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

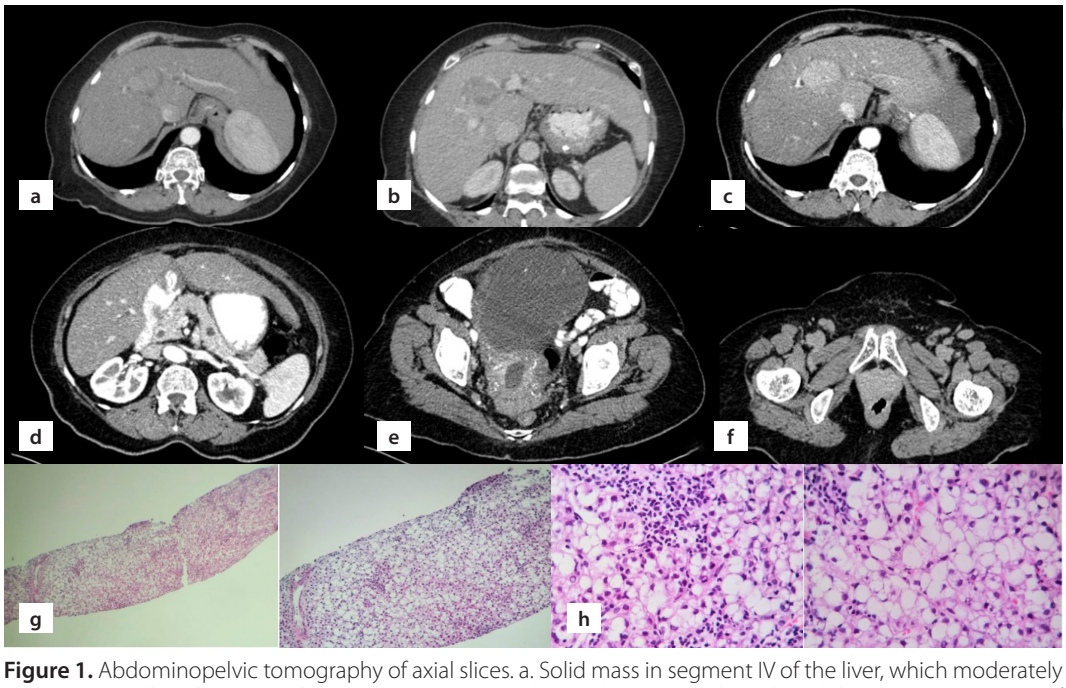

Figure 1. Abdominopelvic tomography of axial slices. a. Solid mass in segment IV of the liver, which moderately and centripetally enhances with intravenous contrast during the arterial phase. b. Solid mass in segment IV of the liver in the venous phase, hypodense is visualized in a heterogeneous way 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,

