

Case report

Lhermitte-Duclos Disease and Cowden Syndrome. A Case Report

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Abstract

Case presentation. The report is of a 45-year-old female patient with a history of high blood pressure and multiple surgeries for cancer, including thyroid cancer, parotid carcinoma, breast cancer, and endometrial cancer. Incidentally, a lesion in the right cerebellar hemisphere was identified in a tomography of the paranasal sinuses, which was later confirmed in a brain magnetic resonance. The lesion had a striated appearance, characteristic of dysplastic gangliocytoma of the cerebellum or Lhermitte-Duclos disease. Considering the history of various types of cancer and the diagnostic criteria proposed by the International Cowden Consortium and the National Comprehensive Cancer Network, the diagnosis of Cowden syndrome, which had gone unnoticed until now, was established. **Treatment.** Subsequently, the patient was hospitalized due to the growth of a metastatic mass in the right hemicollar with involvement of the brachial plexus, cervical, infraclavicular, and right axillary lymph nodes. **Outcome.** She is receiving palliative treatment to control the symptoms and improve her quality of life, since she expressed her refusal to undergo tumor resection surgery.

Keywords

Lhermitte Duclos Disease, Incidental Findings, Diagnostic Imaging.

Resumen

Presentación del caso. Se trata de una paciente femenina de 45 años con antecedentes de hipertensión arterial y múltiples cirugías por cáncer, entre ellas, cáncer de tiroides, carcinoma de parótida, cáncer de mama y cáncer endometrial. De manera incidental se identificó una lesión en el hemisferio cerebeloso derecho en una tomografía de senos paranasales, que fue confirmada a través de una resonancia magnética cerebral. La lesión presentaba una apariencia estriada, característica de gangliocitoma displásico del cerebelo o enfermedad de Lhermitte-Duclos. Considerando los antecedentes de diversos tipos de cáncer y los criterios de diagnóstico propuestos por el Consorcio Internacional Cowden y la Red Nacional Integral del Cáncer, se estableció el diagnóstico de síndrome de Cowden que había pasado desapercibido hasta el momento. **Intervención terapéutica.** Posteriormente, la paciente fue hospitalizada debido al crecimiento de una masa metastásica en el hemicuello derecho con afectación del plexo braquial, adenopatías cervicales, infraclaviculares y axilares derechas. **Evolución clínica.** En la actualidad, se encuentra recibiendo tratamiento paliativo con el objetivo de controlar los síntomas y mejorar su calidad de vida, ya que expresó su negativa a someterse a una intervención quirúrgica de resección tumoral.

Palabras clave

Enfermedad de Lhermitte-Duclos, Hallazgos Incidentales, Diagnóstico por Imagen.

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There are no conflicts of interest.

Introduction

Lhermitte-Duclos disease (LDD), also known as dysplastic gangliocytoma of the cerebellum, is a rare condition first described by Lhermitte and Duclos in 1920. Since then, about 300 cases have been documented in the literature.ⁱ It is a slow-growing benign tumor composed of atypical ganglion cells.

According to the 2021 World Health Organization classification for the central nervous system, it is a grade I mixed glioneuronal tumor.ⁱⁱ It usually occurs in patients between 30 and 50 years of age, both sexes. Clinical symptoms are related to its location in the posterior fossa and may include headache, nausea, and visual problems.ⁱ⁻ⁱⁱⁱ

It is worth mentioning that this type of gangliocytoma can emerge in isolation or association with Cowden syndrome (CS), in up to 35 % of cases.ⁱⁱⁱ This syndrome is a rare multisystem disease characterized by multiple hamartomas in various tissues, particularly in the skin and mucous membranes, as well as in the gastrointestinal tract, breast, thyroid, and brain, resulting in a high risk of malignant neoplasms, especially in the breast, thyroid, and endometrium.^{iv} Cowden syndrome results from loss-of-function mutations in the phosphatase and tensin homologous tumor suppressor gene (PTEN), located on chromosome 10q23.^v It affects approximately one in 200 000 births, considered underestimated due to its variable penetrance.^{vi} As of 2018, only 44 patients had been identified in the literature.^{vii}

