brown tumors in the maxillary area and allows a gradual regression of the tumor[16-18]. Patients with very severe SHPT may not respond to high doses of vitamin D, and patients with large tumors in the maxillary or intraoral area require evaluation for parathyroidectomy to control hormonal imbalance[2,12,19,20].

The choice of treatment of brown tumors in the maxillary or oral area in SHPT depends on the location, size, generated functional alterations, the presence of facial deformations or the invasion of important anatomical structures in the maxillary or intraoral area[9,12].

Surgical treatment was decided in addition to parathyroidectomy because it invaded the nearby anatomical structures with airway involvement and swallowing with a continuous and accelerated expansion of the tumor due to the pathophysiology of the SHPT base disease with Sagliker syndrome.

Ethical aspects

The presentation of this case has the informed consent of the patient and the approval of the Research Ethics and Research Coordination Committee of the Rosales National Hospital was received.

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Case report

Fracture, beyond trauma

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Fractura, más allá del trauma

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Abstract
Case presentation. A 19-year-old patient, with no previous medical history, with a history of trauma to the right thigh, presented with shortening, edema, rotation of the right lower limb and pain. Radiography identified a fracture in the proximal third of multiple fragments of the diaphysis with thickening and periosteal reaction that generated a suspicion of a bone tumor. MRI confirmed a bone neoplasm of malignant characteristics in the upper third of the femur with destruction of the cortex and invasion of the endomedullary canal without signs of metastatic lesions. The biopsy confirmed the diagnosis of localized Ewing's sarcoma. **Treatment.** The intrahospital management consisted of anti-inflammatory drugs and immobilization of the right lower limb for 21 days. Then, she received three cycles of chemotherapy with the Ewing sarcoma phase 1 scheme. In addition, physical therapy, outpatient treatment with analgesic, radiotherapy and finally partial hip resection was indicated. **Outcome.** There was a decrease in local edema, pain control with oral medications, mobility was recovered, although the functional limitation of the right lower limb was maintained, making it impossible to stand and walk.

Keywords
Ewing's sarcoma, Leg bones, sarcoma, needle biopsy.

Resumen
Presentación de caso. Se presenta el caso de un paciente de 19 años, sin antecedentes médicos, con historia de traumatismo en el muslo derecho, que tuvo acortamiento, edema, rotación del miembro inferior derecho y dolor. En la radiografía se identificó una fractura en el tercio proximal de fragmentos múltiples de la diáfisis con engrosamiento y reacción perióstica que generaron una sospecha de un tumor óseo. La resonancia magnética confirmó una neoplasia ósea de características malignas en el tercio superior del fémur con destrucción de la cortical e invasión del canal endomedular sin signos de lesiones metastásicas. La biopsia confirmó el diagnóstico de sarcoma de Ewing localizado. **Intervención terapéutica.** El manejo intrahospitalario consistió en antiinflamatorios e inmovilización del miembro inferior derecho por 21 días. Luego, recibió tres ciclos de quimioterapia con el esquema para sarcoma de Ewing fase 1. Además, se indicó terapia física, tratamiento ambulatorio con analgésico, radioterapia y finalmente se practicará la resección parcial de cadera. **Evolución clínica.** Se evidenció disminución del edema local, control del dolor con medicamentos orales y recuperación de la movilidad, aunque mantuvo la limitación funcional del miembro inferior derecho que imposibilita la bipedestación y la deambulación.

Palabras clave
Sarcoma de Ewing, huesos de la pierna, sarcoma, biopsia con aguja.

Introduction

Ewing sarcoma is a malignant primary bone tumor that presents as a necrotic or hemorrhagic mass mainly located in the metaphysis of the bones[1]. Microscopically, it is presented as a collection of rounded, monomorphic cells[1]. This tumor was described as a round cell sarcoma by James Ewing in 1921; It was initially described as a diffuse endothelioma of bone and later as endothelial myeloma[2].

Primary bone cancers are clinically heterogeneous and their cure depends on the opportunity of appropriate treatment[3]. In the adult population, Ewing sarcoma ranks fourth, being the most common with chondrosarcoma, followed by osteosarcoma and chordoma, unlike the incidence in children and adolescents, which is presented as the second cause of bone cancer in the population among children and adolescents after osteosarcoma[4].

The skeletal distribution is wide, although the most common location is the femur, tibia and fibula, as well as the pelvis in the axial skeleton[5]. Symptoms are usually nonspecific such as pain and sometimes tumor, without others that suggest a local problem or metastasis[6]. The initial diagnostic method is simple radiography, in which the aggressive characteristics and high-grade nature of this malignant lesion are presented[7]. Recommended imaging studies are contrast computed tomography[3], which provides information on cortical, changes in bone structure, and magnetic resonance imaging (MRI) as a technique of choice for identifying bone and extra osseous extent of the tumor and defining local stage definition[3,7].

The diagnosis is confirmed with biopsy of the tumor and should be supplemented with leukogram and blood chemistry[3].

The objective of describing this case is assessing the importance of establishing timely and adequate management in patients with suspected pathological fractures, exploring certain characteristics suggestive of malignancy and using the available diagnostic methods.

Case presentation

This is a 19-year-old male patient, who had a medical consultation at San Rafael National Hospital for severe pain in the right lower limb for two months, followed by episodes of rhabdomyolysis. It was decided to admit him to hospital, where he received treatment with analgesics and muscle relaxants.

Three months later, he consulted at the previous hospital emergency unit for a fall on same level. This generated a trauma to his right thigh. He was treated with 50 mg of diclofenac intramuscularly and then referred to the General Hospital of the Salvadoran Social Security Institute (ISSS).

On physical examination, the patient was conscious, oriented, complaining, unable to roam, with a temperature of 36,7 °C, heart rate of 68 beats/minute and blood pressure of 120/80 mmHg. As far as cardiopulmonary auscultation, he presented 12 breaths per minute, without pathological findings in both pulmonary fields, with oxygen saturation of 95 %. There was not any abnormality in the abdominal evaluation. The right lower limb was rotated to the right, shortened, with edema in the middle and upper third of the thigh and presented pain on palpation and when performing the abduction and adduction movements and inability to walk. The popliteal and dorsal pulses of the foot remained normal (Figure 1).

Laboratory analytical data reported hemoglobin of 12,0 gr/dL without leukocytosis, with neutrophils of 72,5 % and platelets of 443 000. Creatinine, potassium, sodium and glucose were detected at normal values, while C- reactive protein was at 21,5 mg/L; the prothrombin time, in 14,8 seconds and the INR in 1,3.

He was clinically evaluated and an X-ray of the pelvis and right femur was indicated, in which a fracture of multiple fragments of the diaphysis was observed, in the proximal third of the right femur, with thickening and periosteal reaction of the cortical in "Codman's triangle" with heterogeneous density and poorly defined central radiolucent areas (Figure 2). These signs generated the suspicion of a bone tumor with malignant radiological characteristics, a pathological fracture of the right femur was diagnosed and the study was continued with hospital management. The X-ray of the left femur, without abnormalities, allowed to compare both lower limbs. Also, to discard lung metastasis, a chest computed axial tomography (CT) was indicated, and metastatic lesions were not found (Figure 2).

The study of the thigh was continued by means of a magnetic resonance in sagittal slices, in which isointense was described in T1 sequences, heterogeneously hyperintense in T2 and STIR with marked restriction to diffusion and heterogeneous

Figure 1. Right lower limb rotated to the right, with significant edema in the middle and upper third of the thigh

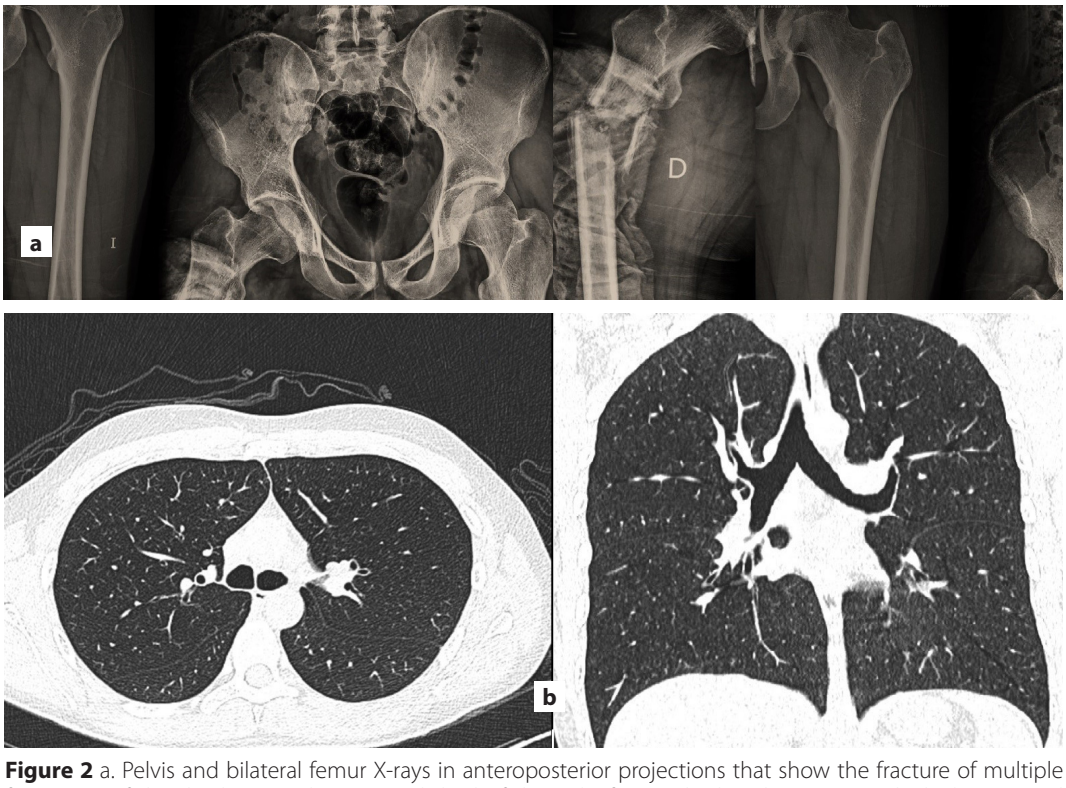

Figure 2 a. Pelvis and bilateral femur X-rays in anteroposterior projections that show the fracture of multiple fragments of the diaphysis in the proximal third of the right femur, displaced in varus, with thickening and periosteal reaction of the cortical in "Codman's triangle" with heterogeneous density and badly defined central radiolucent areas. b. Computed axial tomography of the chest.

enhancement after the administration of paramagnetic contrast material. A mass that destroys the cortical and invades the endomedular canal was described, which produced the complete and displaced pathological fracture of the femur, with displacement of the muscular structures of the anterior and medial compartment, towards superior and medial with edema in the associated soft tissues. It was concluded that these findings were highly suggestive of Ewing's sarcoma (Figure 3).

Treatment

Initially, he received hospital management with ketorolac 30 mg through a vein every eight hours for seven days; then, it was switched to tramadol 100 mg every 12 hours orally and immobilization of the right lower limb was maintained for 21 days. After one week of diagnosis, he was transferred to the ISSS cancer hospital for the start of chemotherapy with the schedule for Ewing sarcoma phase 1, with ifosfamide 2800 g, etoposide 160 mg, vincristine 2 g, MESNA 400 mg intravenously and filgastrim 300 µg subcutaneously from the fourth to the seventh day. Besides, a course of treatment was indicated each month until all three cycles were completed. Besides, physical therapy, oral treatment with acetaminophen 325 mg and codeine 16 mg every eight hours and tramadol 100 mg every 12 hours were indicated, received radiotherapy and finally partial hip resection will be performed.

Ultrasound-guided percutaneous biopsy was performed after extending the proximal femur (Figure 4), where 5 filiform samples varied from 0,3 to 1,7 cm were taken, with hematoxylin and eosin staining. bone fragments and fibrous connective tissue with multiple foci of hepatocellular malignant neoplasm, arranged in nests or lobes were observed. The cells were small, round, with hyperchromatic nuclei with thick chromatin, of scanty cytoplasm densely packed with little mitosis and coagulation necrosis in 30 %. immunohistochemistry was performed with the presence of high activity when applying CD99, Vimentin positive and CD45 negative, which confirmed Ewing's sarcoma in the right femur (Figure 5).

Outcome

The patient evolved with a decrease in local edema, pain control with oral medications, recovered mobility, although he maintained the functional limitation of the right lower limb, which makes standing and ambulation impossible.

Clinical diagnosis

Diagnosis of localized Ewing sarcoma (stage IA)[8] was confirmed by radiological and

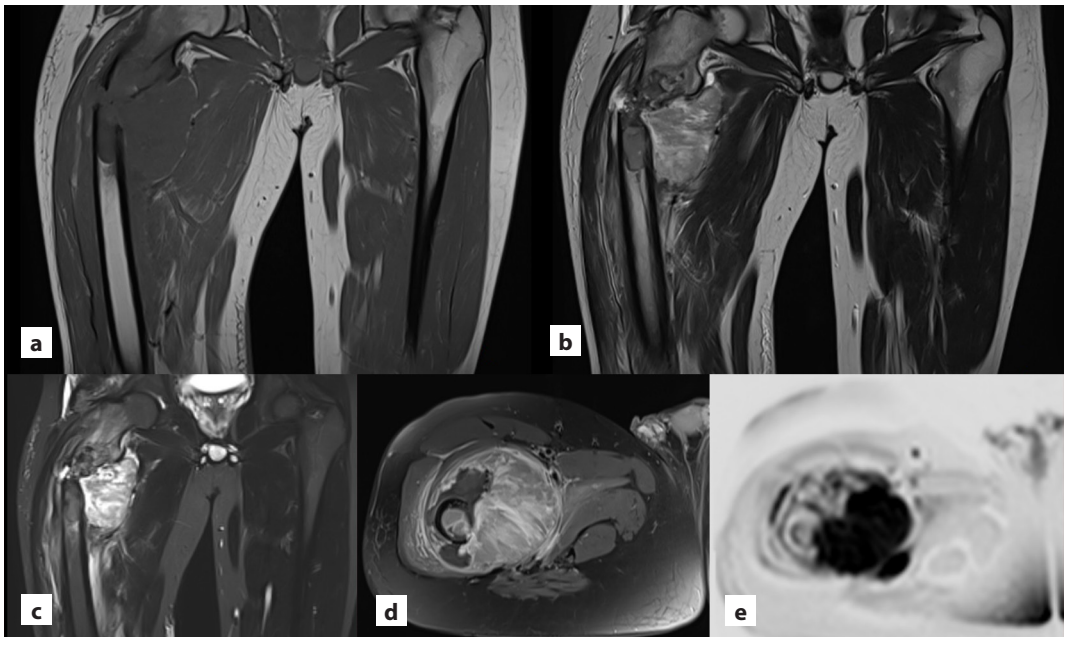

Figure 3. Magnetic resonance of the right thigh. a. T1 sequence. b. T2 sequence. c. STIR sequence d. T1 post gadolinium. e. Dissemination sequence

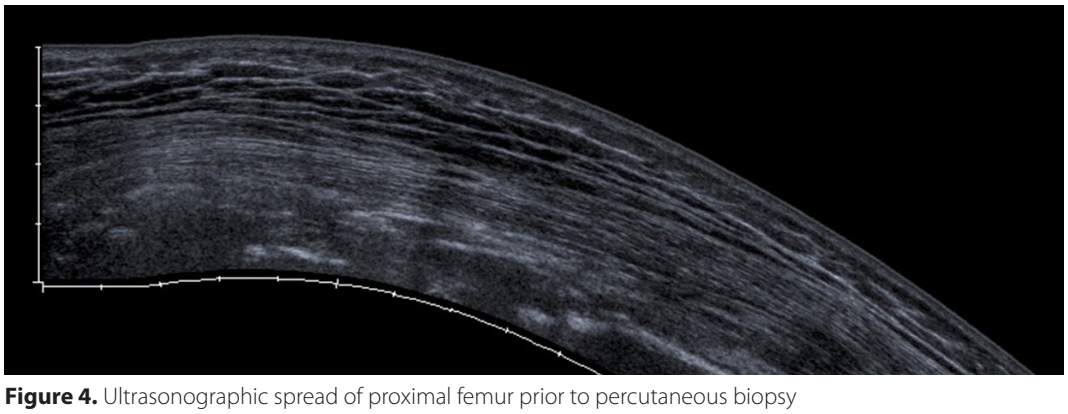

Figure 4. Ultrasonographic spread of proximal femur prior to percutaneous biopsy

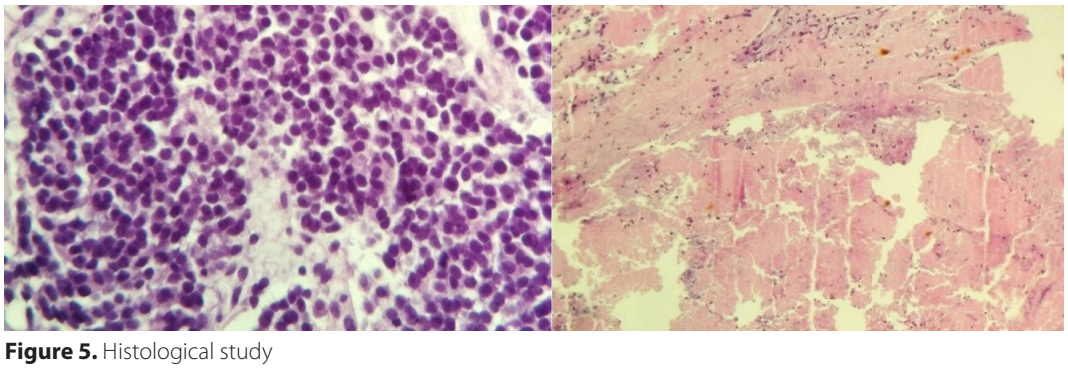

Figure 5. Histological study

histopathological clinical findings in the right femur.

Discussion

Ewing sarcoma is a rare tumor that occurs most often in males aged five to 20 years[9]. Although it can occur at any time of life[10], the highest incidence occurs at the age of 15[11]. The estimated incidence is more than one million cases of children and adolescents worldwide[12]. In Spain, it is the first cause of bone tumor in this population[5], while in the United States of America, it is the second cause between 1 % and 2 % of cancers diagnosed in children under 20 years of age[13].

The most common location of this tumor is the pelvis, femur and chest bones. When this tumor affects the long bones, it is most often located in the diaphysis[3,5]. The clinical presentation of Ewing sarcoma is usually nonspecific. Symptoms such as tumor

with pain on palpation[5] or intermittent and progressive and edema are usually present for more than six months prior to diagnosis[14]. The appearance of a soft mass must lead to a case study[14]. Pathological fractures are unusual as an initial clinical presentation[5]. They occur in 16 % of cases[15].

Imaging studies are important to locate the tumor, define its extent or volume and determine if there is metastasis to decide treatment and predict the evolution and outcome[3].

The origin of bone lesions is the central medullary canal and it affects the soft tissues in more than 80 % of cases; the masses in these tissues are usually large and surround the affected bone[7]. Cortical destruction can be generated that facilitates communication between the medullary canal and soft tissue components[7].

The radiological aspects of these tumors are very variable. The most common findings are the Codman's triangle and the lamellated periosteal reaction or onion skin periosteal reaction, which result from the displacement of the periosteum and the proliferation of bone tissue[7,16]. The periosteal reaction is the most frequent and has an aggressive behavior, followed by the destruction of the cortex associated with a mass of soft parts, and the least common is the destruction of the bone with a wide transition zone[7].

The radiological technique that allows to assess the bone and extraosseous extension of the tumor is magnetic resonance spectroscopy to confirm or discard an involvement of the bone marrow, that is, in phase T1; in these cases, the existence of foci far from the primary tumor should be discarded. If a cortical and soft tissue invasion is found, this is classified as phase T2[7].

Computed tomography presents the aggressive periosteal reaction and bone destruction6, so it is considered useful in complex anatomical areas such as the pelvis, spine and base of the skull[17]. Also, tomography in the chest area allows to identify a lung metastasis, which together with bone marrow and liver metastases are the most common ones. These are presented by hematogenous dissemination and are associated with alterations in laboratory tests, including high levels of alkaline phosphatase, erythrocyte sedimentation rate or lactic dehydrogenase, especially when the latter has extreme values[3].

The diagnosis is confirmed by histological analysis by a closed needle biopsy. In this procedure, local anesthesia is used and experience on the part of the doctor in charge of it is required not to produce pathological fractures and avoid tumor contamination of the surrounding tissues[3,7]. In this case, ultrasound-guided needle biopsy was performed, which was timely for beginning medical treatment consisting of systemic chemotherapy. This is considered the mainstay of treatment and it is sometimes combined with surgery or radiotherapy since these play a role depending on the location and size of the tumor[18].

Survival rates have increased from 10 % to about 70 % over the past 40 years. The prognosis in the evolution of these cases depends on factors such as the presence or otherwise of metastasis, the location and size of the primary tumor, age, response to treatment and the presence of certain chromosomal translocations[14].

In patients older than 10 years, a higher frequency of negative prognostic factors has been described, including the presence in males, the axial location of the tumor, such as the head, spine, chest, pelvis or neck, and the presence and location of metastasis[19].

The survival rate is also related to the stage of the tumor at the time of diagnosis, with a five-year survival greater than 60 %, when the disease is localized, and about 20 % when there is metastasis[15,19]. A survival analysis identified that 50 % of the case studies with localized sarcoma died during six years of follow-up, with a median survival of 25 months, while cases with metastasis had a median survival of 9,75 months[5].

Patients with metastasis who have had a lower survival are cases of bone metastasis or a combination of lung and bone metastases[20].

It is expected that in cases of tumors without metastases, chemotherapy will generate a reduction of the tumor and surgical resection can be continued[3]. Aggressive chemotherapy treatment has led to an increase in survival rates up to 65 % over the past five years[5].

Ethical aspects

For the presentation of this case, the patient was asked for informed consent respecting the principles of privacy and dignity according to the Helsinki guidelines.