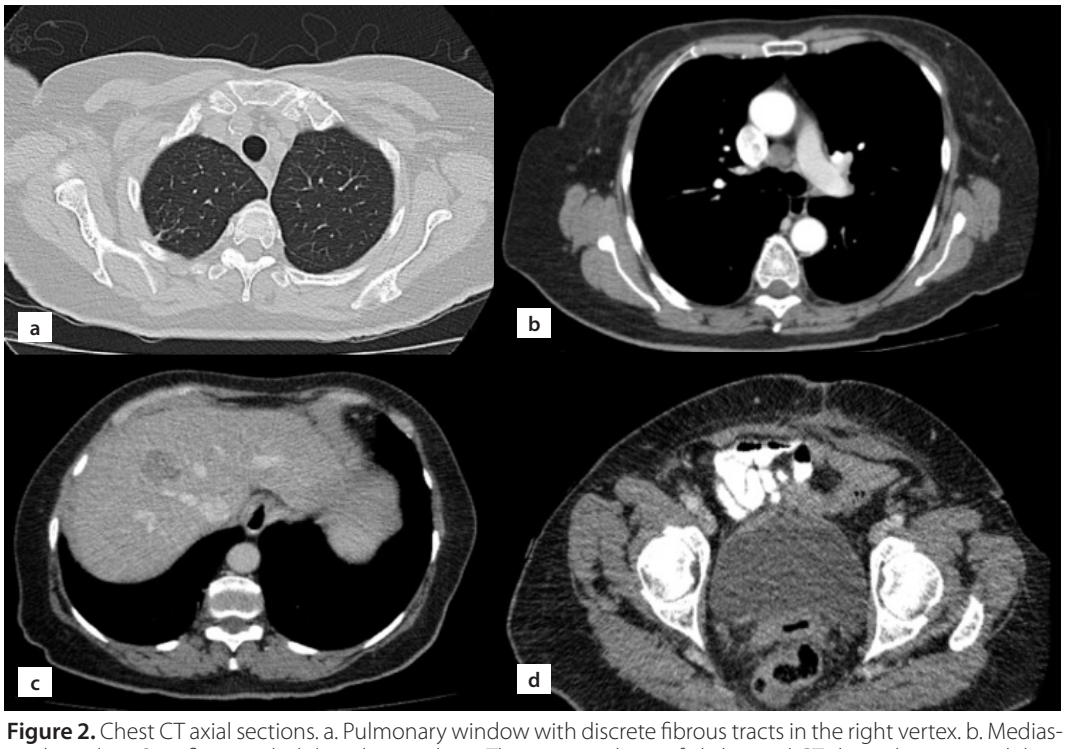

Figure 2. Chest CT axial sections. a. Pulmonary window with discrete fibrous tracts in the right vertex. b. Mediastinal window. Significant right hilar adenopathy. c. The venous phase of abdominal CT shows hepatic nodule in segment IV, suggestive of hepatocarcinoma. d. The venous phase of pelvis CT :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