The diagnosis of Cowden syndrome is eminently clinical, based on the diagnostic criteria proposed by the International Cowden Consortium and the National Comprehensive Cancer Network (NCCN), which include mucocutaneous lesions and the presence of Lhermitte-Duclos disease, which is the primary established diagnostic criterion.^{viii,ix}

Case presentation

The case is of a 45-year-old female patient, who was treated for the past two years in endocrinology service at a tertiary public hospital in San Salvador, El Salvador. The patient had a history of previous interventions in private clinics and a peripheral public hospital for diagnoses of arterial hypertension and a history of several types of metachronous neoplasms without genetic evaluation, including thyroid cancer, with thyroidectomy 14 years ago, developing hypothyroidism and secondary

hypoparathyroidism; epidermoid carcinoma of the right parotid gland with complete resection 12 years ago; invasive micropapillary carcinoma of the right breast, with right mastectomy seven years ago, and endometrial cancer, with a hysterectomy five years ago. The patient received daily treatment with levothyroxine sodium 50 µ, calcium carbonate 1800 mg, vitamin D3 0.25 µ, irbesartan 150 mg, and propranolol 40 mg, all administered orally.

During a routine follow up, the patient reported nasal obstruction and occasional headache, with no other relevant symptoms. On physical examination, the patient presented good general condition, vital signs were within normal parameters, with a blood pressure of 120/70 mmHg, heart rate of 85 beats per minute, respiratory rate of 16 breaths per minute, body temperature of 36.4 °C, and blood oxygen saturation of 98 %. No pathological secretions were found inside the nasal cavities, neither pain on facial palpation, nor neurological alterations.

Laboratory test results (Table 1) showed low thyroid-stimulating hormone levels and elevated free thyroxine levels therefore, the dose of levothyroxine sodium was adjusted, decreasing it to 25 µ compared to the previous dose of 50 µ. In addition, the usual medications to control the associated pathologies were maintained.

The tomographic study of the paranasal sinuses showed signs of adequate pneumatization of the paranasal sinuses and nasal cavities, with no evidence of mucosal thickening or pathologic occupation of the sinuses. Incidentally, an ill-defined hypodense lesion was identified in the right cerebellar hemisphere, without specific features, which did not cause a significant mass effect on the surrounding structures

Table 1. Laboratory exams

Exams	Routine evaluation results	Results at the six-month evaluation	Reference values
Thyroid stimulating hormone	0.21 UI/mL	0.81 UI/mL	0.34 - 5.60 UI/mL
Free thyroxine	1.33 ng/dL	1.59 ng/dL	0.61 - 1.12 ng/dL
Antithyroglobulin	0.00 UI/mL	-	0.00 - 115.00 UI/mL
Thyroglobulin	5.11 ng/mL	-	3 - 42 ng/mL
Calcium	8.44 mg/dL	5.39 mg/dL	8.5 - 10.2 mg/dL
Hemoglobin	-	10.00 g/dL	12 - 16 g/dL
White blood cells	-	11.20 × 10 ³ /µL	5 - 10 × 10 ³ /µL
Platelets	-	328 × 10 ³ /µL	150 - 400 × 10 ³ /µL

Source: Data obtained from clinical records.

(Figure 1). Due to this finding, the Radiology Service recommended complementing with brain magnetic resonance imaging (MRI). Brain MRI (Figure 2 and 3) confirmed the presence of an intraaxial lesion in the right cerebellar hemisphere, with ovoid morphology, regular contours, and striated configuration with alternating hypo- and hyperintense bands in T2-weighted sequences. There was no perilesional edema or mass effect over the fourth ventricle. In addition, it showed a T2 pattern in diffusion sequences, and following intravenous contrast administration, there was a slight peripheral enhancement and punctate areas of intratumoral enhancement with dimensions of 22.3 x 38.8 x 21.8 mm in its dorsoventral, laterolateral, and rostrocaudal axes. Multivoxel spectroscopy showed reduced N-acetyl aspartate and the presence of an inverse lactate peak. These findings were compatible with right cerebellar dysplastic gangliocytoma or Lhermitte-Duclos disease diagnosis.