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Case reports

Diagnosis of four synchronous primary neoplasms in an adult

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Diagnóstico de cuatro neoplasias primarias sincrónicas en un adulto

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Abstract
Presentation of the case. A 72-year-old female patient with a one-year history of abdominal pain in the right upper quadrant, colicky, radiating to the back, accompanied by adynamia and weight loss. Abdominal distension and a painful mass on palpation in the right hypochondrium were evidenced. Imaging studies identified different lesions in the hepatic parenchyma, right adnexa, peritoneum and cecal appendix. The histopathological study described the presence of clear cell hepatocellular carcinoma, borderline mucinous tumor of low malignant potential or borderline, peritoneal pseudomyxoma and low-grade mucinous neoplasm of the cecal appendix respectively, as synchronous neoplasms. **Treatment.** An exploratory laparotomy was performed with excision of the adnexal lesion and the cecal appendix. The hepatic lesion received transarterial chemoembilization by interventional radiology. Follow-up with conservative management by clinical oncology was indicated. **Outcome.** The patient evolved with good general condition, in the follow-up with magnetic resonance imaging was classified with persistence of stable hepatic lesion. Eighteen months after the diagnosis of synchronous neoplasms, basal cell carcinoma was identified, due to the difference in the time of diagnosis this is considered a metachronous neoplasm.

Keywords
Multiple primary neoplasms, liver neoplasms, pseudomyxoma peritonei, appendix, mucinous carcinoma.

Resumen
Presentación del caso. Paciente femenina de 72 años. Mediante estudios de imagen (ultrasonido y tomografía), se le identificó lesión en parénquima hepático, anexo derecho, peritoneo y apéndice cecal, y mediante estudio histopatológico se determinó la presencia concomitante de carcinoma hepatocelular de células claras, tumor mucinoso limítrofe de bajo potencial maligno o borderline, pseudomixoma peritoneal y neoplasia mucinosa de bajo grado del apéndice cecal, respectivamente. Debido a que las neoplasias reportadas no guardan relación con el mismo órgano ni con el sistema, se considera que son neoplasias aparecidas al azar y de tipo sincrónico por ser diagnosticadas en el mismo espacio temporal. **Intervención terapéutica.** Se practicó laparotomía exploradora con exéresis de lesión anexial y de apéndice cecal. La lesión hepática recibió quimioembilización transarterial por radiología intervencionista. **Evolución clínica.** Posterior a la intervención quirúrgica, la paciente presenta buen estado general. En seguimiento con resonancia magnética se cataloga con persistencia de lesión hepática ya tratada, por lo tanto, con enfermedad estable; se refiere a oncología clínica para valoración de quimioterapia en el manejo del pseudomixoma peritoneal. Dieciocho meses después de los diagnósticos iniciales, se documenta carcinoma basocelular y se cataloga como neoplasia metacrónica por la diferencia de tiempo entre los diagnósticos.

Palabras clave
Neoplasias primarias múltiples, neoplasia hepática, pseudomixoma peritoneal, apéndice, carcinoma mucinoso.

Introduction

The term multiple primary neoplasms refer to the simultaneous existence of two or more malignant and independent tumors in the same patient[1]. These are synchronous neoplasms if the detection of tumors is simultaneously carried out or within six months after the first tumor is diagnosed; on the contrary, if a tumor is detected in a period greater than six months after the first one was diagnosed, they are classified as metachronous neoplasms[1].

Multiple primary neoplasms are classified as those that meet the three diagnostic criteria established by Warren and Gates, that is, that each tumor is identified as malignant, according to histopathology; tumors are histologically different; and metastases are excluded[1,2]. Depending on the place of appearance, they are also classified as multicenter if they arise in the same organ; they are classified as systemic if they occur in an organ system or peer organs; and randomly, on unrelated sites[3,4].

Multiple primary neoplasms have been described since 1921, when 4,7 % of multiple primary cancers were found in 3000 cases of malignancy[2]. Clinical features are variable and a low incidence has been identified; however, due to the increased survival of cancer patients, multiple neoplasms are on the increase[5]; besides, it is due to more sophisticated procedures and population longevity[1].

The incidence of a second primary cancer is variable and is described between 2,4 % and 17 %[6]. In the United States of America (USA), the most common neoplasms identified during 2019 were prostate, colon, rectum and melanoma, in men, and those of the breast, uterine body, colon and rectum, in women[7]; among Hispanics living in the U.S., the risk of developing neoplasms is higher, and the most common are colorectal, lung, kidney and liver, as well as prostate in men and breast, thyroid and uterine body, in womens[8]. Another of the most frequent neoplasms is bladder neoplasm[9].

Underlying causes of multiple primary cancers may include host and lifestyle-related factors, environmental, genetic, and treatment-related factors[10].

Factors associated with the development of more than one primary cancer include genetic susceptibility to cancer, exposure to environmental toxicants, and lifestyle related to tobacco or alcohol use, among others; also, the carcinogenic effects of previous cancer treatments are described[6].

Age is an independent risk factor for the development of any type of cancer; if there is a primary tumor, there is an 8,5 % chance of developing a second one[4,11]. The neoplasms that have been reported with more synchronicity are associated with tobacco use as a risk factor, and among these the most frequent are head and neck cancer (4 - 17 %), esophageal (5,5 %), stomach (5,4 %) and lung cancer (2,7 - 4,3 %)[1].

Case presentation

This is a 72-year-old woman who consulted for abdominal pain type colic, one-year-old, located in the right upper quadrant, of moderate intensity, which radiated to the back. Besides, she had adinamia and weight loss, about 15 pounds, in the last three months. She had a history of type 2 diabetes *mellitus* and chronic high blood pressure treated with metformin 850 mg and enalapril 20 mg each day, cholecystectomy for biliary lithiasis ten years ago and left oophorectomy eight years earlier for a benign tumor, without history of alcoholism or other clinical relevance.

In the clinical evaluation, abdominal distension and a mass in the right hypochondrium that generated pain on palpation were found. Besides, dilation was described in the superficial veins of both lower limbs.

Laboratory tests reported hemoglobin of 9,4 g/dL with mean corpuscular volume of 75 fL and mean corpuscular hemoglobin of 28 mg/dL (microcytic and hypochromic anemia), leukocytes in normal values, glucose of 150 mg/dL, bilirubins and transaminases within normal ranges, carcinoembryonic antigen of 14,47 µg/L (0 to 2,5 µg/L) and alpha-fetoprotein of 1,59 ng/mL (less than 10 ng/mL), and hepatitis B and C virus infection was discarded.

Abdominal ultrasonography described a nodular mass in segment I and IV. These studies contributed to the diagnosis of a liver tumor, diabetes *mellitus*, high blood pressure, secondary anemia and venous insufficiency of both lower limbs, so hospital admission was decided to continue with the study.

Due to weight loss as an approach to constitutional symptoms, a thyroid ultrasonography was indicated, which reported a multinodular goiter; nodule suspected of malianity was not reported, so the histopathological study was not indicated. Thyroid function tests reported TSH 2,5 mUI/L, T3 1,8 nmol/L and T4 110 nmol/L, so it was classified as euthyroid multinodular goiter with follow-up plan by endocrinology in the outpatient clinic.

The study of the liver mass was continued with abdominopelvic computed tomography (CT) that described a solid mass of 4.5 × 4 cm in segment IV of the liver, which during the contrasted phase presented a typical behavior of hepatocarcinoma (Figure 1). Follow-up by a clinical oncology in the outpatient clinic was indicated.

The patient attended the clinical oncology consultation after six months due to restrictions on consultations in the context of the COVID-19 pandemic, in which laboratory and imaging tests were updated. In the laboratory reports, tumor markers presented the following values: CA 19-9 cancer antigen of 24,4 IU/mL

(reference value 0 to 39 IU/ml), significant elevation of carcinoembryonic antigen of 93 µg/L (normal range 0 to 5 µg/L), alpha-fetoprotein 1,58 ng/mL(reference value 0 to 5 ng/ml), and CA 125 cancer antigen of 72 IU/mL (normal value less than 46 IU/mL). CT of the abdomen and pelvis described a mass of the hepatic parenchyma of 3,3 × 3,5 cm in segment IV, a cystic lesion in the pancreatic body and a mass in the pelvic cavity of probable adnexal origin of 13 × 14 × 15,7 cm; also, ganglia of infiltrative characteristics in the right superficial inguinal chain (Figure 1).

It was classified as hepatocarcinoma Barcelona A[17] (Child-Pugh A, with liver injury up to 3 cm and associated disease), referred to interventional radiology to perform radiofrequency ablation (RFA) of liver injury and oncological surgery for pelvic mass management.

Treatment

Surgical management of the patient consisted of an exploratory laparotomy, in which a neoplasm of 20 × 20 cm of mucinous consistency was found in the right ovary, carcinomatosis in the pelvis and abdomen with little mucinous fluid and a liver capsule with peritoneal implants; besides, appendectomy and hysterectomy were performed with suboptimal cytoreduction, both surgical pieces were sent for histopathological study (Figure 1).

Outcome

After surgery, the patient progressed in good general condition. Chest CT showed discrete fibrous tracts at the right vertex and both pulmonary bases, as well as significant adenopathies at the mediastinum and right hilum and metastases were ruled out (Figure 2). CT of the abdomen described a liver injury in segment IV and a cystic lesion in the body of the pancreas. The CT scan of the pelvis described the surgical absence of the uterus (Figure 2).

Percutaneous liver biopsy by interventional radiology reported a hepatic parenchyma with invasive malignant epithelial neoplasm grade 3 formed of cells with clear cytoplasm, scarce, binucleated and trinucleated, arranged in cords, in addition to inflammatory infiltrate,moderate to severe and steatosis Ki67: 40 % (Figure 3).

The study was completed with an abdominal magnetic resonance imaging in which a chronic parenchymal liver disease

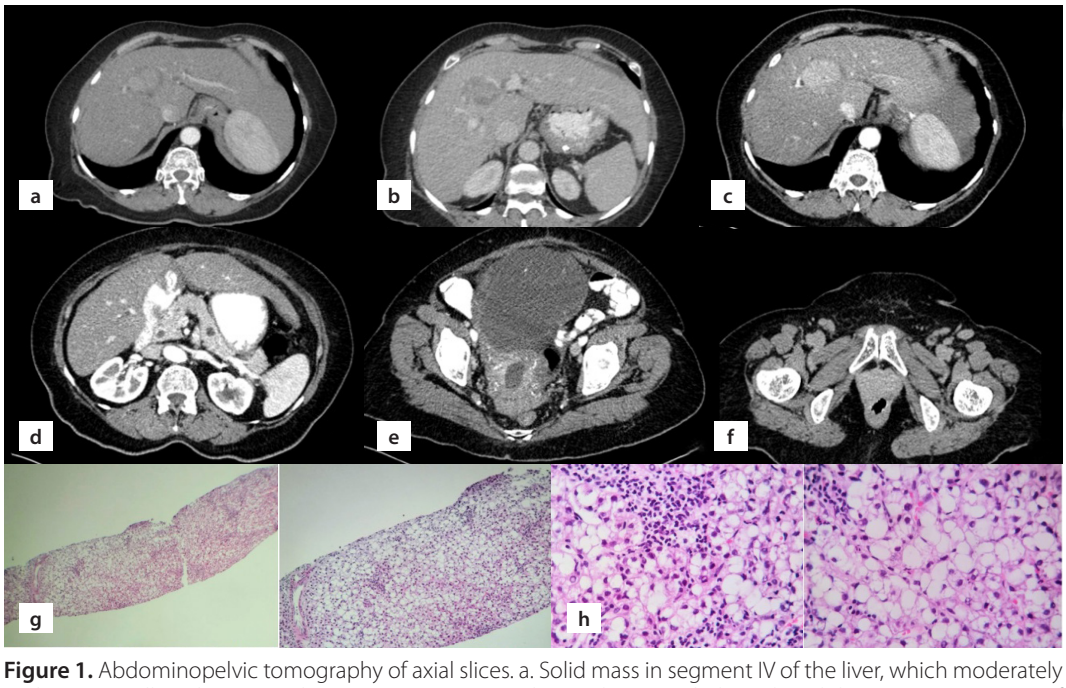

Figure 1. Abdominopelvic tomography of axial slices. a. Solid mass in segment IV of the liver, which moderately and centripetally enhances with intravenous contrast during the arterial phase. b. Solid mass in segment IV of the liver in the venous phase, hypodense is visualized in a heterogeneous way with the "wash out" phenomenon. c. Mass in segment IV of the hepatic parenchyma of 3,3 × 3,5 cm. d. Cystic injury in the pancreatic body. e. Mass in the pelvic cavity of probable adnexal origin of 13 × 14 × 15,7 cm. f. Bone cysts of infiltration characteristics in the right inguinal lymphadenopathy. g. Histological sections of the cecal appendix: its lumen replaced by pseudostratified hyperplastic epithelium of mucinous type, cells with moderate atypia, which are accompanied with abundant extracellular mucin production. Positive surgical margin. h. Peritoneum: fibroadipose tissue with extracellular mucin pools and few cells with mild atypia, which is accompanied by mild inflammatory infiltrate of lymphocytic type

was identified without signs of portal hypertension and a nodular lesion in the hepatic segment IV-a measuring 3,6 × 4,6 × 4,8 cm, of hypointense behavior in sequences weighted in T1, heterogeneously hyperintensive in T2. In the dynamic phases after the contrast, an avid enhancement in the arterial phase with lavage in the venous phase,

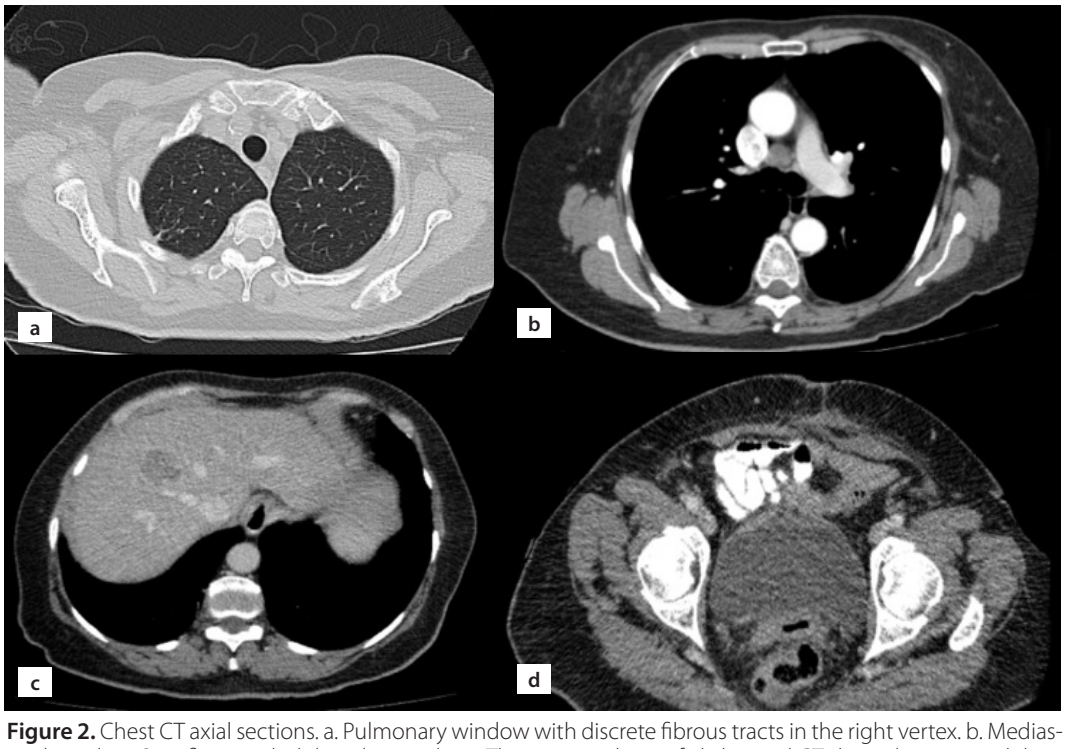

Figure 2. Chest CT axial sections. a. Pulmonary window with discrete fibrous tracts in the right vertex. b. Mediastinal window. Significant right hilar adenopathy. c. The venous phase of abdominal CT shows hepatic nodule in segment IV, suggestive of hepatocarcinoma. d. The venous phase of pelvis CT : surgical absence of uterus and postsurgical changes in abdominal wall

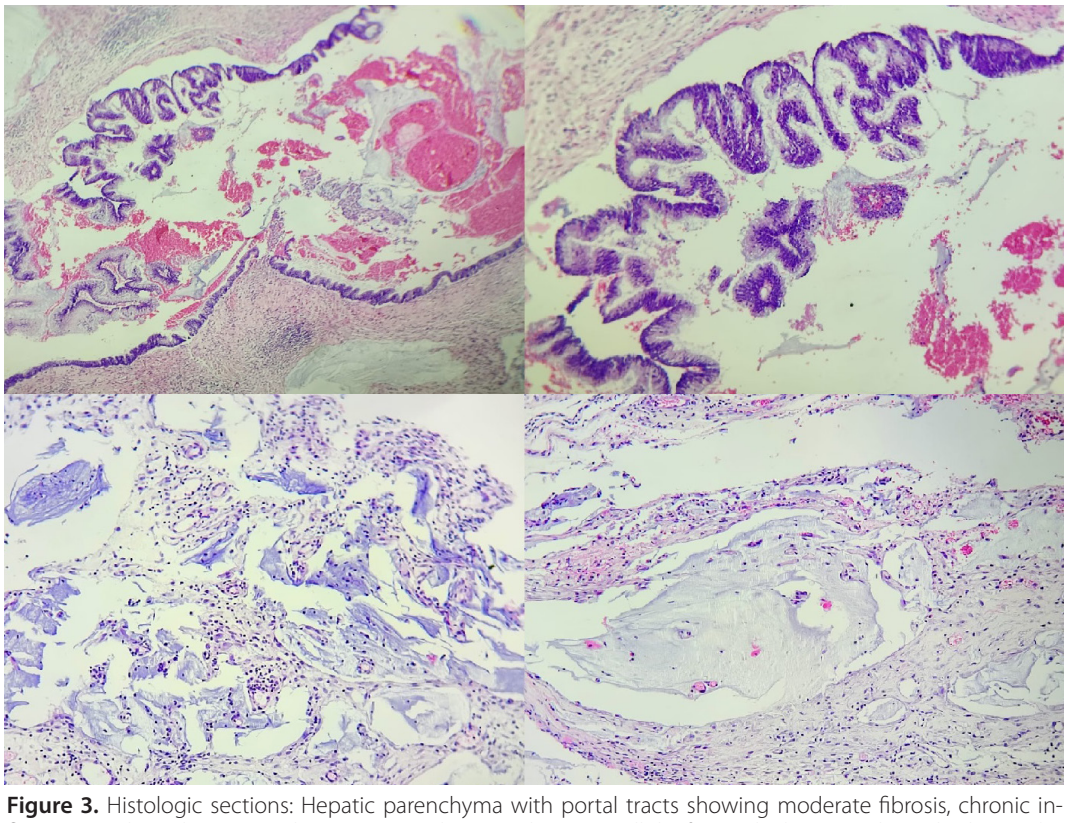

Figure 3. Histologic sections: Hepatic parenchyma with portal tracts showing moderate fibrosis, chronic inflammation; binucleations and regenerative changes. There are cellular foci with clear cytoplasm displacing the nucleus to the periphery, which present mild nuclear pleomorphism

formation of "pseudocapsule" with restriction to diffusion and typical behavior of a hepatocarcinoma was presented, classified by image as LIRADS V[12] (Figure 4). Besides, the pancreatic lesions were classified according to the characteristics of the images as non-neoplastic mucinous cysts[13].

Due to the size of the lesion, it was classified as an intermediate stage according to Barcelona B[17]. Also, transarterial chemoembolization was performed as a management of hepatocarcinoma and after six months it was followed up with an abdominal magnetic resonance in which the persistence in size and behavior of the nodular lesion reported in the IV-a hepatic segment compatible with LIRADS V[18] hepatocarcinoma with stable disease according to mRESIT was identified.

Another transarterial chemoembolization was indicated but the patient did not accept the procedure and follow-up by clinical oncology was decided for conservative management and continued surveillance; Since the tumors did not show signs of aggression, the patient has not received chemotherapy or radiation therapy.

After eighteen-months follow-up, the patient consulted for the appearance of a nodular lesion of six months' evolution that compromised the dorsolateral region of the nose, not painful and slow growing; she was evaluated and managed in a peripheral medical unit, where they decided to perform complete resection of the lesion. After two months it was evident that there was no evidence of this tumor at direct visualization and follow-up by dermatology was indicated. The histopathological study of this reported a basal cell carcinoma with healthy limits (Figure 5).

Clinical diagnosis

The results of the biopsies of abdominal tissue, ovary, cecal appendix, uterus and mesentery helped to get simultaneous diagnostics of a peritoneal pseudomyxoma, a borderline mucinous tumor of low malignant potential, the mucinous neoplasia of low grade of cecal appendix and hepatocellular carcinoma (HC) of clear cells, being defined as synchronous primary neoplasms.

Basal cell carcinoma was added at the follow-up twelve months after the diagnosis of synchronous neoplasms. Due to the difference in the time of diagnosis, this is considered a metachronic neoplasm.

Discussion

Multiple primary neoplasms have different histology and site of origin[2.] According to the time of appearance, they are classified into synchronous and metachronic, the latter being the most frequent forms of presentation[1,14]. These tumors known as multicenter tumors can occur in the same organ, are rare and approximately occur 37 % of cases[3]. The organs most frequently affected by multicenter tumors are: breast, bladder, lung, colon, melanomas, stomach, liver, kidney, thyroid, and esophagus, in that order of frequency[7-9]. The rest are associations of two or more independent tumors in different organs of the same patient; these are described as two metachronic tumors, in more than 50 % of cases, three tumors in less than 10 %, and four or more tumors in less than 1 %[16,20].

Synchronous tumors with an incidence of approximately 56 % are mentioned; the breast, endometrium, ovary and colon are the most frequent[16], and in an incidence of approximately 14 % the oropharynx, larynx, lungs, bladder and esophagus[16]. An incidence of 26 % has been reported in other associations involving lymphomas, myelodysplasias, leukemias, sarcomas, carcinoma of the lung, breast, bladder, thyroid, retinoblastomas, neuroblastomas, carcinoid tumors, multiple endocrine neoplasms and pelvic tumors[3,4,11,16].