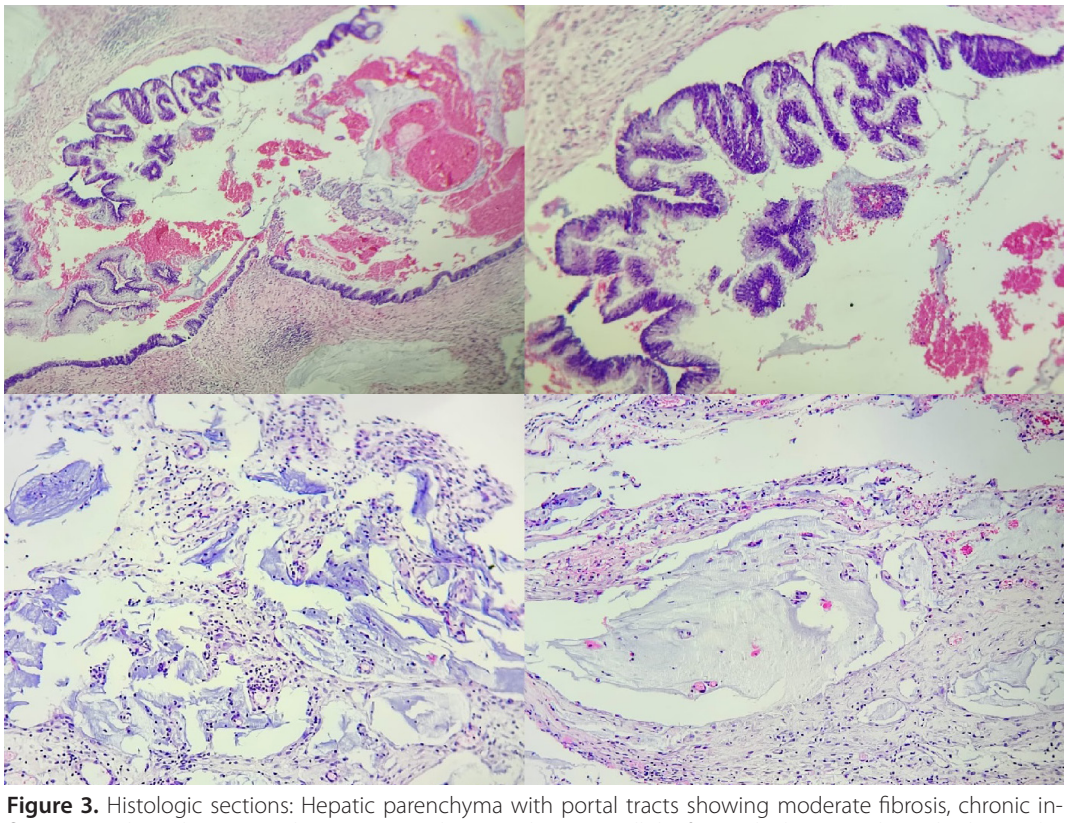

Figure 3. Histologic sections: Hepatic parenchyma with portal tracts showing moderate fibrosis, chronic inflammation; binucleations and regenerative changes. There are cellular foci with clear cytoplasm displacing the nucleus to the periphery, which present mild nuclear pleomorphism