This finding, assessed in combination with the patient's history, and based on the NCCN guidelines for the diagnosis of Cowden syndrome, allowed the identification of and compliance with the main criteria, such as breast cancer, thyroid tumor, uterine cancer, and Lhermitte-Duclos disease. In addition, the presence of multiple forehead papules compatible with trichilemmomas, intentionally identified, corresponds to another relevant criterion in the patient.

Therapeutic intervention

The patient remained asymptomatic; though, six months after diagnosis, she consulted for a right hemicollar mass of progressive growth, accompanied by edema, paresthesias, and progressive paralysis in the right upper limb. The patient denied any other symptoms. On physical examination, the mass showed a solid consistency, firm to the touch with adherence to deep planes, measuring approximately 4 x 3 cm. In addition, the right upper limb showed a loss of muscle strength. Hospital admission was indicated.

Laboratory tests showed normal thyroid stimulating hormone and free thyroxine values, low calcium, hemoglobin levels as well as mild leukocytosis (Table 1).

During the hospitalization, an ultrasound was performed, which reported a heterogeneous mass in the right supra-clavicular region, as well as multiple cervical, infra-clavicular, and right axillary lymphadenopathies. As a result, an MRI of the neck and brachial plexus was ordered (Figure 4), which



Figure 1. Single phase computed tomography study. Axial section of the posterior fossa in brain tomographic window. There is evidence of hypodense lesion in the right cerebellar hemisphere, with ovoid morphology, non-homogeneous appearance. There is no significant mass effect on the fourth ventricle, nor calcifications inside it

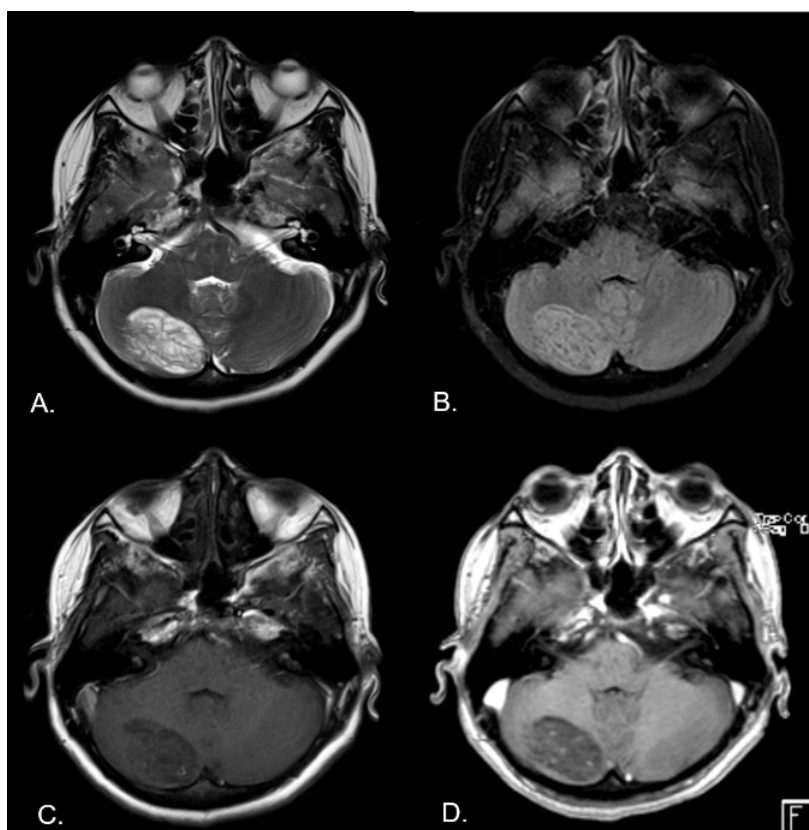


Figure 2. Brain magnetic resonance images. Axial sections of posterior fossa with T2-weighted sequences (A), FLAIR (B) T1 in single phase (C) and T1 postcontrast. Well-defined intraaxial lesion in the right cerebellar hemisphere. The lesion is mainly hyperintense on T2-weighted and FLAIR sequences (A and B), with a striated appearance, with alternating hyperintense and hypointense bands in relation to the adjacent gray matter. On T1-weighted images (C) it presents hypointense to isointense striations in the gray matter. After intravenous contrast administration (D), there is a slight peripheral enhancement and punctate areas of intratumoral enhancement. There is no evidence of vasogenic edema or local mass effect associated with the lesion