In the case described, the neoplasms reported have no relationship between organs and systems since they are considered to be neoplasms that randomly appeared, diagnosed in the same temporal space.

Hepatocarcinoma has been described as one of the synchronous tumors with relative frequency, especially in the gastrointestinal tract[3]. The most frequent association is that of gastric adenocarcinoma with gastrointestinal stromal tumor or with neuroendocrine tumors. Adenocarcinoma and gastric lymphoma are other common synchronies[4,9,10], although the latter has been little treated in the literature since Schuback *et al.* published the first case of coexistence of both types of tumors in the same patient in 1931.

In relation to HC, there are few cases that indicate its association with other neoplasms. Chong *et al.* reported the case of triple synchronous neoplasia, which consisted of HC, diffuse gastric adenocarcinoma, and gastric lymphoma[3]. Maldonado reported a synchronous neoplasm in a man with synchronous gastric cancer with a renal tumor[16].

The clear cell variant of HC can be difficult to differentiate from clear cell renal carcinoma and can exceptionally coexist[4]; they can be distinguished only by immunohistochemistry. Also, a case of sigmoid adenocarcinoma with synchronous hepa-

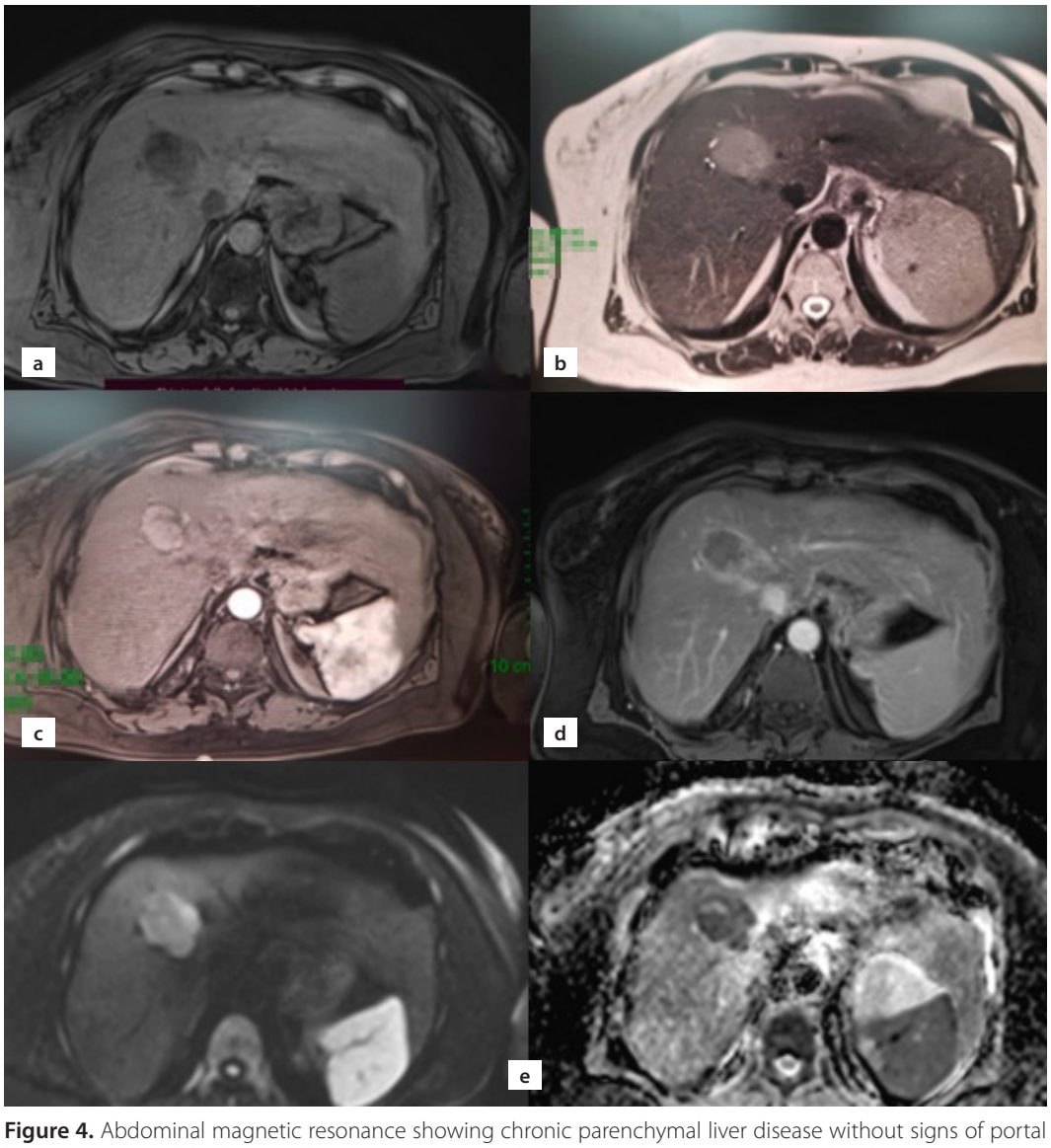

Figure 4. Abdominal magnetic resonance showing chronic parenchymal liver disease without signs of portal hypertension, nodular lesion in hepatic segment IV-a, hypointense behavior in T1-weighted sequences. a. Heterogeneously hyperintense in T2. b. Post-contrast dynamic phases with avid enhancement in arterial phase. c. Phenomenon of "wash out" in the venous phase with the formation of a "pseudocapsule". d. True restriction to diffusion and ADC map. and. Typical behavior of hepatocarcinoma, classified by image as LIRADS V

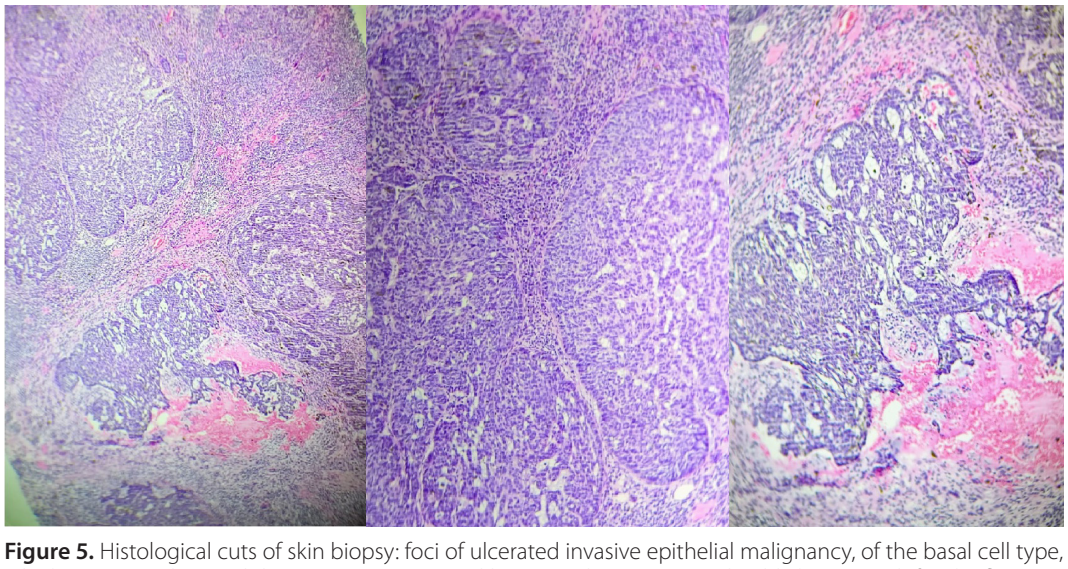

Figure 5. Histological cuts of skin biopsy: foci of ulcerated invasive epithelial malignancy, of the basal cell type, which is arranged in a solid pattern, accompanied by stromal retraction and mild chronic multifocal inflammatory infiltrate. Healthy surgical limits

tocarcinoma has been found and there are series of patients with hepatocarcinoma in which other synchronous tumors such as malignancies of the genitourinary and gastrointestinal tract were detected[3].

Appendicular tumors are classified into epithelial (mucinous adenocarcinoma, non-mucinous and signet-ring cell tumors) and non-epithelial (neuroendocrine tumors, lymphomas and sarcomas)[9,17]. The mucinous group is a heterogeneous group: they are divided into mucinous cystadenoma, mucinous neoplasia of uncertain malignant potential, mucinous neoplasia of low malignant potential and mucinous adenocarcinoma[17].

The classification of mucinous appendix tumors is controversial when aspects of malignancy are lacked but are associated with peritoneal mucin spread. Mucinous ascites known as peritoneal pseudomyxoma is present in more than 50 % of these patients and its presence indicates a more advanced stage and a worse prognosis. It can present as low-grade (diffuse peritoneal adenomcinosis) or high-grade (diffuse peritoneal carcinomatosis)[17]. These have an incidence of less than 0,5 % of all gastrointestinal tumors. The sixth decade of life is the average age of presentation, and more frequent in males[17].

Epithelial ovarian carcinomas are classified, according to molecular and clinical-pathological differences, into type 1 tumors, which include low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma and mucinous ovarian carcinoma and type 2 tumors, which include high-grade tumors of grade serous carcinoma[18].

About 70 % of mucinous carcinomas of the ovary are metastatic, and about 80 % of primary tumors are in stage I[18].

The most frequent primary sites of ovarian metastases are gastrointestinal, although other distant lesions with nonspecific symptoms related to minor disorders of the gastrointestinal tract may occur[18].

Regarding the diagnosis of basal cell carcinoma, there has been no evidence of a direct relationship with other synchronous or metachronic tumors; however, this along with non-melanoma cancer, constitutes 80 to 90 % of skin neoplasms and is the most frequent cancer in the world population, being an additional burden for dermatologists and public health[19].

Ethical aspects

For the presentation of this case, the confidentiality of the patient was respected, the patient was approved through informed consent and it was developed in accordance with the principles of the Declaration of Helsinki.

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Case reports

Complete androgen insensitivity syndrome

DOI: 10.5377/alerta.v5i2.14397

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Síndrome de insensibilidad completa a andrógenos

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Conflicts of interest:
The authors declare there are no conflicts of interest.

Abstract
Presentation of the case. Phenotypically female patient, 18 years old, 46 XY karyotype, who was evaluated in a tertiary care center for pediatric medicine due to primary amenorrhea. Physical evaluation found adequate breast development, female external genitalia with slight hypoatrophy of the labia majora and minora, vaginal canal of 11 cm, ultrasound reports a linear rudimentary uterus and images suggestive of ovaries, magnetic resonance describes the presence of a bilobed tubular structure composed of two nodular images, which are located adjacent to the bladder wall in their aspect posterior, lateral and superior right 27,4 × 15,4× 11,0 mm, left inguinal canal two images, one solid nodular, ovoid, isointense 37 × 21 × 13,8 mm (nodular), cystic 22,7 × 14,0 mm, congenital absence of uterus. **Treatment.** In the laparoscopic examination, the presence of gonads in the inguinal and para-bladder canals was detected, and both gonads were resected. **Outcome.** She was managed with analgesia, antibiotics and was discharged three days after surgery. The biopsy reported cryptorchidism of the right and left testis.

Keywords
Androgen-insensitivity syndrome, testicular feminization, 46 XY gonadal dysgenesis, androgen effect, disorder of sex differentiation.

Resumen
Presentación del caso. Paciente fenotípicamente femenina de 18 años de edad, cariotipo 46 XY, que fue evaluada en centro de atención de tercer nivel de medicina pediátrica, por un cuadro de amenorrea primaria. En la evaluación física se encontró un adecuado desarrollo mamario, genitales externos femeninos con leve hipotrofia de labios mayores y menores, canal vaginal de 11 cm; ultrasonido reporta útero rudimentario lineal e imágenes sugestivas a ovarios. La resonancia magnética describe presencia de estructura de aspecto tubular bilobulada compuesta por dos imágenes nodulares, las cuales se ubican adyacentes a la pared vesical en su aspecto posterior, lateral y superior derecho de 27,4 × 15,4 × 11,0 mm. El conducto inguinal izquierdo presenta en dos imágenes: una nodular sólida, ovoide, isointensa de 37 × 21 × 13,8 mm (nodular), quística 22,7 × 14,0 mm, ausencia congénita de útero. **Intervención terapéutica.** En la exploración laparoscópica se detectó presencia de gónadas en canal inguinal y paravesical. Se procedió a la resección de ambas gónadas. **Evolución clínica.** Se manejó con analgesia, antibiótico y fue dada de alta a los tres días posteriores a la cirugía; la biopsia reportó criptorquidia de testículo derecho e izquierdo.

Palabras clave
Síndrome de insensibilidad a los andrógenos, feminización testicular, disgenesia gonadal 46 xy, efecto androgénico, trastornos de diferenciación sexual.

Introduction

Androgen insensitivity syndrome (AIS), also known as testicular feminization syndrome[1], includes a widely varied group of mutations that is related to androgen receptor dysfunction[2] and resistance of target tissues to the action of male hormones[3]. This is caused by localized genetic alterations in the coding sequence of androgen receptors linked to the chromosome Xq11 - 12[3], which is the gene encoding the androgen receptor, of a genetically male individual (46 XY)[3,4]. Mild, partial or complete clinical entities depend on the degree of androgen insensitivity[3].

Advances in genetic causes have allowed these congenital conditions of development of chromosomal, gonadal or atypical anatomical sex to be called disorders of sexual differentiation[5].

The main characteristic is the resistance of the target tissues to the action of male hormones[5,6]. The presence of the sexual differentiation protein Y promotes the formation of primordial testicles in the fetal abdomen. From the seventh week after conception, the fetal testicles begin to produce testosterone, whose activity is blocked by pathological processes that affect androgen receptors[7], which prevents the normal male development of the internal and external genitalia of genetically male individuals[6,8] and generates the differentiation of the external and female genitalia; Wolff duct derivatives which depend on androgenic action are not developed. The epididymis, deferent ducts and seminal vesicles[9], and the presence of anti-Müllerian hormone produced by the primordial testicles, suppresses the formation of the female genital organs. However, the lower part of the vagina is fully developed because it is not a derivative of the Müller duct. This is shorter than normal and has a blind end, lacks uterus and fallopian tubes[7], absent Müllerian or vestigial structures and testicles located on the lips, inguinal canal or abdomen[7].

AIS is one of the common causes of disorders of sexual development that give rise to varied phenotypes[4]. A prevalence of two to five cases per 100 000 males genetically born has been estimated with an estimated incidence of one case per 20 000 to 90 000 males genetically born[5,10].

The phenotypic spectrum of individuals depends on the residual activity of the androgen receptor and ranges from individuals with a completely female phenotype, with testicles in the absence of derivatives of the Wolff and Müller ducts and absence of sexual hair to a male phenotype with infertility and devirilization[2,3,12]. These variations define the classification in complete and partial AIS[2].

The complete AIS was described by Morris in 1953. This is characterized by presenting in a person of female appearance, with normal breast development, little body hair, primary amenorrhea and undescended testicles located instead of the ovaries[1]; it is part of the most frequent disorders of sexual differentiation.

Case presentation

This is a phenotypically female patient, 16 years of age, who consulted in a child care hospital for amenorrhea with normal breast and external genital development. With the surgical history of bilateral inguinal hernioplasty at three years of age, in which they reported as an incidental finding the presence of ovaries in hernial sacs, so they introduced again to the abdominal cavity. He had not initiated sexual activity; telarquia at 12 years, pubic hair appearance at 13 years, no axillary hair appearance and heterosexual sexual preference. She had no other pathological medical history.

Studies were indicated for the suspicion of primary amenorrhea. Laboratory tests reported hormonal alterations related to anovulation with a slight elevation of follicle-stimulating hormones and luteinizing hormones with low testosterone levels (Table 1). Pelvic ultrasonography reported that the uterus was sparsely visible, child-sized, with no evidence of endometrium; the right ovary of 5 cm^3 and the left one of 3,9 cm^3; no follicles were evident. The karyotype was performed, which reported 46 XY. She was evaluated by pediatric urology, where a diagnostic laparoscopic video was indicated. In this procedure, a sample of the apparent right gonad was taken for biopsy. The histopathological study reported a tissue consisting of multiple foci of hypoplastic seminiferous tubules scattered in ovarian stroma with granulosa cells, histopathological diagnosis ovotestis.

When she turned 18 years old, she was referred to the endocrinology outpatient clinic from another national hospital, with a diagnosis of sexual development disorder XY, with complete androgen insensitivity syndrome suspicion.

In the reference hospital, laboratory studies were started again, which reported maintaining the slight elevation of follicle stimulating hormones, luteinizing and low testosterone levels (Table 1). Moreover, pelvic ultrasonography described the rudimentary linear uterus 3,7 cm with suggestive images of ovaries. It was requested to repeat the revision of the sheets of the previous biopsy and a testicular tissue consisting of underdeveloped seminiferous tubules was reported, some with sclerosis and fibrosis of the tubular basement membrane arranged in their fibrous stroma, no spermatogenesis, no presence of ovarian tissue, diagnosis of testicular hypoplasia.

Abdomino-pelvic magnetic resonance described the presence of a bilobed tubular structure, composed of two nodular images, which were located adjacent to the bladder wall in its posterior, lateral and upper right aspect of 27,4 × 15,4 × 11,0 mm (Figure 1). The left inguinal duct reflected two nodular

images as a solid, ovoid, isointense of 37 × 21 × 13,8 mm (nodular) and another of cystic characteristics of 22,7 × 14,0 mm (Figure 2) and congenital absence of uterus.

She was evaluated by the gynecology unit, where she was instructed to start hormone replacement therapy, after surgical treatment. Also, he referred to the psychological care area where a session was held with the patient's mother to evaluate her response to diagnosis and treatment. It concluded that gender reinforcement was not necessary.

The clinical evaluation of the urology specialty reported that breast development with Tanner V stage was adecuate. Bilateral umbilical and parainguinal scars were evident without other abdominal or inguinal canal abnormalities. He also described the female external genitalia with the presence of sparse fine pubic hair, distribution of genital pubic hair in stage V in the Tanner scale, mild hypotrophy of the labia majora and minora, the hymen of annular shape, when performing the vaginal touch, the wide and functional vaginal canal was identified that only allowed the introduction of a finger, the measurement of the vaginal canal resulted in 11 cm in length. Visualization of the urethral meatus was difficult.

Treatment

Surgical intervention was scheduled seven days after evaluation. The patient was admitted to the endocrinology service three days before her surgery to complete the pre-surgical evaluations. Prophylaxis with cefazolin of one gram intravenously was indicated, 30 minutes before the start of surgery.

The surgical procedure consisted of laparoscopic removal of the gonads by a closed technique. A periumbilical incision a 10 mm trocar was placed through a periumbilical incision ; the pneumoperitoneum of 12 mmHg and an initial flow of 5 L/min were formed. A 5 mm trocar was placed on the lower left and right flanks. The presence of gonads at the level of the bilobed left inguinal canal (Figure 3), the bilobed right paravesical gonad (Figure 3) and the uterus of linear appearance was evidenced. Finally, the bilateral gonadectomy was performed and sent for histological study.

Outcome

In the immediate postoperative period, the patient was treated with ketorolac and ceftriaxone intravenously and started

Table 1. Laboratory test results

Laboratory test	Pediatric hospital results	Result of the reference hospital	Reference value
Follicle stimulating hormone	15,4 mIU/mL	13,19 mIU/mL	2 – 9 mIU/mL
Luteinizing hormone	47,6 mIU/mL	55,51 mIU/mL	1 – 12 mIU/mL
Thyrotropin	0,6 µUI/mL	0,347 µUI/mL	0,3 – 5,6 µUI/mL
Triiodothyronine	2,8 pg/mL	3,64 pg/mL	2,5 – 3,9 pg/mL
Thyroxine	5,2 µg/dL	0,85 ng/dL	0,61 – 1,12 ng/L
Testosterone	1407 ng/mL	12,67 ng/mL	1,75 – 7,81 ng/mL
Estradiol	36,46 pg/mL	-	30 – 400 pg/mL
Cortisol AM	-	3,45 ug/dL	6 – 23 ug/dL
Prolactin	-	16,06 ng/mL	1 – 23 ng/mL

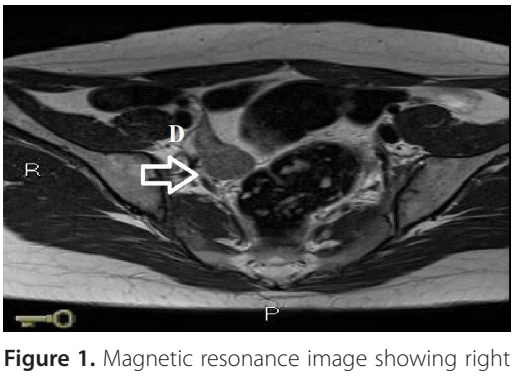

Figure 1. Magnetic resonance image showing right gonad

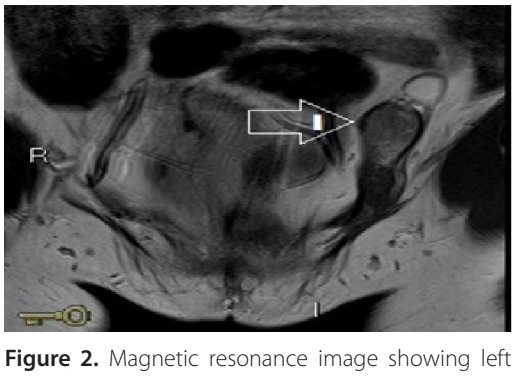

Figure 2. Magnetic resonance image showing left gonad

feeding six hours after surgery. Hospital discharge was indicated on the third post-operative day. After four days, follow-up was given for post-surgical evaluation and for the report of the biopsy that showed vascularized fibromuscular stroma with testicular tissue. He presented lumenless seminiferous tubules composed solely of Sertoli cells; the interstitium presented Leydig cell hyperplasia (Figure 4), without the presence of epididymis, vas deferens or malignancy. Also, there are small tubules lined by columnar epithelium that probably corresponded to paramesonephric remnants.

Clinical diagnosis

Clinical imaging and histological evaluations allowed to define the diagnosis of complete insensitivity syndrome to androgens or Morris syndrome.

Discussion

In complete AIS, there is no response to androgens, which prevents the development of any male characteristic and normal female external genital development occurs[12]. That is why they are educated as women and their identity and sexual inclination are not affected. In addition, its gonads are azoospermic testicles of variable localization, they are most often found in the inguinal ducts, with the presence or not of epididymis[6].