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-

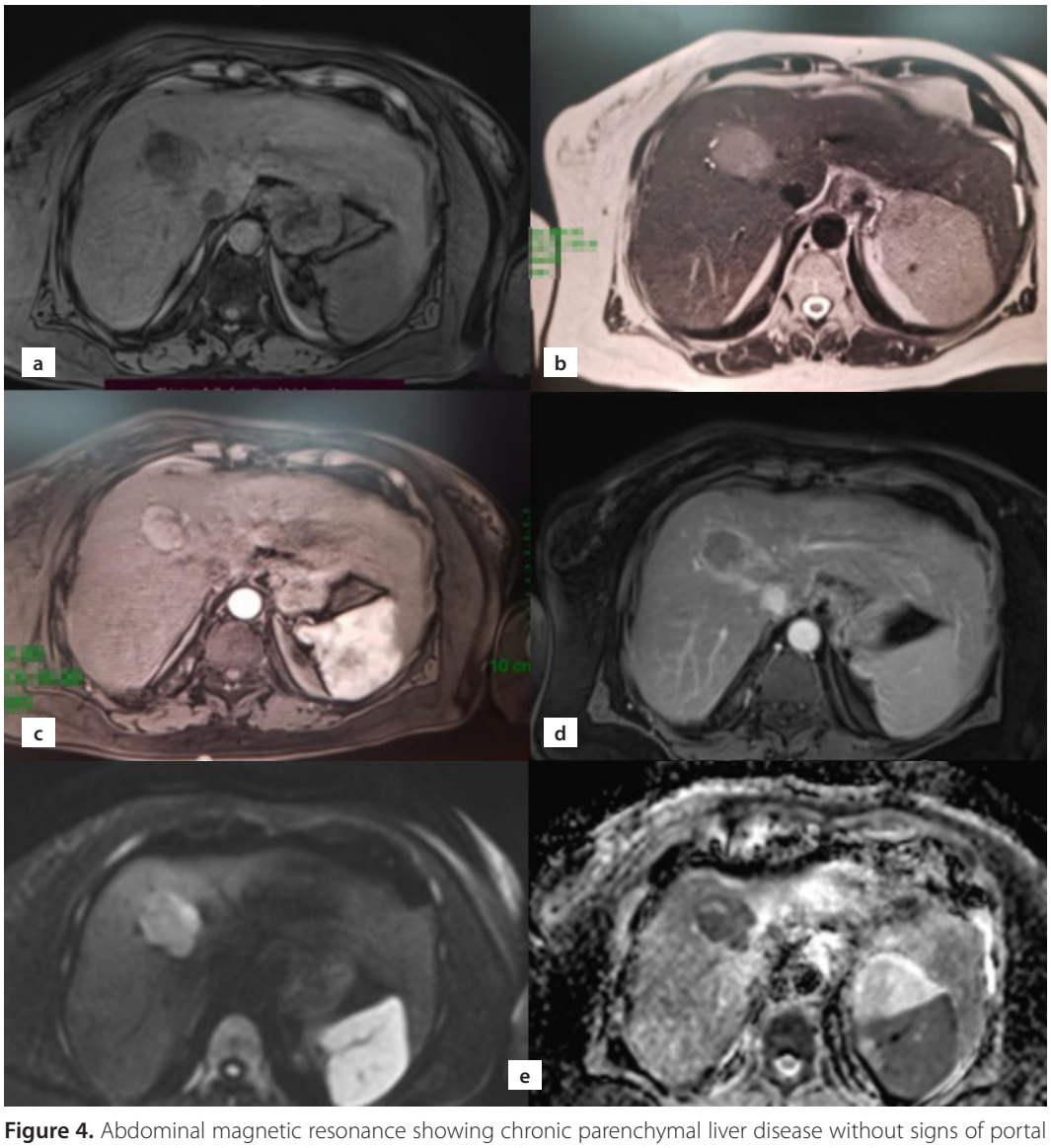

Figure 4. Abdominal magnetic resonance showing chronic parenchymal liver disease without signs of portal hypertension, nodular lesion in hepatic segment IV-a, hypointense behavior in T1-weighted sequences. a. Heterogeneously hyperintense in T2. b. Post-contrast dynamic phases with avid enhancement in 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

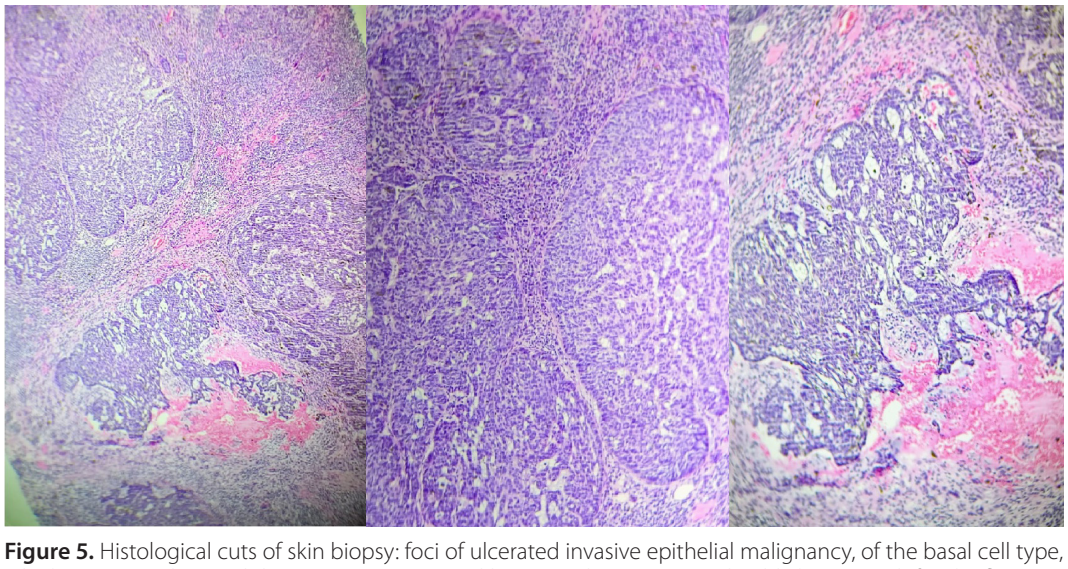

Figure 5. Histological cuts of skin biopsy: foci of ulcerated invasive epithelial malignancy, of the basal cell type, which is arranged in a solid pattern, accompanied by stromal retraction and mild chronic multifocal inflammatory infiltrate. Healthy surgical limits

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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