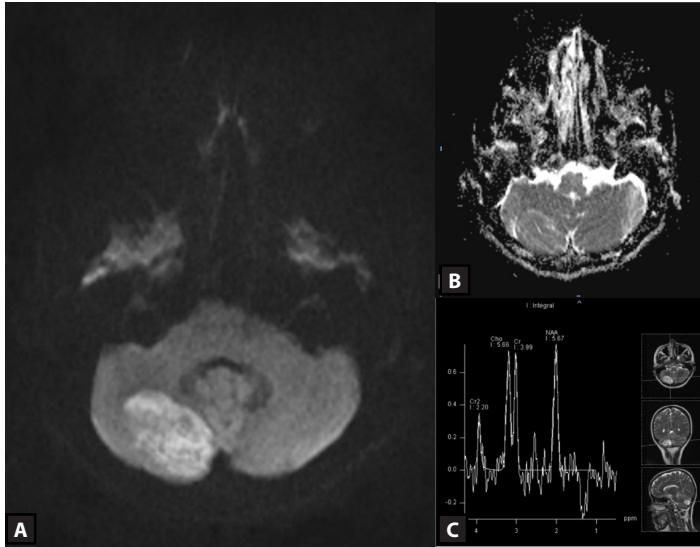


Figure 3. Brain magnetic resonance images. Diffusion sequences (A), ADC mapping (B) and long TE multivoxel spectroscopy, 135 ms (C). The cerebellar lesion shows a T2 effect in the diffusion sequences and ADC mapping (A and B), without areas of restrictive pattern. Multivoxel spectroscopy shows a reduction of N-acetylaspartate and the presence of an inverted lactate peak

confirmed the presence of the mass in the right supraclavicular region, infiltrating the brachial plexus and the ipsilateral scalene, trapezius, and shoulder girdle muscles, with muscle atrophy and the presence of cervical and right axillary lymphadenopathy. The mass biopsy confirmed the presence of a malignant epithelial neoplasm arranged in nests and cords infiltrating the stroma. Immunohistochemistry analysis with breast panel reported estrogen receptor-positive in 90 % of screened cells, progesterone receptor positive in 60 % of cells, HER2: negative (+/+++), and P53: positive in 1 % of cells. Ki67: negative. The findings could correspond to metastasis from breast cancer.

Clinical evolution

The patient was discharged from the hospital 11 days after admission, since she expressed her refusal to undergo surgery for tumor resection. At her last medical follow-up, palliative treatment was prescribed to control her symptoms and improve her quality of life. The patient continued with medications for the underlying chronic conditions and tramadol 50 mg orally indicated every eight hours for pain management.

Due to the autosomal dominant inheritance pattern of this disease, genetic counseling was provided to family members, informing them about Cowden syndrome, its clinical features, and the different associated tumors. The relevance of regular medical follow-up was emphasized, including periodic evaluations and specific screening tests according to established guidelines.

Clinical diagnosis

Lhermitte-Duclos disease in association with Cowden's syndrome (COLD syndrome).

Discussion

Lhermitte-Duclos disease is a rare, slow-growing hamartomatous lesion of the cerebellar cortex. Its main characteristic is the presence of dysplastic rather than neoplastic cells in the cerebellum.¹ It occurs most frequently in the third and fourth decades of life. However, it can manifest at any time from birth to the sixth decade.^{1x}

The nature and pathogenesis of LDD are still a matter of debate. Histologically, it is characterized by abnormal thickening and myelination of the molecular layer in the cerebellum, attenuation or absence of Purkinje cells, infiltration of the granular cell layer by abnormal dysplastic ganglion cells, and variability in white matter vacuoliza-