It is unlikely to be diagnosed during childhood. The detection of an inguinal hernia or signs of edema in the labia majora in preschool age should make this syndrome suspect[13]. The association among inguinal hernia in prepubertal girls has been known for more than 60 years. Doctors who treat inguinal hernias in childhood may have the first chance to diagnose it[6]. In these cases, the diagnosis is made by the pathologist after analyzing the surgical piece[13]. It is usual to diagnose it during puberty, for primary amenorrhea, and even later, when consulting an endocrinologist or gynecologist for sterility.

Puberty occurs without virilization and the risk of developing a testicular germ cell tumor[13,14] is 0,02 % in children under 30 years of age; above that age, the risk increases to 22 %[5,7]. Therefore, prophylactic gonadectomy has been recommended after puberty, when the feminization of the affected person has completed, since it is produced in part by testicular estrogen production and by the peripheral conversion of androgens to estrogens. Only in cases where the testicles are palpated in the groin

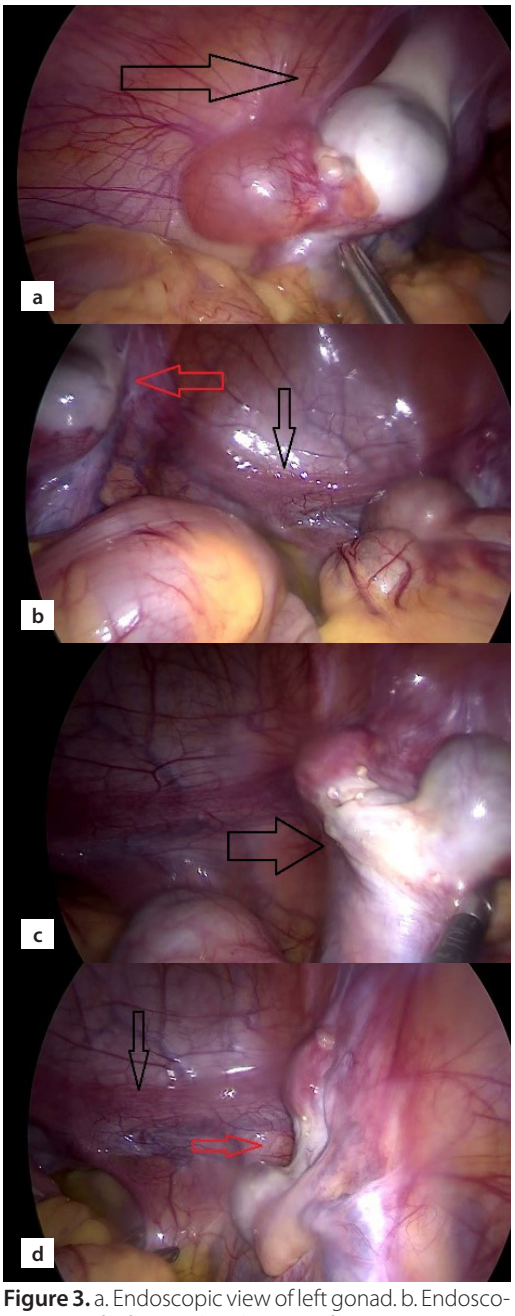

Figure 3. a. Endoscopic view of left gonad. b. Endoscopic view of left gonad and uterus of linear appearance. c. Endoscopic view of right gonad. d. Endoscopic view of right gonad and uterus of linear appearance

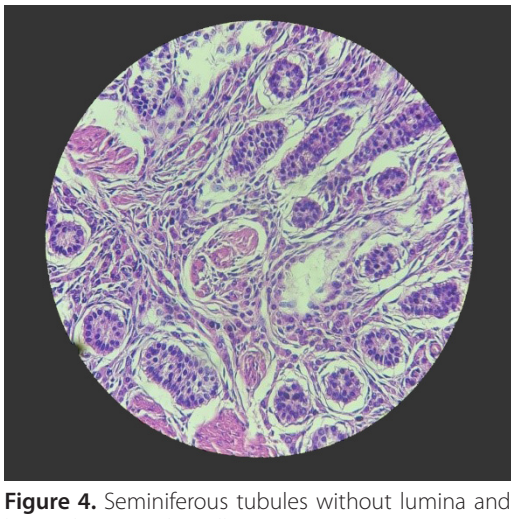

Figure 4. Seminiferous tubules without lumina and hyperplastic Leydig cells

area and cause discomfort or for aesthetic reasons, it will be necessary to remove them before puberty, with hormone replacement therapy to initiate puberty until the desired breast and genital development is reached[10].

Subsequently, estrogens should be started at sufficient doses to allow vaginal lubrication and bone gain[5,10]. For short vaginas, dilation techniques or surgery can be used to allow sexual intercourse and avoid dyspareunia. Periodic monitoring should be maintained in the areas of endocrinology, gynecology, psychology and urology[9,10,15]. Morris describes that after castration there are hot flashes, vaginal dryness and breast atrophy, so it was not advisable to perform this procedure[1].

Women who do not accept gonadectomy should maintain an annual follow-up, due to the risk of malignant degeneration, with pelvic ultrasound and abdomino-pelvic magnetic resonance imaging to evaluate the size and location of the gonads in addition to the verification of tumor markers such as alpha fetal protein, human chorionic gonadotropin beta fraction and lactate dehydrogena[16].

It has been described in women with normal breast development and high height, female hair and without baldness, who less frequently present some masculinization of external genitalia, such as clitoromegaly or fusion of the lips. In some of the revisions, it has even been possible to find remains of Müller's ducts (fallopian tubes) in up to a third of those affected[10].

Testosterone levels rise in the period of puberty at the same time that follicle stimulating hormone levels increase with decreased luteinizing hormone levels, which suggests that there is androgenic resistance in the pituitary hypothalamic level[17]. The increase in gonadotrophins, as a result of insensitivity, produces an increase in the production of testosterone and estradiol by Leydig cells[5,17]. Similarly, because aromatase activity (an enzyme that transforms testosterone into estradiol) is preserved, it increases the synthesis of estrogens, which are responsible for breast development during puberty in these individuals[5].

The recommended imaging studies to confirm the diagnosis of absence of Müllerian structures and location of the gonads are pelvic ultrasonography and magnetic resonance imaging[13,18]. The testicles are bilaterally retained in the abdomen between 50 and 70 % of cases; in the inguinal region, in 20 %; located one in the inguinal region and one in the abdomen, between 10 and 30 % of cases. Other rare locations occur in the labioscrotal region[8].

The differential diagnoses to be taken into account correspond to the deficiency of the enzyme 5α-reductase, the Mayer-Rokintansky-Küster-Hauser syndrome, the Kallmann syndrome, the pure gonadal dysgenesis 46 XX, 46 XY, the agenesis of Leydig cells due to abnormality in the receptor for luteinizing hormone and the enzymatic deficit that are expressed as sexual ambiguity at birth[18].

In the complete AIS, personal characteristics and external genitalia correspond to those of a woman. In general, these women do not differ from others with respect to patterns of marriage or other types of relationships, so it is not often that sex assignment dilemmas arise, although some of them may present conflicts of sexual identity[19]. Hence the importance of multidisciplinary care, and including the collaboration of a psychologist or psychiatrist in treatment considerations, to assess the patient's need to reinforce sexual identity; to the family, to prepare them for the sequences of diagnoses and treatments that await them during their lifetime[9].

Ethical aspects

For the publication of this case, the informed consent of the patient and the person in charge was obtained, both for the hospital care in which the physical examination was carried out and for the publication of this article with the commitment to maintain the privacy of the patient, as established in the Declaration of Helsinki.

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Original Article

SARS-CoV-2 breakthrough infection after artificial and hybrid immunization in healthcare workers

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Infección por SARS-CoV-2 posterior a la inmunización artificial e híbrida en el personal de salud

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The authors declare there are no conflicts of interest.

Abstract
Introduction. Current reports suggest that people with a history of SARS-CoV-2 infection and a complete vaccination status have greater protection against the symptomatic presentation of SARS-CoV-2. **Objective.** To compare the risk of becoming ill with COVID-19 between health personnel with a complete SARS-CoV-2 BNT162b2 vaccine status and a history of SARS-CoV-2 infection. **Methodology.** Historical cohort study in 1874 health workers of the New Civil Hospital of Guadalajara immunized with the BNT162b2 vaccine between January and March 2021. After six months of follow-up, the non-exposed group (without a history of infection) was 1397 and the group exposed (with a history of infection) of 477 subjects. **Results.** The incidence of SARS-CoV-2 infection in the cohort was 39 cases, the risk of infection after immunization was 0,021, the lowest risk was identified in the hybrid immunization group (0,015 and 0,243), with a relative risk of 0,43 (95 % CI 0,17 to 1,09). Hybrid immunization contributed to a population-attributable risk reduction of 0,003 (R0 0,024; Rp 0,020). Hospitalization occurred in 7,69 % of confirmed cases with SARS-CoV-2. The risk of hospitalization in hybrid immunization is 0,210 and 0,143 in the artificial immunization group (RR 1,4 95 % CI 0,13-16,11). **Outcome.** Hybrid immunization could contribute to reducing the risk of infection for future variants of SARS-CoV-2 by enhancing the immunity generated by the vaccine against COVID-19.

Keywords
COVID, vaccines, reinfection.

Resumen
Introducción. Reportes actuales sugieren que el antecedente de infección por SARS-CoV-2 y completar un esquema de vacunación otorga mayor protección contra la presentación sintomática de COVID-19. **Objetivo.** Comparar el riesgo de enfermar de COVID-19 entre el personal de salud con esquema completo de vacuna contra SARS-CoV-2 BNT162b2 y el antecedente de infección por SARS-CoV-2. **Metodología.** Estudio de cohorte histórica en 1874 trabajadores de la salud del Nuevo Hospital Civil de Guadalajara inmunizados con vacuna BNT162b2 entre enero y marzo de 2021. Después de seis meses de seguimiento, el grupo de no expuestos (sin antecedente de infección) fue de 1397 y el grupo expuesto (con antecedente de infección), de 477 sujetos. **Resultados.** La incidencia de infección por SARS-CoV-2 fue de 39 casos. El riesgo de infección en la cohorte posterior a la inmunización fue de 0,021. El grupo de inmunización híbrida presentó un riesgo menor de infección comparado con el grupo de inmunización artificial (0,015 y 0,243). La inmunización hibrida contribuyó a una reducción del riesgo atribuible a la población de 0,003 (R0 0,024; Rp 0,020). La hospitalización se presentó en el 7,69 % de los casos confirmados con SARS-CoV-2. El riesgo de hospitalización en inmunización hibrida es de 0,210 y de 0,143 en el grupo de inmunización artificial (RR 1,46 IC95 % 0,13-16,11). **Conclusión.** La inmunización híbrida podría contribuir a reducir el riesgo de infección por SARS-CoV-2, potenciando la inmunidad generada por la vacuna contra COVID-19.

Palabras clave
COVID-19, vacunas, reinfección.

Introduction

At the end of 2019 in Wuhan, China, an outbreak of respiratory infection was reported and a new virus, from the coronavirus type 2, was identified as the cause of severe acute respiratory syndrome (SARS-CoV-2)[1]. On January 13, 2020, the first case outside of China was identified in Thailand; subsequently, the virus rapidly spread globally and was declared a pandemic by the World Health Organization on March 11, 2020[2].

In Mexico, the first case of infection with the SARS-CoV-2 virus, which causes the Coronavirus disease 2019 (COVID-19, for its acronym from coronavirus disease) was registered on February 27 2020[3]. In Jalisco, thirteen days later, the first two cases were reported, one of them was a worker at the New Civil Hospital of Guadalajara, with the history of having traveled to an area with active community transmission[3].

The first COVID-19 vaccine, Pfizer-BioNTech (BNT162b2) was authorized by the United States Food and Drug Administration on December 11, 2020. Similarly, in Mexico, the Federal Committee for Protection against Sanitary Risks authorized the emergency use of this vaccine within the national health policy against SARS-CoV-2. The first phase of vaccination started on December 24, 2020 and the first dose was applied in the health personnel of the New Civil Hospital of Guadalajara on January 13, 2021, extending the coverage until August of the same year[4].

The effectiveness of the second dose of BNT162b2 against SARS-CoV-2[5] infection has been demonstrated. An overall incidence between 0,001 and 0,011 (per 100 persons at risk for developing the infection) has been described in post-vaccination healthcare personnel[6]. The occurrence of infection in health personnel with complete vaccination schedules, specifically with the biological BNT162b2, reported an incidence of infection of 4,4 per 1000 among women and 5,7 per 1000 among men (p = 0,57) and has been correlated with low neutralizing antibody titers during the peri-infection period[7].

Factors such as old age, immunosuppression, comorbidities or variants prevalent in population dynamics increase the risk of infection in six months after immunization[8,9]. As long as the pandemic continues, subsequent cases of infection will be a common scenario in the occupationally exposed population. This study compares the risk of COVID-19 over the first six months in relation to have completed the vaccination schedule and have a history of infection.

Methodology

A historical cohort of health personnel immunized with the SARS-CoV-2 BNT162b2 vaccine was conducted from January to February 2021 at the New Civil Hospital of Guadalajara Dr. Juan I, Menchaca. The population studied included all health personnel registered in the online vaccination platform to complete the scheme with the application of the second dose of BNT162b2 during February in 2021. From a universe of 2105 subjects, 1874 were included who completed their 2-dose schedule by March 1, 2021.

The subjects were naturally grouped, considering the group not exposed to personnel without the history of SARS-CoV-2 infection (n = 1397) and the exposed group composed of individuals with a history of SARS-CoV-2 infection (n = 477)

The history of SARS-CoV-2 infection was determined by the history of COVID-19 confirmed by a molecular or immunoassay test, diagnosed prior to the administration of the second dose and referred to in the vaccination registration form, epidemiology records or electronic file. Nursing and medical positions were classified as medical personnel. This study considered subjects with a complete vaccination schedule and no history of primary SARS-CoV-2 infection up to ten days after the application of the second dose were considered as the artificial immunity group. Subjects with a complete vaccination schedule and a history of primary SARS-CoV-2 infection in the 14 days prior to the application of the second dose were defined as the hybrid immunity group.

Active surveillance and sources of information

Active surveillance of cases of SARS-CoV-2 infection in health personnel was established. A person of any age who in the last ten days has presented at least one of the following signs and symptoms was used as an operational definition of a suspected case of respiratory infection: cough, dyspnea, fever or headache, accompanied by: arthralgias, rhinorrhea, anosmia, among others, which is established in the manual for epidemiological and laboratory surveillance of the viral respiratory disease in force of the General Directorate of Epidemiology of Mexico[10]. Personnel who had symptoms compatible with viral respiratory infection or with a history of recent exposure to an active case of SARS-CoV-2 by the employee medical service were clinically evaluated. Only those cases confirmed by molecular or antigenic tests with the start of symptoms from March 1 to August 31, 2021 were considered an incident case of SARS-CoV-2 infection.

The information obtained from each evaluation and the results of the diagnostic tests were recorded in the epidemiological study of suspected cases of viral respiratory disease[10]. Cases were traced in the data-

bases of the epidemiological survey and the electronic file. The variables that were considered were the following: age, sex, medical personnel, history of diabetes, heart diseases, lung diseases, asthma, smoking, date of application of first and second doses, dates of application of first and second dose, date of symptoms onset and diagnostic test.

The data were analyzed with the free software version R edition 4.0.5. The "dplyr" library was included for data manipulation, means and proportions were estimated for the sample description. The inferential analysis was performed using the Ep R library for the calculation of the risk and hypothesis test of the qualitative variables, performing Fisher's exact test for the history of lung disease due to the expected values, and for the rest of the qualitative variables, and chi-square test for the rest of qualitative variables, with determination of confidence intervals to evaluate the relative risk, and point probability estimates for proportions.

In the case of age, the Kolmogorov-Smirnov test was used as a hypothesis test to determine the difference in the distribution of the groups because they did not present a normal distribution. Because the data were collected during the institution's routine operating procedures of standardized epidemiological surveillance, this analysis of secondary data does not require informed consent and was conducted in a consistent manner with applicable federal law on the protection of personal data.

Results

As of March 1, 2021, the vaccination coverage with full schedule represented 89 %. The mean age of the 1874 health workers included in the study was 40,23 years (SD 10,75), with a minimum age of 19 years and a maximum age of 69 years, showing a bimodal distribution with a predominance of 29 and 48 years, where 36,98 % (693) of the registered personnel were male and 29,08 % corresponded to non-medical personnel

74,55 % (1397) of the subjects were classified in the artificial immunization group (30,1 % were non-medical personnel), while 477 (25,45 %) had a history of natural infection with SARS-CoV-2, so they were classified as the hybrid immunization group. A significantly higher proportion for the male gender was presented by the artificial immunization group (38,4 % compared to 32,9 %, p = 0,033); similarly, age showed a significant difference between the distribution of both groups (KS test $p = 3 \times 10^{-3}$) (Table 1). The evaluation of homogeneity of the articial immunity groups compared to the hybrid immunity group showed a similar distribution for occupation (69,9 %; 74,0 %), history of diabetes *mellitus* (6,3 %; 5,03 %), heart disease (2,36 %; 2,1 %) or pulmonary (0,04 %; 0,84 %), asthma (5,73 %; 7,97 %) or smoking (12,5 %; 10,5 %), without any significant difference for both groups.

The first case of confirmed SARS-CoV-2 infection occurred 99 days after administration of the second dose of the BNT162b2 vaccine, with an average case presentation time of 158,9 days. In the hybrid immunization group, the mean to present infection was 149,20 days, while in the artificial immunization group the mean was 160,32 days (difference -11,12, 95 % CI -50,96 to 28,71), with no significant difference between the two groups (Figure 1).

During follow-up, there was an incidence of 39 cases of SARS-CoV-2 with a risk of infection of 0,021 after immunization, a lower risk was identified for the hybrid immunization group (0,015 compared to

Table 1. Evaluation of the homogeneity of the groups

	Hibrid inmunity n = 477 (%)	Artificial inmunity n = 1397 (%)	*p*
Age†	38,6 (10,50)	40,78 (10,79)	0,003*
Masculine	157 (32,9)	536 (38,4)	0,033*
Medical personnelᵚ	353 (74,00)	976 (69,9)	0,086
Diabetes	24 (5,03)	88 (6,30)	0,313
Heart disease	10 (2,10)	33 (2,36)	0,738
Lung disease	4 (0,839)	5 (0,0358)	0,244Ω
Asthma	38 (7,97)	80 (5,73)	0,082
Smoking	50 (10,5)	174 (12,5)	0,251

P value estimated by chi-square test.
*† The results are shown as mean and standard deviation, the p statistic was estimated using the Kolmogorov-Smirnov two-tailed test, as it did not present normal distribution. * Value with statistically significant difference. ᵚ Medical and nursing posts were considered medical personnel. Ω Using Fisher's-exact test*

0,243), with a relative risk of 0,43 (95 % CI 0,17 - 1,09). Hybrid immunization contributed to a population-attributable risk reduction of 0,003 (R0 0,024 compared to Rp 0,020). 7,69 % of confirmed cases with SARS-CoV2 received hospital care. The risk of hospitalization for the hybrid immunization group was 0,210 and 0,143 for the artificial immunization group (RR 1,46 95 % CI 0,13 - 16,11), with no significant difference in the risk of confirmation by SARS - CoV-2 infection or in the evolution of the disease requiring hospitalization. Deaths were not occurred during the follow-up of the cohort.

Discussion

This study reviewed the information recorded in the electronic medical record, the epidemiological background questionnaire and the contact tracing that was installed during the follow-up of health personnel during the six months following the administration of the second dose of the BNT162b2 vaccine in response to an infection prevention and control protocol.

The analysis of the data found a lower proportion of confirmed COVID-19 cases in the hybrid immunization group with a risk reduction of more than 50 %. In the non-medical staff group, the attributable risk in the population and the impact on case reduction was high. Considering this population with a lower risk of exposure and a prevalence of a history of lower infection than estimated in the group of medical personnel, the impact would be related to the lower occupational exposurel[11]. Besides, the implementation of strategies by health personnel with respect to other effective interventions to reduce the risk of infection, such as adherence to personal protection measures, correct use of a mask, social distancing and isolation of sick personnel, would also explain this difference compared to non-medical personnel[12,13]. Therefore, variable compliance with protective measures in the hospital environment and higher immunization coverage among health personnel would explain the lower incidence of SARS - CoV-2 when general population is compared[14].

The average time of infection in health personnel with a complete vaccination schedule in both groups was similar and there were no cases in vaccinated personnel in both groups during the first three months of follow-up. It is possible that the decrease in cases could be attributable to immunization, as observed by Chodick *et al.*, where one dose of the vaccine was associated with a nearly reduction of 50 % in the risk of SARS - CoV-2 infections in the 25 days following application[15] and even as part of the additional protection against reinfection from one dose in people with a history of COVID-19 subsequent to the vaccine[16].

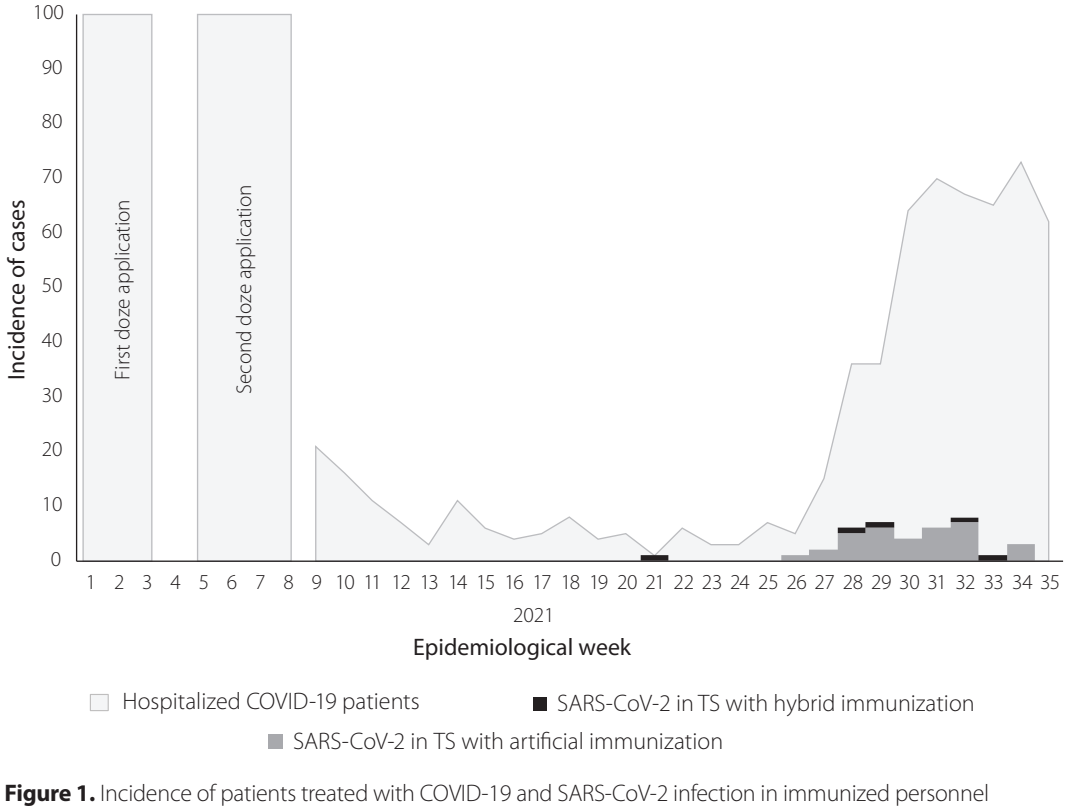

Figure 1. Incidence of patients treated with COVID-19 and SARS-CoV-2 infection in immunized personnel

Estimating the response to vaccination and protection over time is complex because of its multicausal nature. The protection generated by natural immunity may differ from the immunity generated by the vaccine due to several factors, such as the apparent increase in the immune response due to antigenic exposure with additional boosters in the population with a history of primary infection and a probable protection against variants of concern of SARS-CoV-2[17] due to the induction of higher levels of IgG antibodies and neutralizing antibodies[18]. These neutralizing antibody titers are not available in the Latin American hospital setting/context. Although the use of anti-S IgG titers could be considered as a more accessible method to assess long-term protection, this insufficient immunogenicity of the vaccine may not really be correlated at the time of diagnosis and the development of symptoms with low levels of these neutralizing antibodies and their measurement and therefore not be a good indicator of the progression of the disease or its ability to spread[19]. In this sense, the interaction of multiple epitopes after natural SARS-CoV-2 infection and the particular interaction of vaccines in a single epitope is recognized, with the result of permanent immune protection, due to the diversity of these interactions of long-lived memory T cell populations in hybrid immunity[20].

The results reinforce the possible increase in protection in health personnel with a history of SARS-CoV-2 infection, probably due to a greater immune response to vaccination, but it is necessary to evaluate the true impact on the general population[21,22]. Also, the results are consistent with what was published by Hall *et al.*, where greater short-term protection against SARS-CoV-2 infection in health workers was associated with a complete BNT162B2 scheme at the follow-up at six months and protection preserved up to one year after vaccination, in the group with a history of primary infection[23]. In this case, hybrid immunization contributed to a reduction in risk attributable to the population of 0,003 (R0 0,024; Rp 0,020), this in relation to a memory protection mediated by the immune system and T cells, although at the time the study was carried out the omicron variant was not in circulation[16].

A significant difference was found in the sex of the cases related to the evaluation of the groups. Similar findings are commented by other publications and suggest differences in innate and adaptive immune responses, where there is a difference in susceptibility to infections, variations in behavior patterns, perception and response to pathogens or vaccines, in the frequency and severity of adverse events, but without differences in efficacy or immunogenicity[24]. This difference could be considered due to a greater representation of the female sex in health personnel and their distribution within the health population, which establishes an unequal representation within the study to properly assess these relevant differences between women and men[25].

During cohort follow-up in the first six months' post-vaccination, deaths were not reported and both groups had very low risks of hospitalization. The BNT162b2 vaccine is an anti-COVID-19 mRNA vaccine. Vaccination with biological anti-COVID-19 mRNA has been shown to decrease the probability of hospitalization, complications or death and are consistent with reducing the risk of infection compared to the absence of vaccination[26].

Previous studies have documented successful rates for the prevention of symptomatic SARS-CoV-2 infection and protection against general hospitalization with complete vaccination schedules with the BNT162b2 mRNA vaccine with a 90 % effectiveness during the protection period in previously healthy individuals[5,27]. The prevention of COVID-19 mortality in health personnel is associated with evidence-based interventions, such as ensuring vaccination coverage, infection monitoring and control programs, procuring hospital capacity and hospitalizations, and specific protection strategies in vulnerable personnel due to age or comorbidities[28].

In the characterization of the cohort, a low prevalence of chronic diseases was described; this is relevant because chronic-degenerative diseases, such as diabetes, high blood pressure or cardiovascular or pulmonary diseases are recognized as important risk factors for hospital mortality in the age groups of 30 to 50 years when combined with obesity and smoking[29]. Participants had an average age of 40 years. The risk of developing a serious infection in men after 40 years old is higher compared to the 0- to 39-year-old group. In the 40-59 age range, increase by approximately 4 % of the overall total, while in the over-60 category the total number of deaths amounts to about 92 % of all deaths recorded in both men and women[30].

Within the limitations of the study, we identified that a large part of the follow-up took place in the period between the second and third waves of COVID-19 cases, which could interfere with the incidence of cases in health personnel. The present study

has naturally assigned groups, so there is no control of the intervening variables. Also, the tracing of incident cases of SARS-CoV-2 was carried out historically through routine passive surveillance, which limits the detection of confirmed cases, mainly asymptomatic cases. Artificial immunization alone has proven to be effective against the disease, so it is suggested to evaluate the impact that this protection could generate in the general population.

It could not be established that the observed reduction in cases was due to the history of infection with a complete immunization schedule due to the lower proportion of cases presented and it will be important to continue long-term follow-up to validate whether this reduction is attributable to hybrid immunization and whether it will provide protection against new variants[31]. It is necessary that the evaluation of the efficacy of vaccines considers a wide range of confounding factors in systematic sampling and those generated in epidemiological surveillance to improve the interpretation of the results[8], and that subsequent studies establish other aspects of the social determinants of the individual, the time that elapsed since immunization, the number of doses applied and the measurement of neutralizing antibodies[32].

Conclusions

The risk of SARS-CoV-2 infection is low in the first six months after completing a vaccination schedule regardless of COVID-19 history. Hybrid immunization could contribute to reducing the risk of SARS-CoV-2 infection in health personnel, enhancing the immunity generated by immunization against COVID-19. The history of primary infection by SARS-CoV-2 was proportionally more present in male health personnel and with an average age of 40 years.

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Original article

Relationship between dental caries and body mass index in children

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Abstract
Introduction. Nutrition and oral health are topics of interest in public health, due to their high impact on the well-being and development of people. There is a high prevalence and incidence of caries and malnutrition in the first years of life. **Objective.** To determine the relationship between the dental caries index and body mass index in permanent and temporary dentition in children aged 5 to 11 years in the San Miguel Tepezontes and Panchimalco health units in 2019. **Methodology.** Quantitative research with a sample of 265 children aged 5 to 11 years . The body mass index and the caries index were evaluated. A descriptive and inferential statistical analysis was performed, using the Spearman correlation statistical test. **Results.** Findings show that the caries index is 2,11 in permanent dentition with a prevalence of 70,5 %, and the caries index is 7,02 in temporary dentition with a prevalence of 94,98 %. Spearman's correlation coefficient between body mass index and caries index in permanent dentition was 0,226, indicating a low positive correlation, and body mass index and caries index in primary dentition was -0,158, indicating a very low negative correlation. **Conclusion.** There is a relationship between caries index in both dentitions and body mass index.

Keywords
Dental caries, body mass index, El Salvador.

Resumen
Introducción. La nutrición y salud bucal son temas de interés en salud pública por su alto impacto en el bienestar y desarrollo de las personas. Existe una alta prevalencia e incidencia de caries y malnutrición en los primeros años de vida. **Objetivo.** Determinar la relación entre el índice de caries en dentición primaria y permanente e índice de masa corporal en niños de 5 a 11 años en las unidades de salud de San Miguel Tepezontes y Panchimalco en el año 2019. **Metodología.** Investigación cuantitativa con una muestra de 265 niños de 5 a 11 años. Se evaluó el índice de masa corporal y el índice de caries; se hizo un análisis estadístico descriptivo e inferencial, realizando la prueba estadística de correlación de Spearman. **Resultados.** Se encontró que el índice de caries es de 2,11 en dentición permanente con una prevalencia de 70,5 % y el índice de caries de 7,02 en dentición primaria con una prevalencia de un 94,98 %. El coeficiente de correlación de Spearman entre índice de masa corporal e índice de caries en dentición permanente fue de 0,226, que indica una correlación positiva baja y el índice de masa corporal e índice de caries en dentición primaria fue -0,158, que indica una correlación negativa muy baja. **Conclusión.** Existe relación entre el índice de caries en ambas denticiones y el índice de masa corporal.

Palabras clave
Caries dental, índice de masa corporal, El Salvador.

Introduction

Dental caries is an infectious-contagious disease in which modulating factors intervene that allow its presence in the oral cavity[1,2], affecting children and adults[3,4]. Around 520 million children suffer from dental caries in primary dentition and 2 billion people suffer from dental caries in permanent dentition worldwide[5]. Dental caries is a disease of great importance for the stomatognathic system since its presence affects its proper functioning, being essential for optimal development and biopsychosocial well-being in humans[5-7].

The type of nutrition or food that is acquired in the first years of life is essential for adequate oral health. A diet high in sugars can affect since carbohydrates are fermented by bacteria, producing acids that degrade the hard tissues of the tooth and produce dental caries[8,9]. It is important to consider that malnutrition can be a risk factor for causing different health problems in children, which can be cognitive, mental and neurological, in addition to chronic non-communicable diseases[10,11].

It has been shown that inadequate nutrition, accompanied by bad habits in oral hygiene, is an adjuvant factor in the appearance of dental caries, and there is a strong relationship between dental health and food. Besides, it is important to consider that malnutrition carries a greater risk for poor development of dental structures, becoming more susceptible to dental caries. Likewise, problems in oral health can generate orofacial pain, causing people not to feed properly due to discomfort at the time of chewing, affecting their nutritional status. It is necessary to address these two components together and not in isolation since one influences the other, affecting people's health[12-14].

Dental caries is a public health problem in Latin American countries. In 2008, in Paraguay, 98 % of the population suffered from morbidities affecting the oral cavity and the prevalence and incidence rates of caries were high, despite improvements in the scope of health care[15].

In El Salvador, the prevalence of dental caries for primary dentition is 70,5 % in children aged five to six years and 81,3 % in children aged seven to eight years. In the permanent dentition, the prevalence of caries in children aged seven to eight years is 16,6 %; it is 47,3 % in 12-year-olds and it is 65,1 % in 15-year-olds. The prevalence of dental caries in both dentitions is 70,8 %[16].

According to the World Health Organization (WHO), dental caries and malnutrition are public health issues since they affect a large number of people at different stages of life. In recent years, overweight and obesity have reached epidemic figures worldwide[3,17-19], so malnutrition has been considered a risk factor for dental caries[20]. Data from the 2014 National Health Survey indicate a reduction in chronic malnutrition of 51,7 %; however, obesity has increased by 50 % in the last five years[21].

Because dental caries and nutritional status are related and have a high impact on health in children, it is necessary to characterize the nutritional and dental status of populations for the creation of preventive measures for diseases that harm the general health of children. Research has associated dental caries and body mass index (BMI) in children. Therefore, it was considered to carry out this study, which objective is to determine the relationship between the dental caries index in primary and permanent dentition and BMI in children from 5 to 11 years at the health units of San Miguel Tepezontes and Panchimalco in 2019.

Methodology

Quantitative, analytical, transversal research. The research hypothesis for this study was that there is a relationship between dental caries and BMI; the null hypothesis states that there is no relationship between dental caries and BMI.

The study population was composed of children aged 5 to 11 years who attended the health units of Panchimalco and San Miguel Tepezontes in 2019. Data were extracted from the dental clinical records of the selected children. The population of both cities is 5381 children aged 5 to 11 years. The sample for this research was 396, calculated by Epi Info 7 with a confidence level of 95 % and a margin of error of 0,05. The sample was proportionally divided to the population of each city: 84 % for Panchimalco and the rest for San Miguel Tepezontes. However, all the records of the children who attended the dental consultation in both health units in 2019 were reviewed; even so, the desired sample was not reached, managing to obtain at the end only 265 files that met the study variables.

Among the inclusion criteria, it was taken into account that they were children aged 5 to 11 years who attended their dental control in 2019; that the patients resided in the coverage area of Panchimalco and San Miguel Tepezontes health units; that the variables of weight, height and complete odontogram were present in the file. The information was reviewed by the researchers of the study.

The dental charts of the clinical records were checked and the odontogram was observed, where the cariogenic index of each patient was cataloged according to the DMF-T and dmf-t indexes. Also, other general data were taken from the file, such as the name of the health unit, sex, age and nutritional status of the patient. All this information was placed on the observation sheet.

In El Salvador, a BMI graph is implemented and used in children over five years of age and adolescents to obtain nutritional status. When obtaining the BMI, through the

division of the real weight in kilograms by the size in meters, this data must be located in this graph on the Y axis and intersect with age on the X axis, obtaining a nutritional diagnosis. Depending on the results obtained, it will be classified into obesity, overweight, normal, malnutrition and severe malnutrition.

The DMF-T dental caries index is obtained by performing the sum of decayed, missing and filled teeth of the permanent dentition. The dmf-t index is obtained from the sum of decayed teeth, extracted by caries and filled in the primary dentition.

The data collected from the odontogram and the observation sheet were tabulated in the Windows Excel, creating a database coded with each of the variables. A complete statistical analysis was performed, in which descriptive statistics were used since the means of the dental caries indexes and BMI were compared. Inferential statistics were used for the association of variables and the Spearman correlation statistical test was performed since the distribution of the data was not normal. The analyses were performed in the Statistical Package for the Social Sciences (SPSS), version 23.

The research was evaluated by the Ethics Committee of the Evangelical University of El Salvador for its authorization. Likewise, letters of authorization were obtained from the directors of both health units to carry out the research and have access to the clinical records.

Results

265 children aged 5 to 11 years from the Panchimalco and San Miguel Tepezontes health units in El Salvador were observed. 51,3 % of the population was female. In terms of geographical location, 70,9 % of the children were from the city of Panchimalco, in the department of San Salvador; the rest, from the city of San Miguel Tepezontes, La Paz.

The DMF-T index in children aged 5 to 11 years in the cities of Panchimalco and San Miguel Tepezontes is 2,11, considered as a low cariogenic index in the permanent dentition. However, the prevalence of the disease in the permanent dentition in children is 70,5 %. The dmf-t index is 7,0, considered as a very high index of caries in the primary dentition. The prevalence of caries in this type of dentition is 94,9 % (Table 1).

The ceo-d index for San Miguel Tepezontes was 5,45 and it was 7,62 for Panchimalco. The prevalence of caries in San Miguel Tepezontes in the permanent dentition was 62,07 % and 91,55 % was the primary dentition. For the Panchimalco health unit, caries in permanent dentition has a prevalence of 75,51 % and 96,27 % in primary dentition (Table 2).

When comparing the classification according to the BMI of boys and girls aged 5 to 11 years of the cities of Panchimalco and San Miguel Tepezontes, it is observed that Panchimalco has the largest number of children with normal weight, registering 74 % of the total population of both cities, being evident the difference with San Miguel Tepezontes. However, in the case of overweight and obesity it is also the city with the highest number, registering 77 % of overweight children and 56 % with obesity, compared the group of San Miguel Tepezontes (Figure 1).

The calculated value of $r_s = 0{,}226$ is less than the critical Spearman value, at a significance level of $\alpha = 0{,}05$, so the null hypothesis is rejected. Therefore, it

Table 1. Index of dental caries of children aged 5 to 11 years

Caries index	Mean	Minimum	Maximum	Standard deviation	Mode	25 %	Median	75 %	Prevalence
DMF-T	2,1	0,0	12	2,0	0	0,0	2,0	4,0	70,5 %
dmf-t	7,0	0,0	17	3,5	8	4,0	7,0	9,0	94,9 %

Table 2. Index of dental caries of children aged 5 to 11 years at the health units of Panchimalco and San Miguel Tepeontes in 2019

Caries index	Mean	Minimum	Maximum	Standard deviation	Mode	25 %	Median	75 %	Prevalence
DMF-T Panchimalco	2,14	0,0	6,0	1,74	0,0	1,0	2,0	4,0	75,51 %
DMF-T San Miguel Tepezontes	2,06	0,0	12,0	2,56	0,0	0,0	1,0	3,0	62,07 %
dmf-t Panchimalco	7,62	0,0	17,0	3,43	8,0	6,0	8,0	10,0	96,27 %
dmf-t San Miguel Tepezontes	5,45	0,0	15,0	3,36	4,0	3,0	5,0	8,0	91,55 %

is concluded that the two variables are considerably correlated with a low positive correlation; that is, as BMI increases, so does the rate of caries in permanent dentition.

Spearman's correlation between BMI and children's dmf-t index shows a value of $r_s = -0,158$, which is lower than Spearman's critical value. The p-value obtained was 0,01, so the null hypothesis is rejected. The two variables are considerably correlated with a very low negative correlation between them. This indicates that as BMI decreases, the index of dental caries increases.

Discussion

This study shows that there is a relationship between dental caries in both dentitions and BMI. The ratio of BMI and DMF-T in the study population was 0,226 with a p-value of 0,005. This indicates a low positive correlation similar to a study conducted in an educational center in Peru in 2017, which confirmed the relationship between BMI and the dental caries index since the group with normal BMI, the dmf-t index was low in contrast to the groups with malnutrition, overweight and obesity, in which the dmf-t index was moderate to high[22].

Likewise, there is a correlation between BMI and dmf-t in children in the cities of Panchimalco and San Miguel Tepezontes, since $r_s = -0,158$ indicates that there is a very low negative correlation. Some studies mention that there is a relationship; however, further research is needed on this public health issue[23]. Nevertheless, authors such as Shen, indicate that underweight children seem to be more susceptible to dental caries since the formation of dental structures is more deficient, making them more susceptible[24].

According to the WHO, the prevalence of caries is 60 to 90 % in the school population[25]. In the present study it was determined that the prevalence of caries for permanent dentition is 70,5 % and 94,9 % in the primary dentition of children in the cities of Panchimalco and San Miguel Tepezontes, which is consistent with the WHO prevalence estimate. Also, the prevalences found are similar to studies carried out in Latin American countries, where there are high prevalences of caries[26]. In children, this can be determined by modulating factors such as parental education, the economy of cities and the influence of health services[1,2].

According to the Oral Health Diagnosis of El Salvador, the prevalence of dental caries for primary dentition is 70,5 % in children aged five to six years and it is 81,3 % in children aged seven to eight years[16]. This differs with the results of the population studied for the present research, since the prevalence in primary dentition in children aged five to six years in the population of Panchimalco and San Miguel Tepezontes is 93 %; and those aged seven to eight years is 98,9 %, these being higher than those described in the diagnosis[16]. Similarly, permanent dentition has a prevalence of caries of 16,6 % in children aged seven to eight years according to the diagnosis; in children aged 12 years it is 47,3 %, which differs with the data found in this research, since children aged seven to eight years have a prevalence of caries in permanent dentition of 87,5 % and 80 % in children of 11 years old, being the prevalences found in both dentitions higher than those shown in said report[16].

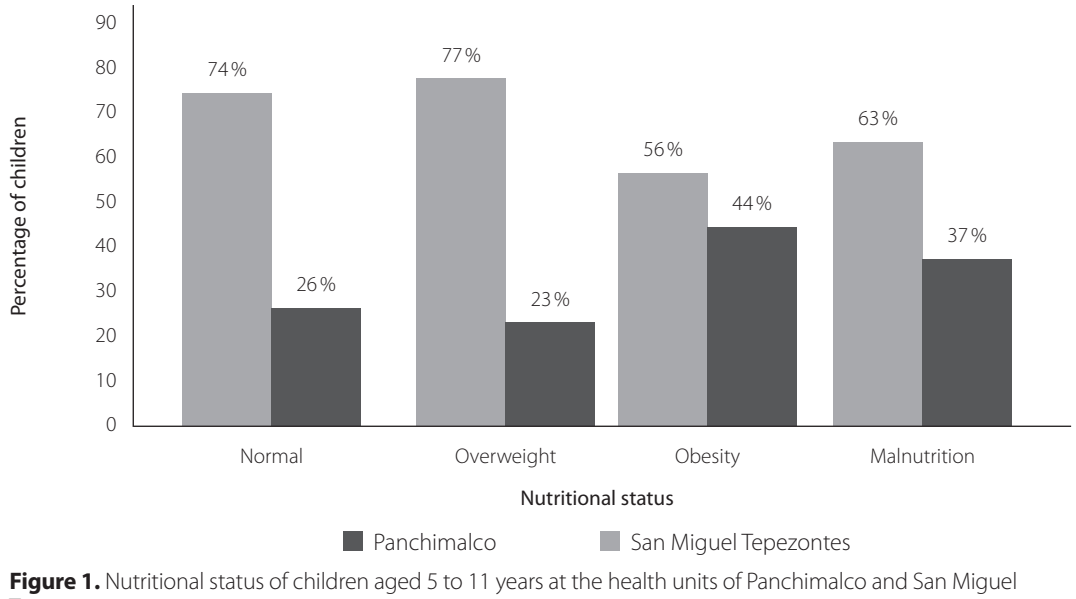

Figure 1. Nutritional status of children aged 5 to 11 years at the health units of Panchimalco and San Miguel Tepeontes in 2019

This study shows that the DMF-T index is 2,1, cataloged according to the WHO as a low cariogenic index in the permanent dentition, which agrees with studies of countries such as Chile, where the cariogenic index is 1,9, classifying it as a low index of caries. However, it differs with other studies such as one conducted in Peru, which has a DMF-T index of 5,8, being a high index of caries[26] with respect to the dmf-t index, which is seven. This is a very high cariogenic index for the primary dentition, becoming a risk factor for permanent teeth, which begin their eruption at six years of age. That is why the presence of dental caries at an early age can be influenced.

According to this study, the female sex is the one with the highest percentage of overweight and malnutrition. According to the ages, there is an increase in overweight from the age of seven, which is consistent with a study in Spain, in which it was found that overweight in schoolchildren is more frequent in the female sex and that this health problem increases at an older age[27]. This can be influenced from an early age, since the female sex has a higher percentage of body fat compared to men, in addition to a poor diet with high sugar and fat content, which may be contributing to the increase in overweight.

Also, according to the study carried out, there is an increase in malnutrition from the age of six years compared to the age of five years. There is a 6 % of severe malnutrition, which indicates that the necessary actions are not carried out by the multidisciplinary team of the different health units, who focus attention especially on the first five years of life to prevent malnutrition, neglecting the actions in the following years, among which are the home visit, preventive consultation in the different areas, surveillance of food and nutritional security, education on habits and oral health care in the family, school and community, among others. This allows for an increase in malnutrition and the risk of it becoming severe malnutrition.

74 % of the children of Panchimalco and 26 % of those of San Miguel Tepezontes, have a normal weight. However, these figures could change according to what is observed in the clinical record, since many children are barely within the limits. If they are not cared for in a timely and comprehensive manner, taking into account their specific needs, they could go to the extreme of overweight or malnutrition.

It is very important to consider that although San Miguel Tepezontes presented the lower percentages in overweight, obesity and malnutrition, they have a lower population than Panchimalco. Therefore, they are worrying and very significant data for the city of San Miguel Tepezontes, taking into account that it belongs to the department of La Paz, which is considered one of the departments at the national level with the highest poverty, registering 26,2 % of households in a situation of food insecurity, remaining in the category of severe, according to national results[21]. Thus, the results obtained in the study become relevant, since it contributes to the risk of incidence and prevalence of malnutrition and dental caries.

Within the limitations of the study, it was not possible to reach the established sample, since most of the records did not have the complete study variables, due to the poor registration of data in the clinical records, lack of multidisciplinary follow-up and the patients left without receiving care.

According to the results of the study, a balanced and nutritious diet, low in sugar and carbohydrates, should be encouraged in children through their families to prevent the incidence and prevalence of malnutrition and caries[8,9]. Likewise, oral education actions must be carried out for a correct brushing technique in an integral way and in different scenarios such as school, home, health units promoting in turn the importance of preventive and timely visits to the dentist and different health professionals for an early diagnosis, contributing to preserve and improve health. Moreover, it is necessary to consider that there are modulating factors for the appearance of caries[1] and some of them can be addressed through oral health education.

It is necessary to strengthen oral health education programs and strategies in pregnant women, since poor oral health can lead to premature births and babies with low birth weight, which also increases the risk of the development of early dental caries in children[28,29]. Also, it is important that child health programs continue to be strengthened to provide follow-up and timely care. The approach to health must be carried out holistically[30] in the care centers since this will allow a comprehensive approach to the general well-being of the person.

Conclusions

There is a relationship between caries in both dentitions and BMI in children aged 5 to 11 years, affecting the female sex more and increasing at an older age. The prevalence of caries in primary and permanent teething in children in both municipalities is currently high.

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Narrative review

Factors that hinder the diagnosis of postural orthostatic tachycardia syndrome

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Abstract
Dysautonomias are the result of a malfunction of the autonomic nervous system, among which is the postural orthostatic tachycardia syndrome, a variable and complex health problem that has a considerable prevalence, mainly in adolescents and women. It produces a wide variety of signs and symptoms that are similar to those of other pathologies, which, added to the lack of specific diagnostic tests, often delays diagnosis. Despite the existence of standardized criteria to determine the presence of the syndrome, there is still a gap in knowledge about it. This hinders the approach to the condition and, consequently, its timely treatment. Understanding more about this syndrome and the factors that hinder its early diagnosis would improve patient care and quality of life.

Keywords
Postural orthostatic tachycardia syndrome, dysautonomia, diagnosis.

Resumen
Las disautonomías son el resultado de un mal funcionamiento del sistema nervioso autónomo, entre las cuales se encuentra el síndrome de taquicardia ortostática postural, un problema de salud variable y complejo que tiene una prevalencia considerable, principalmente en adolescentes y mujeres. Este produce una amplia variedad de signos y síntomas que son similares a los de otras patologías, lo que sumado a la falta de pruebas diagnósticas específicas, muchas veces retrasa el diagnóstico. A pesar de la existencia de criterios estandarizados para determinar la presencia del síndrome, existe aún una brecha en el conocimiento acerca del mismo. Esto dificulta el abordaje del padecimiento y por consiguiente, su tratamiento oportuno. Conocer más sobre este síndrome y los factores que dificultan su diagnóstico temprano permitiría mejorar la atención de los pacientes y su calidad de vida.

Palabras clave
Síndrome de taquicardia postural ortostática, disautonomía, diagnóstico.

Introduction

The autonomic nervous system (ANS) has a cardiovascular domain mediated by its sympathetic and parasympathetic divisions that is responsible for regulating heart rate, blood pressure and homeostasis within the body; alterations in the functioning of one of the branches of this system trigger dysautonomias[1]. These conditions have adquired relevance in recent years. In addition to the most prevalent, which is high blood pressure, there are others less known but of equal importance, including postural orthostatic tachycardia syndrome (POTS)[1]. Experts have estimated that from 500 000 to 3 000 000 Americans could be affected[2].

OPEN ACCESS

Factores que dificultan el diagnóstico del síndrome de taquicardia ortostática postural

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POTS is a variable and complex health problem, present in adolescents and adults[2] whose symptoms are characterized by palpitations, stunning, generalized weakness, tremors, blurred vision, fatigue and tachycardia, when standing or sitting[3].

An early diagnosis is important to be able to provide adequate management, otherwise the patient's quality of life tends to decrease due to physical and mental deterioration[4]. Although there is a consensus to clinically define POTS, misdiagnoses are common, due to the similarity of symptoms to other conditions. This causes patients to undergo extensive and unnecessary investigations, receiving fragmented care from multiple specialists[5,6].

Learning more about POTS can facilitate timely diagnosis and treatment[7]. For this reason, it aims at describing factors that hinder the early assessment of this syndrome through a bibliographic review.

Discussion

POTS and the tests used in its diagnosis

The ANS, made up of the sympathetic and parasympathetic nervous system, is responsible for regulating the functioning of the internal environment, heart rate, blood pressure, breathing, among others. Dysautonomias are generated by alterations of ANS with POTS being one of the most common[8].

POTS is mainly manifested by orthostatic intolerance characterized by an excessive increase in heart rate after sitting or standing and that occurs most often in young people, mainly affecting women. This is one of the disorders observed most regularly in clinics of autonomic dysfunction[9]. It can occur primarily or secondarily to systemic diseases such as paraneoplastic syndrome or diabetes. It is often underdiagnosed, which can eventually compromise the quality of life of those who suffer from POTS[10].

Federowski states that early clinical observations showed that POTS frequently occurs after an acute, typically viral, infection. However, experts believe that it could be caused by an unidentified implicit factor or be a heterogeneous condition with multiple etiologies[11]. However, Spahic et al. state that the etiology of POTS is still unknown nowadays[12].

The syndrome is still considered idiopathic with a large number of explanations proposed[13]. Because of this, POTS is often described as a clinical syndrome consisting of multiple heterogeneous disorders often classified into different subtypes of POTS[14]. The complexity increases because a single patient with POTS can have multiple coexisting diagnoses, the most frequent being autoimmune disorders. There is currently no clear interpretation of how these disorders relate to each other and how each contributes to the symptoms of a single patient[15].

As has been mentioned, POTS is an autonomic disorder in which a great diversity of signs and symptoms is experienced, including the characteristic presence, according to studies carried out by Kichloo *et al*., 99 % of stunning, tachycardia in 97 % of tachycardia, 94 % of presyncope, 88 % of dyspnea and 87 % of palpitations[16]. Similarly, Bryarly *et al.* mention that a characteristic that seems to be universally present in all POTS is cardiovascular deconditioning, a specific biological process characterized by atrophy and hypovolemia[17].

Regarding its epidemiology, Dahan *et al.* estimate that the prevalence was 170:100 000 in 2016[18]. In 2020, Tahirovic adds that the individuals who predominantly present it are the age groups of adolescents and women from 15 to 50 years old[19].

When evaluating a patient with suspected dysautonomia, laboratory tests are usually performed to establish the diagnosis. Nowadays, there is no laboratory test that indicates its presence or absence in an individual in the case of this syndrome so far. However, the results of these can help to discard other conditions[20].

The tests to be taken into account are usually as follow: metabolic profile to rule out renal failure, diabetes or metabolic disorders, complete blood count to discard any type of infection or anemia, thyroid stimulating hormone or thyrotropin, thyroxine, cortisol and adrenocorticotropic hormone to discard thyroid and adrenal dysfunction, serum albumin level to discard malnutrition, among others. From the results, the options for a differential diagnosis are reduced in large numbers and the possibility that the definitive diagnosis of the patient is POTS increases[20].

Similarly, it is necessary to perform imaging tests and functional tests, although there is no established examination for its detection, but they are executed to carry out a differential diagnosis. Electrocardiograms and echocardiograms are commonly performed[20,21].

Nevertheless, when there is suspicion of POTS in an individual, the best examination performed is the head-up tilt table test, which allows to observe hemodynamic changes during orthostatic provocation.

Zhao *et al.* describe that this test consists of the patient having to remain in a supine position for ten minutes by measuring his basal blood pressure and heart rate. Subsequently, the patient must remain standing to take the measurements again at intervals of one, three, five and ten minutes[21].

Influence of symptomatic variability and mimicry with other diseases on the diagnostic delay of POTS

The POTS is regularly identified by a detailed medical history, blood tests and the tilting table test, which serve to ensure that the patient's symptoms are not the result of other medical conditions. This process is rarely simple[22].

The most common clinical manifestations of an individual with POTS have been mentioned above. However, patients typically show much more complex associated symptoms that cannot be explained physiologically such as orthostatic intolerance. This is interpreted as symptomatic variability[22].

Although some individuals usually do not meet all the standard criteria, they still suffer POTS since it is a heterogeneous disorder[23]. It is possible to classify POTS according to the pathophysiological mechanisms that occur in the patient, thus existing the subtypes detailed below.

Neuropathic POTS consists of a decrease in norepinephrine (NE) levels in the lower limbs. The problem is not the production of such a hormone, as it remains normal; however, release of hormone is decreased and its reuptake is increased. The reason for this is the peripheral nerves are injured and cannot normally work. Low levels of NE cause loss of autonomous innervation in its sympathetic division of the lower extremities, presenting as a consequence reduced venoconstriction, which affects venous return and causes accumulation of blood in the respective regions, which can be observed clinically as a redness[24].

In hyperadrenergic POTS, present in approximately 30-60 % of patients with POTS, a continuously elevated level of plasma NE (≥ 600 pg/mL) is shown, triggering an increase in sympathetic tone. On physical examination, this manifests as palpitations, tachycardia, hypertension, tremors and anxiety[25].

Hypovolemic POTS gets its name because 70 % of people who suffer from it show a decrease in plasma, red blood cells and total blood volumes. From studies carried out, it is inferred that it may be due to damage to the renin angiotensin aldosterone system related to the decrease in renin and aldosterone levels[26].

Autoimmune POTS can also be found, whose name is due to the fact that it appears after a viral process, since the antibodies produced and released to combat this infection attack the peripheral nerves and affect the innervation in general, including therefore the sympathetic innervation. Also, it presents characteristics similar to other autoimmune disorders, such as the predominance of the female sex, postviral onset and elevation of autoimmune markers. Studies indicate that in 25 % of these patients the triggering disease is Hashimoto's thyroiditis, which has been demonstrated from positive results of antinuclear antibodies for this condition[21]. It was observed that individuals who have developed COVID-19 occasionally present with this subtype of POTS as a result of SARS-CoV-2 infection[27].

Boris *et al.* establish that the variety of symptomatic combinations of this syndrome causes the delay of the diagnosis of two years on average, since by not observing what is established as determinant symptoms of the syndrome, the manifestations of the patients do not lead to think about POTS in the first instance[28].

The symptomatology of POTS varies; therefore it can mimic other diseases because some symptoms are absent or others are found in addition to those commonly associated with POTS[29].

Often the syndrome overlaps with other conditions because there are no established or universally "even" symptoms for it. Those that are common in POTS (headache, fatigue, sleep disturbances and diarrhea) are also present in other diseases[29], which generates dilemmas when establishing a diagnosis, which is why it is done by discarding diseases that present all or most of the physical indications that the patient shows, usually the POTS being the last to be taken into account[20].

Blitshteyn states that the psychological diseases with which there is the greatest confusion. Some of the diseases that are frequently misdiagnosed about POTS are panic disorders and chronic anxiety, since they also have characteristic episodes of tachycardia or palpitations, angina, nausea and headache. However, their etiology is different, which helps to differentiate them. In the case of POTS, these are related to cerebral hypoperfusion in response to changes in heart rhythm, while anxiety and panic may be due to the increase in biochemicals mediated by the limbic system[30].

Another psychological pathology that is usually diagnosed instead of POTS is depression due to the presence of fatigue, headaches, agitation or restlessness. Also, the etiology helps to distinguish them, since in patients with POTS fatigue occurs when performing activities that due to their physical condition trigger fatigue, headaches are due either to hypertension or to the same dyspnea or motion sickness that they present and agitation is related to dyspnea due to the performance of activities that normally do not involve fatigue. In patients with depression, the mental fatigue they possess turns into physical fatigue and remains still at rest, headaches may be due to lack of sleep or poor nutrition and crying and agitation may be due to anxiety[4].

Although psychological disorders occupy the first place in the diseases that mimic the POTS, these are not the only ones; likewise, there are the gastrointestinal and urinary ones. According to Goodman, the gastrointestinal symptoms that POTS patients may present are dysphagia, early satiety, nausea, vomiting, abdominal pain, constipation and diarrhea, which are related to visceral motility disorder or primary gastrointestinal disorders (celiac disease, gastroesophageal reflux, esophagitis, gastritis, eosinophilic disorders and inflammatory bowel disease)[31].

Likewise, the presence of urinary symptoms is often observed in patients with POTS, such as frequent urination, difficulty urinating, nocturnal enuresis and incomplete emptying of the bladder. Such ailments lead to misdiagnosis of urinary tract infection, prostate cancer, kidney and bladder stones. Therefore, it is necessary to perform exclusive diagnostic tests and not rule out the possibility that it may be POTS[32].

For differential diagnosis, imaging tests and functional tests, such as transthoracic echocardiography, electrocardiograms for intraarterial pressure control and extended electrocardiography tests, are necessary, as these usually show normal results in patients with POTS[20].

Impact of widespread knowledge of POTS by health personnel on its late diagnosis

Due to knowledge gap, the care of patients with POTS is suboptimal since the scope of clinical presentation is not known with certainty, in addition to the lack of information on the pathophysiology of the syndrome[2].

Although there are standardized criteria for the diagnosis of the syndrome, as there is no record in the presentation of these, there is not diagnosed by clinicians making the care of patients deficient. Collins *et al*. comment that there is still disagreement between the scientific and medical communities about the definition of POTS and whether it is a condition or a set of related conditions[33].

Shaw *et al*. astate that an online survey conducted by academic institutions and the Dysautonomia International Organization, between 2015 and 2017, 4835 people who were diagnosed with POTS participated and reported prolonged delays in diagnosis with an average waiting time of two years after the first medical consultation. 75 % of them reported being misdiagnosed before the diagnosis of POTS, 67 % of them mentioned that their doctor recognized their symptoms as a physical illness, but they were not sure how to address it; a large number of participants received "psychological and psychiatric problems" as a diagnosis and even had to suggest POTS as a potential diagnosis to their doctor. On average, patients in the study consulted 7 ± 11 doctors before being diagnosed with POTS[7].

POTS is not the only puzzling condition doctors face every day ; however, the symptoms of this are vague and inconsistent, which makes it difficult to approach. Lama establishes the possibility that the diagnosis may be delayed even ten years after the appearance of the first discomfort[34].

Conclusion

Either different manifestations that can be found in each patient or the superficial knowledge that clinicians have about POTS, make it difficult to detect. Because the usual or common symptoms are not shown , the diagnosis takes a wrong path towards other diseases that the person suffers, which generates delays not only in its detection, but in its treatment. Consequently, those who suffer from it experience a decrease in their quality of life.

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Narrative review

Lifestyle factors with immunomodulatory effect against respiratory viral infections in adults

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Abstract
The role of lifestyles on the immune system is currently being studied. Respiratory viral infections are a cause of morbidity and mortality in adults, and can cause serious conditions. A balanced diet, consumption of micronutrients and exercise have possible benefits in the evolution of these infections. A narrative review was carried out using bibliographic reviews and original articles obtained in PubMed, SciELO, HINARI and Elsevier. Studies describe that the consumption of vitamin supplements modulates the susceptibility to pathogens due to their antioxidant activity and allows the proper functioning of innate and adaptive immunity. Along with this, lipids and carbohydrates in the diet are basic elements of the immune system cells and, accompanied with 45 minutes of moderate exercise, improve the immune response and reduce the risk of respiratory viral infections. The consumption of micronutrients, moderate intensity aerobic exercise and a balanced diet, are factors that decrease the duration of symptoms due to acute respiratory viral infections in adults. However, the exact mechanism of action of exercise on the immune system is still unknown.

Keywords
Virus, life style, vitamins, immune system, exercise.

Resumen
Actualmente se estudia la importancia de los estilos de vida sobre el sistema inmunológico. Las infecciones virales respiratorias son una causa de morbimortalidad en el adulto y pueden ocasionar cuadros graves. Una dieta balanceada, el consumo de micronutrientes y el ejercicio, presentan posibles beneficios en la evolución de estas infecciones. Se realizó una revisión narrativa utilizando revisiones bibliográficas y artículos originales obtenidos por PubMed, SciELO, HINARI y Elsevier. Los estudios describen que el consumo de suplementos vitamínicos modulan la susceptibilidad a agentes patógenos debido a su actividad antioxidante y permiten el funcionamiento adecuado de la inmunidad innata y adaptativa. Acompañados a ello, los lípidos y los carbohidratos de la dieta son elementos básicos de las células del sistema inmune que, acompañado de 45 minutos de ejercicio moderado, mejoran la respuesta inmune y reducen el riesgo de infecciones virales respiratorias. El consumo de micronutrientes, el ejercicio aeróbico de moderada intensidad y la dieta balanceada son factores que disminuyen la duración de los síntomas por infecciones virales respiratorias agudas en el adulto. Sin embargo, aún se desconoce exactamente el mecanismo de acción del ejercicio en el sistema inmune.

Palabras clave
Virus, estilo de vida, vitaminas, sistema inmune, ejercicio.

OPEN ACCESS

Factores del estilo de vida con efecto inmunomodulador ante infecciones virales respiratorias en el adulto

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Introduction

The immune system is a network of elements that collaborate with one another to recognize infectious agents and coordinate their elimination[1]. A sedentary lifestyle combined with a high caloric intake and high fat content are factors that alter normal function of the system and predispose to acquire viral infectious diseases[2]. Overweight, obesity, malnutrition and micronutrient deficiency can lead to immunosuppression, increased frequency of infections and decreased antibody response[3].

Infections associated with respiratory-type viruses are usually self-limiting and benign; however, they can aggravate a picture, especially in immunocompromised depending on the level of vulnerability of the patient[4]. Among the agents with the highest epidemiological virulence are respiratory syncytial virus, adenovirus and coronavirus[5].

The immune system requires multiple micronutrients to perform its functions; therefore, since the COVID-19 pandemic, several Latin American countries, are using vitamin C, vitamin D, iron and zinc[6].

Physical activity is another factor related to the degree of immune response. Adipose tissue in obese people contains macrophages that cause low-grade inflammation, inhibiting immunity[7]. However, Simpson *et al.* establish that exercise promotes a pro-inflammatory state. Therefore, in the face of a respiratory tract infection, a healthy adult must wait for ten days to return to moderate aerobic exercise[8,9].

A moderate-intensity and short-duration exercise routine is recommended, as it benefits the immune system, reduces oxidative stress, increases energy generation deficiency and decreases the inflammatory response, thus limiting the development of chronic diseases[10]. For this reason, this research work objective is to identify the influence of lifestyle factors with potential immunomodulatory effect against viral respiratory infections in adults.

Discussion

Lifestyle factors with possible immunomodulatory effect

The World Health Organization defines healthy lifestyles as "a general way of life based on the interaction between living conditions in a broad sense and individual patterns of behavior determined by socio-cultural factors and personal characteristics"[11]. It has been acknowledged that several lifestyle factors play an important role in positive health modification and disease prevention.

Nowadays, the role of healthy lifestyle factors as immunomodulatory agents is being studied. Some of these factors are nutrition, physical activity, sleep and the consumption of substances such as vitamin supplements, quitting smoking, avoiding alcohol and illicit substances[12,13].

Diet and its effect on the immune system

López *et al.* describe that the functioning of the immune system is improved by an adequate supply of nutrients and energy[14]. Adequate food has been shown to have beneficial effects on the immune system, as it provides the host defenses against infections[15].

The importance of maintaining a balanced diet is related to the supply of nutrients since malnutrition, either obesity or malnutrition, affects the body's immunocompetence[16]. These nutritional states lead to induced atrophy of the thymus and wear and tear of peripheral lymphatic tissue, increasing the risk of infections[16]. People with obesity have a noticeable decrease in T and B lymphocytes; however, it was not possible to conclude the mechanism responsible for the increased risk of infections or the poor antibody response in these subjects[17].

An adult requires an average consumption of 2000 kcal/day to maintain immunocompetence through good nutritional status. Therefore, as the consumption of daily energy is reduced by 20 %, the risk of microbial infections and pneumonia increases[15].

There must be a balance of the entry of energy into the body to strengthen the immune system; This energy source revolves around carbohydrates. However, this does not mean promoting excessive intake because it could lead to excess body mass with a negative effect on health[14]. Therefore, a carbohydrate-fat of 70:30 should be maintained.

As crucial as any component in diets, lipids are substances that have a strong influence on the modulation of the immune system. The composition of fatty acids present in lymphocytes is altered proportionally with those present in the diet[18]; therefore, De Pablo *et al.*, suggest a role of lipids provided in the diet, influencing the composition of pro-inflammatory cells of the immune system[17].

Factors such as proper nutrition and sun exposure for the absorption of vitamin D (with protectors from ultraviolet rays), provide the necessary amount of nutrients and vitamins to the body in an easy and effective way. However, when neither this is not possible or proper levels, and vitamin supplements can be used[18].

Consumption of vitamins and micronutrients, and risk of respiratory viral infections

Vitamins are essential nutrients that cannot be synthesized by the human body, so they are found as food supplements. Since they are antioxidants, they help in the balance of free radicals which damage the integral

structure of the cells of the immune system. Neutrophils and macrophages produce superoxide and H_2O_2 free radicals, essential for defense against invaders. In this state, vitamins are necessary to regulate the reactions released by free radicals and as a result, are related to the modulation of host susceptibility or resistance to infectious pathogens[18].

Vitamin C or ascorbic acid is classified as a key antioxidant in the synthesis of collagen, carnitine and catecholamines. Also, it reduces the damage caused by free radicals, which influence ageing and tumor processes, as well as contributes to cholesterol metabolism and different chemical reactions[19].

Besides reducing oxidative stress, vitamin C is accumulated in leukocytes, monocytes and neutrophils. It is believed that concentrations in these cells help prevent damage by oxidants in the environment and thus prevent these cells from being phagocytosed[18, 19].

Vitamin D is also characterized by being an excellent modulator in the inflammatory response and in the prevention of infections. As an antioxidant, it is responsible for the protection of fatty acids present in membranes against the peroxidation of lipids, free radicals and oxygen atoms, becoming the most important antioxidant found in the lipid membrane. Serum vitamin D levels are directly involved with the formation of immune system cells, such as macrophages, monocytes, dendritic cells, and T and B lymphocytes[20].

Due to the immunomodulatory effect of vitamin C, a prophylactic intake is recommended to maintain adequate plasma levels of 100-200 mg/day to prevent respiratory tract infections and systemic infections[19]. Ran *et al.* report in a meta-analysis that vitamin C intake significantly improves symptoms such as fever (p 0,009), chest pain (p 0,03) and chills (0,01)[21].

Vitamin C and D supplementation is recommended as these vitamins cause a significant reduction in the risk and impact of upper and lower respiratory tract infections such as the common cold and pneumonia, including the severity of the disease and the risk of death in the elderly[22].

These results coincide with those of Johnston *et al.* who report that vitamin C consumption reduces the duration of the cold by 59 % compared to the placebo group (-3,2 days, 95 % CI -7,0-0,6, p 0,06). But the severity of the symptoms and their impact on everyday life did not differ between the two groups[25]. Vitamin C supplementation in acute respiratory infections is not justified as it does not reduce its incidence; however, due to its low cost and its effect on the reduction of symptoms, it can be assessed depending on the case[24].

Vitamin D induces antimicrobial peptides such as cathelicidin which alters the membranes of viruses, fungi and even some bacteria such as *Mycobacterium tuberculosis*[25]. Also, this decreases the cytokine storm that occurs in severe viral infections such as Coronavirus disease; Vitamin D levels of 30 ng/mL are required for adequate vitamin D production and to reduce the incidence of respiratory infections[26].

The role of vitamin D in different viral infections has been described, such as the production of peptides LL 37 and β-defensin in respiratory syncytial virus infection, which prevent the entry of the virus into the body by decreasing its spread in the host[27]. Vitamin D supplementation has also related to the improvement of results and prevention of Hepatitis C virus infection recurrence[26]. Besides, vitamin D supplementation is recommended in patients with human immunodeficiency virus since vitamin D levels are an indicator of the prognosis of the disease and adequate levels can improve the course of the disease[25,26].

Daily or weekly vitamin D supplementation results in significant reduction in experiencing at least one acute respiratory infection (OR 0,88, 95 % CI 0,81 – 0,96, p 0,003; NNT 33, 95 % CI 20 - 101, p 0,001)[28]. There is an important relationship between vitamin D deficiency and mortality from COVID-19, especially in older adults who have the lo-west levels of vitamin D[29].

Micronutrients play an important role in the innate immune response through the development of physical barriers, regulate the activity of neutrophils and macrophages as well as inflammatory processes through the production of cytokines and their antioxidant effect; while in the adaptive response they allow an adequate lymphocyte differentiation, proliferation of cytokines, antibodies and memory cells[19].

Proper nutrition is necessary for proper function of the immune system at all stages of life because inadequate consumption of micronutrients increases susceptibility to infections especially in adults in whom a wide variety of lifestyle factors produce oxidative stress[30].

It has been established that an adequate intake of vitamins and minerals presents benefits for the innate and adaptive immune response, mainly vitamins A, B12, C, D and trace elements such as zinc[31,32].

Maintaining adequate amounts of each micronutrient is crucial for the proper func-

tioning of the immune system because deficiencies of vitamins and essential elements alter the response to pathogens, since when an infection occurs, malnutrition of micronutrients is exacerbated and the demand for these increases, affecting important aspects such as alterations in the integrity of the skin and mucous membranes, chemotaxis, humoral response and cell-mediated immunity[33].

Zinc promotes the production of antibodies, influences macrophage activity and regulates lymphocyte apoptosis. It has been shown that the inclusion of this mineral in the diet, in addition to its contribution to strengthening the components of the immune system, also helps to improve intestinal absorption and promote growth[34]; besides, zinc is a component of multiple transcription factors and enzymes and has an important role in gene expression and cell division[35]. Zinc supplementation considerably reduces the duration of acute res-piratory infections and prevents mortality in severe pneumonia[36]. In a cohort study, zinc supplementation with 45 mg per day showed a reduction in the incidence of the common cold (p 0,067) of other infections and fever during the study[37].

Zinc's role as an antiviral can be separated into two categories: supplementation to improve antiviral response and zinc treatment, specifically to inhibit viral replication. They report that zinc in vitro significantly reduces influenza virus replication and inhibits elongation of the SARS-CoV-2 coronavirus[38-39]. Consequently, an increase in the consumption of supplements was observed as a result of the COVID-19 pande-mic, which forced doctors to emphasize the adequate consumption of micronutrients and avoid an excess that can lead to symptoms such as nausea, vomiting, headache, dry skin, among others[40].

Exercise and its effect on the immune system

A sedentary lifestyle is associated with abdominal adiposity, a pro-inflammatory state, and an increased risk of infection[10].

The profound impact that exercise has on the immune system has been demonstrated. Practicing physical exercise regularly promotes improvements in quality of life and can act on the immune response, reducing the risk of developing systemic inflammatory processes and stimulating cellular immunity[10].

Physical exercise and training with moderate-intensity aerobic exercise, that is, up to 45 minutes, improve immune responses to vaccination, reduce the risk of viral infections, and improve several immune markers in various disease states, including cancer and cardiovascular disease[41,42].

On the contrary, Walsh *et al.* demonstrate that high-intensity exercise, generally practiced by high-performance athletes, has been associated with suppressed cellular and mucosal immunity, increased symptoms of upper respiratory tract infections, latent viral reactivation, and impaired immune responses to new vaccines and antigens[9].

Exercise practice and risk of respiratory viral infections

The proper functioning of the immune system must be boosted from before the infection occurs. Moderate-intensity aerobic exercise stimulates the exchange and redistribution of immune cells present in the circulation and peripheral tissues. Each aerobic session improves the activity of tissue macrophages and helps the movement of immunoglobulins, anti-inflammatory cytokines, neutrophils, immature B cells and lymphocytes. Intense exercise greater than one hour a day decreases the circulation of these cells. However, all this remains under debate due to the lack of studies that support this response[43].

Chubak *et al.* conducted a study in obese and sedentary postmenopausal women, divided into two groups, one group of moderate intensity exercise and the other group of stretching sessions, both lasting 45 minutes, for a period of 12 months, it was found that the group that performed moderate exercise had a lower incidence of respiratory symptoms than the stretching group[44].

Klentrou *et al.* found that an average of 12 weeks of mo-derate exercise managed to reduce the symptoms of respiratory infections and was correlated with an increase in IgA, however, there are still no studies that explain this relationship to prove this theory[45].

Another theory of immunosuppression caused by strenuous exercise is provided by Simpson *et al.*, who establish that the function of biomarkers of the immune system (NK cells, lymphocytes, neutrophils, IgA, among others) are altered for hours and even days during the recovery of the body after intense exercise, making pathogen entry more accessible the facilitating the entry of pathogens. However, although it is well known that this increases the pro-inflammatory state and can alter the immune response, the exact mechanism of action

of this phenomenon is unknown since for ethical reasons there are not many studies on the matter[8].

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Narrative review

Non-pharmacological strategies as adjuvants in needle associated acute pain management in pediatrics

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Estrategias no farmacológicas como adyuvantes para manejo de dolor agudo por punción en pediatría

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Abstract
Pediatric pain is a public healthcare problem present in 78 % of hospitalized patients and it is frequently associated to needles. Fast and effective controls are needed, therefore, sensory stimulation and psychological strategies have been developed. The aim of this study was to describe the use of non-pharmacological strategies as adjuvants in needle associated children pain management. A review was made searching through original articles and other reviews. Pain mechanism involves C fibers and Aδ fibers, which respond to short term needle pain. Buzzy® device is among the innovative physical strategies to relieve pain, which acts according to the pain threshold theory, diverting attention from pain to a pleasurable sensory stimulus (cold and vibration) decreasing its intensity when compared to topical anesthesia ($p < 0,001$). Meanwhile psychological strategies such as virtual reality divert the child's attention to a pleasant visual and auditory stimulus. It creates a tridimensional environment with an electronic device, decreasing pain while distracting the child when compared to the control group ($p < 0,05$). The use of innovative non-pharmacological strategies as adjuvants for needle pain management is effective decreasing children pain and reducing stress and anxiety in parents and healthcare workers.

Keywords
Needles, acute pain, pain management, patient satisfaction, virtual reality.

Resumen
El dolor en pediatría es un problema de salud pública que afecta al 78 % de pacientes hospitalizados y está frecuentemente asociado a punciones, por lo que es necesario un control rápido y efectivo. Existen en la actualidad estrategias psicológicas y físicas de estimulación sensorial para abordarlo. Se pretende describir el uso de estas como coadyuvantes en el manejo del dolor agudo por punción en pediatría. Se realizó una revisión narrativa de artículos originales y revisiones bibliográficas. El mecanismo del dolor involucra a las fibras C y a las fibras Aδ, que responden al dolor por punción. Entre las estrategias innovadoras se encuentra el dispositivo Buzzy®, que actúa mediante la teoría de compuerta del dolor, desviando la atención del dolor hacia un estímulo sensorial placentero (frío y vibración) que disminuye la intensidad en comparación con anestésicos locales ($p < 0,001$); así mismo, la realidad virtual desvía la atención del niño hacia un estímulo placentero, visual o auditivo, creando un ambiente tridimensional y produciendo analgesia por distracción en comparación al control ($p < 0,05$). El uso de estrategias no farmacológicas innovadoras como coadyuvantes para el manejo de dolor por punción son efectivas para disminuir el dolor en el paciente pediátrico, así como el estrés y la ansiedad, tanto en los padres como en el personal de salud.

Palabras clave
Agujas, dolor agudo, manejo del dolor, satisfacción del paciente, realidad virtual.

Introduction

Acute pain, one of the most frequent reasons for consultation, is defined by the International Association for the Study of Pain as an uncomfortable sensory and emotional experience associated with imminent or confirmed tissue injury[1,2]. In pediatrics, pain is an important public health problem[3], due to the sensation of discomfort, alteration of the patient's vital signs and hemodynamic parameters[4]. It has been reported that 78 % of patients suffer pain during their hospital stays, being more frequent when associated with venipuncture and intravenous insertions[5].

Inadequate pain management causes stress, anxiety, prolonged hospital stays and increased costs in a short time[6], while causing hyperalgesia, rejection of health facilities[7] and post-traumatic stress in the long term[8], causing a reduction in adherence to chronic treatments[9].

Nowadays, the gold standard in pediatrics for pain management in venipuncture procedures is topical anesthesia; however, its use is limited due to its delayed effect[10]. Since effective strategies for pain management are needed, alternative non-pharmacological methods such as virtual reality[11] and Buzzy® emerge, which immediately act by distracting the senses and can even prevent sedation[12]. Bergomi *et al.* refer that, because these methods involve different senses, they modify the perception of pain and reduce stress in the patient. Therefore, this method achieves greater adherence to procedures and treatments, especially in those that are long-term[13].

Sahiner and Bal describe that when the child is distracted by non-pharmacological strategies during venipuncture, they reduce the sensation and perception of pain and anxiety in both the patient and the parents[14], achieving a positive effect since adverse effects are presented[15] and hospital stay is reduced[16]. Therefore, their objective is to describe the use of these non-pharmacological strategies as adjuvants in the management of acute pain associated with puncture in pediatrics.

Discussion

Mechanism of the area of puncture pain

Pain is a multisensory and complex phenomenon that requires a complete evaluation for proper management[17]. It is classified into inflammatory, neuropathic and nociceptive; the latter is subdivided into visceral and somatic pain, which is perceived by stimulating pain receptors (nociceptors) distributed in skin, muscles, joint capsules, bones and some organs, activated by mechanical, chemical or thermal damage[18].

Pain perception is the result of multiple and dynamic mechanisms which belong to the central nervous system (CNS) and the peripheral nervous system (PNS), which inhibit or facilitate stimulation and pain response[19]. When the nociceptors are stimulated, sensory information is transmitted to the dorsal ganglion and subsequently to the laminae I to V of the gelatinous substance in the dorsal horn of the spinal cord, where the axon of the second-order neuron is decussed. Then, this information ascends on the opposite side, through the anterolateral fascicles in the spinothalamic tracts. Afterwards, it is processed in the medial and lateral nuclei of the thalamus. Finally, the message is sent to the somatosensory cortex through the third-order neuron, where the intensity and location of the lesion are perceived[11].

As to the mechanism of puncture pain, it involves the two main types of pain receptors, which are the unmyelinated C fibers, slow conduction velocity (0,5-2 m/s), responsible for 70 % of afferent information, whose response is poorly localized and the myelinated Aδ fibers, fast conduction velocity (5-15 m/s) and localized response, that respond to pain by puncture of short duration[20].

Among the inflammatory mediators involved in the emission or continuation of the painful signal in the ascending pain pathway are 5-hydroxytryptamine, hydrogen ions, cytokines, bradykinin, histamine, prostaglandins and leukotrienes. Signal transmission is inhibited or attenuated through inhibitory downstream pathways by endogenous opioids and cannabinoids, gamma aminobutyric acid, cholecystokinin and nitric oxide[11].

Nowadays, needle procedures are indispensable because they are necessary for diagnosis, treatment and prevention of pathologies, so people are exposed to them from birth[21]. The pain associated with venipuncture is one of the most intense, uncomfortable and stressful experiences for pediatric patients[22,23]. Orenius *et al.* conducted a study that showed that 21 to 75 % of pediatric patients suffer fear and phobia of needles[24]. The procedures frequently involved are: intravenous canalization, intramuscular injection, subcutaneous injection and lumbar puncture[25].

Non-pharmacological strategies for pain management

A study conducted in the United States of America reports that 80 % of pediatric pain management medications are for "off-label" use[26], showing that oligoanalgesia exists as compared to the adult population[27]. In the absence of effective drugs for the production of analgesia in pediatric patients, there is a need to use non-pharmacological strategies as adjuvants in pain management in the child population.

These non-pharmacological techniques are divided into physical, such as massage, vibration, hot compresses, comfort repo-

sitioning, ice placement or physical and psychological activities, which include behavioral strategies, such as relaxation and distraction through visual or auditory stimulation[28]. The combination of at least two of these is more effective than their individual use[29].

Regarding the role of sensory stimulation devices in pain relief, physical strategies are based on the modulation of pain sensation, transmitted by the Aδ and C fibers, by non-harmful stimulation of thermoreceptors (temperature) and mechanoreceptors (Aβ fibers, pressure, vibration and fine touch), activating inhibitory interneurons that block the afference of the painful signal, a phenomenon known as the gate control theory of pain[30].

The mechanism of action of the Buzzy® portable device consists of mechanical stimulation combined with sensory stimulation through cold measures such as the application of ice that blocks pain on contact[31]. This device does not use drugs and is adjustable by means of an elastic band close to the puncture site and can be combined with mechanical sensory measures such as vibration, which increases the pain threshold producing hypoalgesia at the site of injection[32]. The variety of these devices consists of the combination of stimuli and medical grade material that allows disinfection in those used in patient care areas as opposed to those for home use[31].

Psychological or cognitive distraction techniques act diverting the child's attention from the harmful stimulus to a pleasant one through the senses of sight, touch and hearing, with the ideal distractor being the one that manages to stimulate them simultaneously[33]. Nowadays, the use of virtual reality (VR) as a therapeutic tool[34], has been implemented, which consists of the creation of an artificial environment in three dimensions through the use of a computer or cell phone, connected to a visor adjusted to the child's head, its main mechanism is the simulation[35] which plays *Aqua, Virtual Reality Gorilla Exhibit,* or interactive games such as knocking down teddy bears with balls[33].

Virtual reality allows the user to experience immersion in a three-dimensional environment generated by computer[36], which has proven to be effective in relieving acute pain associated with punctures, dressing changes in second and third-degree burns and in post-surgical cardiovascular recovery. However, the specific mechanism for action has not yet been determined[37].

Buzzy®, virtual reality and traditional techniques

Non-pharmacological techniques of the physical type include the Buzzy® portable device, whose effectiveness in relieving pain continues to be tested.

AlHareky *et al.* conducted a study in Saudi Arabia with 74 children from 5 to 12 years old, whose objective is to compare the intensity of pain by maxillary block, infiltrating local anesthesia (traditional technique) as a control group, against the group treated with local anesthesia plus the Buzzy® device, finding that, based on the visual analog scale (VAS), the intensity of pain in the treated group (6,68) was lower than in the control group (8,42), a statistically significant difference ($p = 0,001$). Similar data were reported when using the face, legs, activity, crying and consolability (FLACC) scale, according to which the treated group expressed less pain (5,92) as compared to the control group (8,16), with a p-value of 0,002, showing that adherence to the device considerably decreased the intensity of pain associated with puncture in children[38].

These results are consistent with what was reported in the study of 50 children from five to ten years old in India, who found a significant reduction in the perception of pain associated with the application of local anesthesia in dental procedures according to the FLACC scale (treated: 1,4 and control: 3,96; $p \leq 0,05$) with the use of the Buzzy® device compared to the perception evaluated according to the Wong-Baker face scale (WBFPRS) (treated: 5,68 and control: 6,15; $p \leq 0,05$)[39].

Bilsin *et al.* also found that the use of the Buzzy® device two minutes before the procedure reduces the intensity of pain associated with the application of local anesthesia prior to tooth extractions, in a study conducted in Turkey with 60 children aged 6 to 12 years old, using the WBFPRS scale (treated: $0,86 \pm 1,13$ and control: $3,33 \pm 1,91$; $p < 0,05$) a mean difference of 2,47 points in favor of the treated group was shown[40].

The aforementioned studies differ from the results obtained by Yilmaz *et al.*, who included 60 children between 8 and 16 years old, since they did not find statistically significant difference in the intensity of pain after peripheral venous catheterization with the use of the Buzzy® device between the experimental group and the control group[41].

In Italy, a study was conducted which showed that the use of a non-pharmacological technique of a physical type in conjunction with a distraction method decreases the perception of pain. 72 patients

from 3 to 10 years old were included in order to compare the level of pain associated with puncture in two study groups: a treated group, using the Buzzy® device in conjunction with distraction cards, and as a control group, using the hospital's routine distraction technique. Pain was lower in the intervention group with the device than in the control group according to the VAS scale (treated: 3,65 ± 2,011 and control: 4,67 ± 2,14; p < 0,05; CI 95 %)[42].

Non-pharmacological techniques have not shown the same efficacy when applied in isolation, compared to the use of topical anesthetics, such as lidocaine patches for the reduction of puncture pain, being this evidenced in a study carried out in three vaccination centers in France with 220 patients from 4 to 15 years old, where they demonstrated that the Buzzy® device was not equivalent to the placement of lidocaine patches in the prevention or reduction of pain associated with intramuscular injection[43].

Özalp Gerçeker *et al.* evaluated the effect of two different virtual reality methods (VR-Rollercoaster y VR-Ocean Rift), on pain associated with blood sampling in 136 children aged 5 to 12 years old. The pain intensity of the patients was measured using the Wong-Baker faces pain rating scale (WBFRPS), which showed that mild pain values (1-3 points) were reached in both virtual reality groups when as compared to the control group, which maintained moderate pain (4-6 points) (VR-Rollercoaster 1,2 ± 2,2; VR-Ocean Rift 1,0 ± 1,5; control: 4,1 ± 3,5; p < 0,05). However, there was not statistically significant difference between the two groups that used virtual reality[44].

The results mentioned before contrast with those obtained in a study carried out in 59 children from 8 to 17 years old at a hospital in Ontario, Canada, which reported that the use of virtual reality compared to distraction by television or "Child Life" interventions program, represented a statistically significant decrease in fear of pain, but did not significantly affect pain intensity[45].

The effect of distraction cards, virtual reality and the Buzzy® device on puncture-associated pain in 142 children aged 7 to 12 years old was evaluated in a study in a peripheral venous canalization hospital unit in Turkey. The researchers measured the pain intensity reported by the patient using VAS. The study revealed that the Buzzy® group (VAS 2,2 ± 2,0) had the lowest average pain, followed by the virtual reality group (VAS 2,7 ± 2,8), the distraction cards group (VAS 3,4 ± 2,4), in contrast to the control group (VAS 5,2 ± 2,8). There was statistical significance among all intervention groups versus the control group (p < 0,05). There was not significant difference between Buzzy® and virtual reality[46].

Satisfaction of innovative non-pharmacological techniques

Redfern *et al.* evaluated the satisfaction of parents in 50 children when using Buzzy® compared to no intervention during vaccination in Spain. When used a visual scale by faces to measure anxiety, they found that Buzzy® did not decrease fear or anxiety about vaccines according to parents (intervention: 4,34 ± 3,4, control: 4,58 ± 1,6; p < 0,05)[47].

In Turkey, the perception of the vaccinating nurse when using Buzzy® and its impact on the WBFPRS scale and Children's Fear Scale (CFS) in two groups of 45 first-grade school children was evaluated in a study finding that the device decreased pain (experimental: 1,86 ± 1,61; control: 5,46 ± 1,97, p < 0,05) and fear (experimental: 1,42 ± 0,62; control: 1,77 ± 0,7, p < 0,05) according to healthcare personnel [48].

In Australia, Chan *et al.* conducted a study to verify the impact of VR on standard management to decrease pain during venipuncture and parental perception during procedures; therefore, they used the VAS scale in the emergency department, finding that on average the intervened group expressed lower pain intensity, with a mean difference of 4 points as compared to 1 point in the control group (p < 0,05)[49]

In a sample of 58 individuals aged 4 to 15 years admitted to a hospital in Spain, the perception of pain (using WBFPRS in patients aged 4 to 6 years, VAS in patients aged 7 to 15 years) and fear (CFS) in children was rated through the parents and health care staff. The population was divided into control group, VR group and VR group plus traditional technique. The results indicate that VR decreased the median intensity measured by the pain scales, according to parents (control: 4 of 5 points, VR: 2 of 5 points, VR plus traditional technique: 1 of 5 points; p < 0,001) and health personnel (control: 4 of 5 points, VR: 2 of 5 points, VR more traditional technique: 0 of 5 points; p < 0,001), as well as on the fear scale, according to parents (control: 3 of 4 points, VR: 1 of 4 points, VR plus traditional technique: 1 of 4 points; p < 0,001), and according to health personnel (control: 3 of 4 points, VR: 1 of 4 points, VR with traditional technique: 0 of 4 points; p < 0,001)[50].

It has been shown that both health personnel and parents report a decrease in anxiety, fear and pain in patients.

Conclusions

The use of non-pharmacological strategies such as Buzzy® and virtual reality, for pain management in pediatrics, are effective in puncture procedures, since they present lower intensity score in the different pain scales compared to the non-intervened groups. Also, they have no adverse effects, and are ideal for emergency units due to their short time to take effect.

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Brief communication

Oral diagnosis in preschool children living in a marginal urban area

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Abstract
Introduction. Dental caries is a public health problem, in 2016 it affected 3500 million people. In children under six years of age, the progression of the lesion is faster, exposing them to early childhood caries and premature dental loss. **Objective.** To determine the health/disease status of the oral component of nursery school children from a school with social and economic vulnerability in the municipality of San Salvador, in 2018, according to the index and prevalence of dental caries disease. **Methodology.** The study is descriptive, quantitative, cross-sectional, prospective. The units of analysis are children between four and five years of age, respecting all ethical aspects and confidentiality. The total of the universe made up of 96 children was taken. **Results.** The frequency of dental caries in the study population is 95 %, the decayed, missing and filled caries index is 6,38, which according to the World Health Organization is very high. The most affected tooth surface is occlusal, in the upper quadrants with approximately 40 % and in the lower quadrants with approximately 20 %. **Conclusion.** The majority of the population under study suffers from dental caries, being a minority that maintains the oral cavity in an optimal state.

Keywords
Dental caries, oral health, oral diagnosis, DMF index, mouth diseases.

Resumen
Introducción. La caries dental es un problema de salud pública que para el año 2016 afectaba a 3500 millones de personas. En los menores de seis años, la progresión de la lesión es más rápida, exponiéndolos a la caries de la temprana infancia y pérdidas dentales prematuras. **Objetivo.** Determinar el estado de salud/enfermedad del componente bucal de niños de parvularia de un centro escolar con vulnerabilidad social y económica del municipio de San Salvador, en el año 2018, según el índice y la prevalencia de la enfermedad de caries dental. **Metodología.** El estudio es descriptivo, cuantitativo, de corte transversal, prospectivo. Las unidades de análisis son niños de cuatro y cinco años de edad, respetando todos los aspectos éticos y la confidencialidad. Se tomó el total del universo, conformado por 96 niños. **Resultados.** La frecuencia de caries dental en la población en estudio es del 95 %, el índice de dientes cariados, extraídos y obturados es de 6,38, que según la Organización Mundial de Salud es muy alto. La superficie dental más afectada es la oclusal, en los cuadrantes superiores, con un aproximado del 40 %, y en los inferiores, un aproximado del 20 %. **Conclusión.** La mayoría de la población en estudio padece de caries dental, siendo una minoría la que mantiene la cavidad bucal en estado óptimo.

Palabras clave
Caries dental, salud bucal, diagnóstico bucal, índice CPO, enfermedades de la boca.

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Diagnóstico bucodental en niños de parvularia residentes de una zona urbanomarginal

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Introduction

The world population is affected by diseases of the stomatognathic system throughout the life cycle, which cause pain, disorders such functional, aesthetic, communication and even death; among these diseases, tooth decay is the most prevalent[1]. According to data from the World Health Organization (WHO) on the global burden of disease in 2016, tooth decay affects 3500 million people, being the most frequent disorder in permanent teeth[2].

Caries in permanent teeth has a prevalence of 40 % on a global scale, and is the most frequent condition, according to the processes evaluated by the World Dental Federation (FDI)[3]. In Asia and Latin America, the prevalence of tooth decay in schoolchildren ranges from 32,5 % to 52,7 %[4–6].

In children under six years of age, caries in early childhood is common, which is rapidly progressive and represents an international public health problem[7,8]. The disease begins in the dental enamel, demineralizing the inorganic components of the tooth; afterwards, it causes severe tooth decay, even more so if the modulating factors of the disease are not in balance[9,10].

As for oral health, the causal factors are biological, lifestyle, socioeconomic and the intervention of the dental professional who provides preventive treatments. Inequality is associated with the multicausal factors of dental caries, which determine the conditions of quality of life[11]. The most affected people by oral diseases are the most socially and economically disadvantaged, who are in a situation of vulnerability from the moment of conception, taking into account that their mother is not well nourished; if their basic needs are not met throughout the life cycle, these disparities break again the state of homeostasis of the health-disease process in the population[12].

To quantify and measure how the dental organs are affected by caries, it is not enough to present the prevalence, since it only reflects its presence; therefore, it is necessary to use the index that adds the decayed, missing and filled teeth (DMF-T) for permanent dentition. The dmf-t index is used for deciduous or temporary teeth[13].

A study on the prevalence of caries in Salvadoran school children aged seven to eight years identified that each child had an average of 9,52 teeth affected by caries, according to the criteria of the international system of detection and evaluation of caries[14]; and another study aimed at the adult population presented a prevalence of 95 %[15].

Likewise, a high rate of caries was identified in children aged six to eight, who were from economically and socially vulnerable communities in El Salvador from 2014 to 2019. Therefore, it is suggested to investigate more about socioeconomic factors and the risk of dental caries in order to reinforce oral health strategies to cover the family group[16].

The objective of this study is to determine the state of health/disease of the oral component of pre-school children of a school with social and economic vulnerability in the city of San Salvador in 2018, according to the index and prevalence of dental caries disease.

Methodology

The study design is descriptive, cross-sectional, prospective, with a quantitative approach. For this research the entire universe was taken as the study population, which was made up of 96 children without noncommunicable diseases, between four and five years of age, from a public school located in a marginal urban area of the city of San Salvador, El Salvador, enrolled in kindergarten grades four and five.

The inclusion criteria were: children aged four to five years of age without the presence of permanent teeth; the exclusion criteria were: suffering systemic diseases that present alterations in the stomatognathic system. The variables in this study were gender, dental caries and reinfection by caries in already restored teeth. The dmf-t index was used from the variable of dental caries according to parameters established by the WHO[17].

The data was collected, through observation, by two dentists and recorded in a clinical record, as a data-collection instrument; this was taken from the file that is used in the pediatric dentistry clinic of the Dental School of the Evangelical University of El Salvador. Aspects that allowed the collection of data more effectively were simplified and validated for this study.

For the analysis of the information, a database was developed in the *Statistical Package for the Social Sciences* version 23, where the tables and frequency graphs and the mean of the dental caries index were designed, which were compared with the severity criteria established by the WHO[17] that were established on the basis of the number of decayed or lost teeth due to caries with the following categories: very low with a score from 0,0 to 1,1; from 1,2 to 2,6 is low; 2,7 to 4,4 is moderate and 4,5 to 6,5 is high.

For the development of this research, the approval of the National Committee of Ethics of Health Research of El Salvador was obtained, the parents of the participating children signed an informed consent for the development of the diagnosis and an assent was obtained from the schoolchildren where anonymity and confidentiality were always safeguarded.

Results

In relation to the sex distribution of the population, 54,2 % were female; 85 % were

five years old, residents of an urban-marginal neighborhood of San Salvador.

Regarding the number of teeth affected by caries, 46,2 % of the study population presented from six to ten teeth with caries; 43 % of them had zero to five affected teeth and 10,7 % of them had from 11 to 17 decayed teeth (Figure 1).

24 % of the study population had reinfection due to caries in teeth that had already been previously treated. 76 % of them presented restorations in good condition.

Besides, the average is six for the dmf-t index, which means that 20 of teeth present, six or more have already had a caries experience; this reveals a prevalence of more than 95 % of caries in the study population, with a total population score of dmf-t 6,38, which is a high score according to the WHO[17]. 70,9 % of the population has a dmf-t score between 5 and 17, placed in a very high range (Table 1).

The consolidation of the dental surfaces most affected with carious lesions per quadrant highlights that the most affected is the occlusal surface both in the upper and lower arcade; quadrant III is affected by 79,1 % and quadrant IV by 78,1 %. It is followed by the mesial surface of the upper dental arch, with 21,9 % affected in quadrant I and 18,8 % in quadrant II (Table 2).

Discussion

The prevalence of dental caries in the study population was very high and affects the majority of the population. A study conducted in schoolchildren in 2018 identified a prevalence of caries of 26,6 %[14]. The results of this research contrast with this percentage, as they show that in this sector of the population, far from decreasing the prevalence, it shows a considerable increase in the disease, which may be due to the low motivation in oral health care, the lack of oral hygiene habits and little attendance at preventive dental services[18,19].

The dmf-t score of the population under study is high, considered according to the WHO classification, which implies that of 20 primary teeth that a child between four and five years old has, six teeth already have carious lesions, which throughout the life cycle will generate premature losses of

Table 1. dmf-t index observed in four to five year old children in a school in San Salvador, El Salvador

dmf-t index	Frequency	%
0	3	3,1
1	4	4,2
2	5	5,2
3	4	4,2
4	12	12,5
5	4	4,2
6	16	16,7
7	9	9,4
8	11	11,5
9	5	5,2
10	7	7,3
11	4	4,2
12	6	6,3
14	3	3,1
15	2	2,1
17	1	1,0
Total	96	100

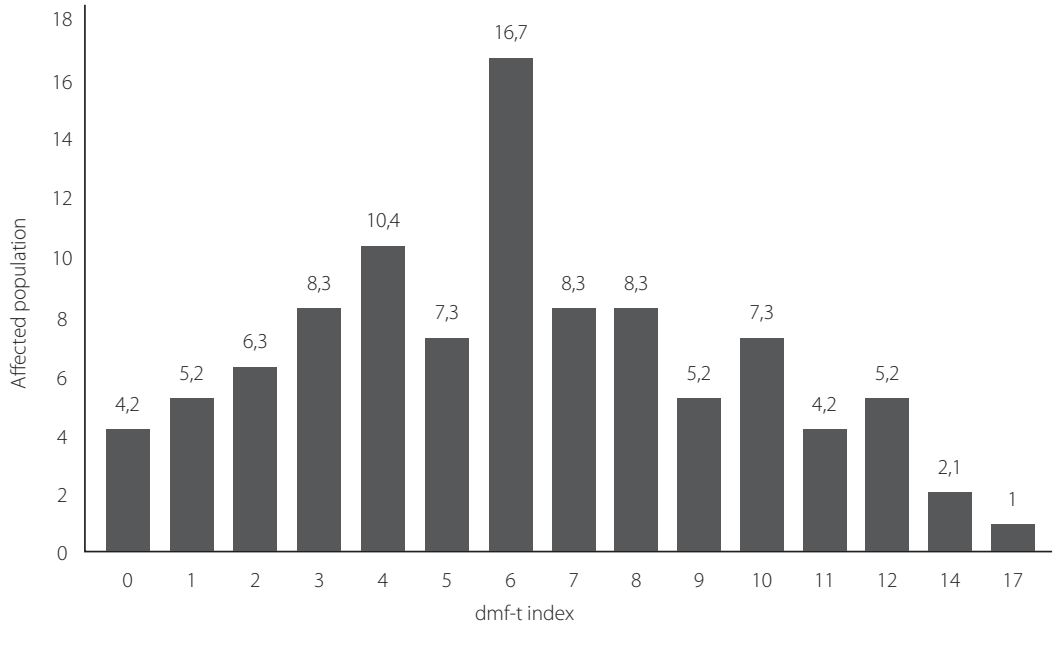

Figure 1. Number of teeth with caries in children between four and five years of age in a school in San Salvador, El Salvador

teeth. These results are comparable to those found by Ramírez Puerta in 2017[20], who states that in the first years of life, specifically in early childhood, the control of carious disease represents a greater challenge that must be faced and treated through preventive approaches from conception on and that cannot be faced from a germ-disease approach. It must be considered that in order to improve the oral health status of the populations, the social determinants of health must be taken into account, being crucial in the first years of life: the prevention of the spread of *Streptococcus mutans* cariogenic, the establishment of oral care habits, specifically the correct tooth brushing and a balanced diet[18].

The most affected tooth surface was the occlusal face. The occlusal surfaces belong to the molars, which due to their anatomy with grooves and fissures are more vulnerable to dental caries, since this particularity in the anatomy does not allow adequate tooth brushing[19]. The results of the research are consistent with data from a study conducted with preschool children aged four and five years of both sexes in Argentina, where it was reported that the occlusal surface was the most affected in 42,6 %[21]; Likewise, in Cuba, a study was carried out that reported the affection of the first permanent molar in children aged 6 to 11 years, in which it was found that the occlusal surfaces of the molars were the most affected by caries in 36,5 %[22].

In a study published in a population in Peru, low educational level and family income are directly related to the number of carious lesions[23]. In El Salvador, the condition of poverty in 2021 still affected 31 % of the Salvadoran population[24]. Homelessness is a real problem, given the inability of offering urbanized land, housing and adequate living conditions, it places them in a "vulnerable" condition. Therefore, it is necessary to generate alternative housing and habitat solutions, which, in principle, in the face of the expectation of a concrete urban solution, are considered transitory, but which are consolidated over time, at the edge of the increasingly intricate urban boundaries, in the so-called urban slums[25].

The population for this study is located in a geographical area classified as marginal urban, which meets the vulnerabilty characteristics described.

The main limitation was that socio-economic data were not obtained due to the security vulnerability of the area. Likewise, the sample size of the study was limited, due to the capability of the institution and the demand for initial education from the place of origin of the population, so the study had a small population that extrapolation of results is not allowed.

To control dental caries, it is necessary to propose strategies of action at an early age, covering the three levels of prevention, and thus avoid premature tooth loss[13].

It is important to establish plans and public policies that involve the health sector in the prevention of dental caries in early childhood, which allows an optimal development of the child in the first years of life: without pain when eating, being able to express themselves and smile without any health problems in their oral cavity. Therefore, it is necessary to implement preventive and educational strategies, accompanied by the placement of sealants of pits and fissures sealants in these dental organs[26]. It is important to take into account in public health policies the placement of sealants on deciduous teeth and thus reduce the condition on the occlusal surface, which is the most affected surface by its anatomy.

Morbidity from oral diseases must have a comprehensive approach that allows its reduction through public health interventions directly focused on the most common risk factors[9]. Preventive strategies begin from pregnancy, with the mother having

Table 2. Carious lesions by quadrant of children aged four to five in a school in San Salvador, El Salvador

Presence of carious lesions by surface and quadrants	Quadrant I Frequency	%	Quadrant II Frequency	%	Quadrant III Frequency	%	Quadrant IV Frequency	%
None	21	21,9	20	20,8	14	14,6	17	17,7
Occlusal	40	41,7	39	40,6	76	79,2	75	78,1
Buccal	6	6,3	8	8,3	0	0,0	1	1,0
Mesial	21	21,9	18	18,8	1	1,0	2	2,1
Lingual/palatal	2	2,1	3	3,1	0	0,0	0	0,0
Distal	6	6,3	8	8,3	5	5,2	1	1,0
Total	96	100	96	100	96	100	96	100

adequate diet, health education, among others. When the child is born, it is advisable not to share eating utensils to reduce the bacterial load; when the first tooth appears, attend control according to cariogenic risk at least every six months, and appropriate oral hygiene techniques allow to maintain the oral cavity without diseases[8,9]. Adequate tooth brushing with fluoride toothpaste (500 ppm in children under seven years of age), at least twice a day[8], maintains a low and constant level of fluoride in the oral cavity, and in the long term determines lower levels of incidence and prevalence of dental caries at any age, being effective preventive strategies[8].

Conclusion

In reference to the diagnosis of oral health, the majority of the population in study suffers from dental caries, being a minority that keeps the oral cavity in optimal condition. The dmf-t score was considered high, and the most affected tooth surface is the occlusal.

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Letter to the editor

First human case of *Rickettsia felis* reported in Guatemala

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Dear Editor:

Rickettsia felis infection (*R. felis*) is considered a threat to human health. *R. felis*, a gram-negative bacterium considered an emerging arthropod-borne pathogen that has been identified in numerous human cases worldwide, represents an important cause of febrile illness, usually associated with *Ctenocephalides felis* found in cats and dogs[1]. Early clinical manifestations include fever, headache, myalgia, rash, cough and vomiting, which can mimic other febrile diseases such as dengue and malaria, thus complicating clinical diagnosis[1,2]. Severe, potentially lethal symptoms could be developed without treatment.

The sentinel surveillance of acute febrile diseases, through the Collaborative Integrated Surveillance that was developed in Guatemala from 2013 to 2018[3], allowed the discovery of the first case of *R. felis* in Guatemala. 612 patients who met the criteria of the case definition for acute febrile syndrome were chosen[3]: medical consultation or hospitalization for fever without apparent cause with less than seven days of evolution, or quantified fever greater than or equal to 38 °C during the consultation or during the first 24 hours of hospitalization. Blood samples were taken for the analysis of malaria, leptospirosis, dengue and rickettsiosis, which were processed in the laboratories of Universidad del Valle in Guatemala. The positive sample for *Rickettsia spp*. was analyzed by conventional polymerase chain reaction (PCR) for the detection of the rickettsial antigen gene 17 kDa, found in spotted fever group (SFGR) and typhus group *Rickettsia* DNA. Semi-nested amplification of 70–602 nucleotide fragment of rickettsial outer membrane protein (OmpA) gene was performed for identification of SFGR. Finally, the finding was confirmed by the Rickettsial Zoonoses Branch at U.S. Centers for Disease Control and Prevention, where *Rickettsia spp*. was confirmed by real time PCR using PanR8 assay and nested PCR targeting the SFGR 17 kDa gene. *R. felis* was identified by the sequencing of the SFGR 17 kDa amplification product.

The sample belonged to a three-year-old boy treated on December 2017 at a health center in Santa Rosa, Guatemala. At the time of sample taking, the patient reported two days of fever, cough, dyspnea, vomiting, abdominal pain and fatigue. It was reported as an exposure risk factor that his pet was a cat.

R. felis infection can cause an acute febrile syndrome with other symptoms[1]. In some cases, it is a mild illness without fever; also, isolated cases of children who had rashes or scabs have been registered[1]. Afebrile presentation also may contribute to non-detection[4].

The identification of this infection in febrile illness surveillance studies in Africa

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Primer caso humano de *Rickettsia felis* reportado en Guatemala

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and Asia suggests that it produces clinically relevant illness in individuals with immunosuppression[2].

The low availability of diagnostic tests is a limitation. Besides, since there is a cross-reactivity of serology among Rocky Mountain spotted fevers (RMSF), this makes it difficult to interpret the results, which limits the usefulness of the diagnosis[1]. Studies have shown serological evidence of a disseminated exposure to RMSF, coinciding with the isolation of *R. felis*[5]. Also, molecular testing gives a species-specific result, but sensitivity could decrease over time and treatment[1]. A high proportion of immunofluorescence assay cases never receive a definitive diagnosis.

Non-human mammals are the asymptomatic reservoirs. The paucity of reported human cases in Central America, despite ample documented evidence of *R. felis* in arthropod vectors, also suggests that the disease is being under-detected[5].

Given the known prevalence in the region of *R. felis* in fleas, human infections by *R. felis* are likely undiagnosed and may be among the causes of undifferentiated acute febrile illness (AFI). Molecular assays can distinguish between several species of *Rickettsia*, which allow a better characterization of these infections[4,5]. This finding points to consider *R. felis* as an etiology in the differential diagnosis of febrile patients with respiratory, digestive or non-specific symptoms that can guide appropriate treatment and medical care. Besides, potential risk factors such as proximity to animals that may be carriers of infected fleas should be evaluated[5].

Although only one case of *R. felis* was detected in this study, the actual burden in Central America could be underreported. It is considered important to propose that molecular laboratory techniques are accessible in the region to provide a better characterization of the burden of rickettsial diseases[4].

Despite the lack of a convalescent serum sample to confirm that the immune response matched the acute disease, the proximity to acute symptoms, the lack of another etiology after exhaustive testing, and the positive result in a trial with a high limit of detection, supported *R. felis* as the etiology of this child's febrile illness. Besides, there is a known prevalence of *R. felis* in domestic animals in the same geographic area and there are multiple febrile illness studies that are relevant sources of this acute illness in children in Africa and Asia.

Expanding surveillance would allow a better description of the distribution of rickettsial diseases in the population, with consequent improvements in the clinical management and treatment of these emerging infections. Therefore, greater awareness of the presentation and diagnosis of this pathogen in Central America is suggested, which may contribute to a more complete understanding of the true burden of these diseases in the region.

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