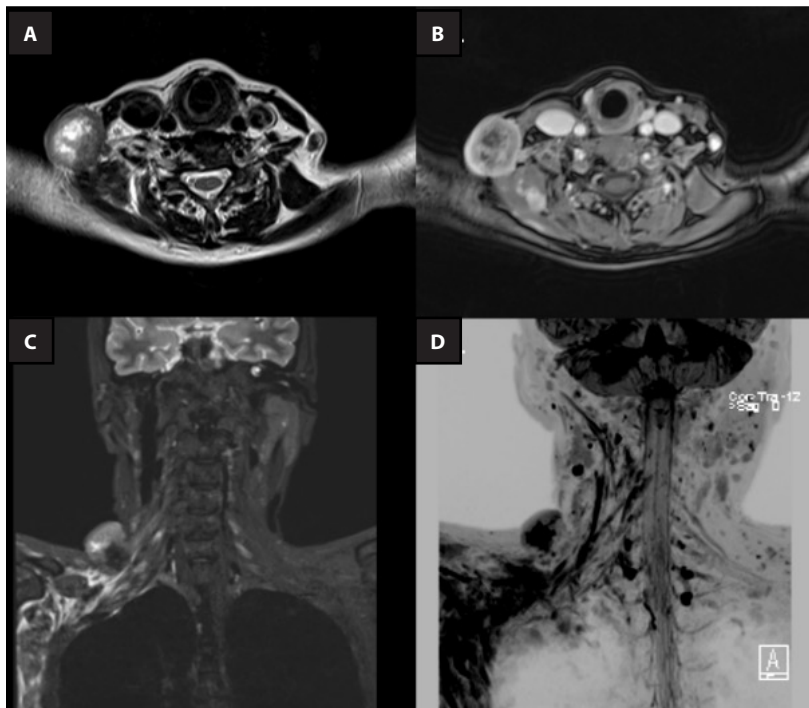


Figure 4. Magnetic resonance images of neck and brachial plexus. Axial sections of T2-weighted sequences (A), post-contrast T1 (B), oblique coronal section T2 SPACE / STIR sequence, coronal section of T2 SPACE / STIR 3D-MIP inverted grayscale sequence (C). A right supraclavicular solid mass is identified with irregular borders and heterogeneity in the T2-weighted sequence, showing a hyperintense center and heterogeneous enhancement after intravenous contrast administration, with central necrosis area. It infiltrates the deep tissues and roots of the brachial plexus. Brachial plexus trunks and fascicles show nodular thickening and alterations in signal intensity on T2/STIR sequence, and show enhancement after intravenous contrast administration. In addition, multiple cervical, infraclavicular and axillary adenopathies are observed on the right side (A-D). These findings are associated with atrophy and diffuse hyperintensity of the trapezius, scalene, as well as supraspinatus and infraspinatus muscles on the right side, with enhancement in relation to denervation (not shown)

tion. These histological findings are hallmarks of the disease.^{vii}

Characteristic symptoms include cranial nerve palsy, gait instability, ataxia, and sudden neurological deterioration due to acute or chronic hydrocephalus.^x The severity of symptoms can vary depending on the volume of the lesion.ⁱⁱⁱ As the tumor grows, signs of increased intracranial pressure may occur, such as headaches, nausea, vomiting, papilledema, mental disorders, and loss of consciousness. The duration of symptoms varies from a few months to more than ten years. Moreover, the tumor may present asymptotically and be discovered incidentally during imaging studies.^{xi}

Radiology plays an essential role in the diagnosis of ELD.^{iii,x-xiv} MR is preferred over computerized tomography for evaluating the posterior fossa because of its ability to provide detailed soft-tissue imaging and perform specialized sequences that provide additional information on the structure and function of the cerebellum and brainstem. On computerized tomography, it is seen as a hypo-attenuated or iso-attenuated cerebellar mass adjacent to the normal cerebellum, without contrast uptake, and calcifications may be present.^{xxi}

On MR images, it is observed that in T1-weighted sequences there is a hypointense signal, while in T2-weighted sequences there is an alternating pattern of high and low signal with a classic striated appearance similar to "tiger stripes."^{xi-xiv} These radiological findings correlate with pathological changes where the central core of the T1 hypointensity and T2 hyper-intensity corresponds to thinned white matter, widening of the granular cell layer and the inner portions of the dysplastic molecular layer. The outer layer (T1 isointense, T2 iso to hypointense) is attributed to the outer molecular layer and leptomeninges. On susceptibility sequences, abnormal vessels and areas of calcification can be observed.^x

In special MR sequences, specifically in diffusion sequences, a T2 effect is evident in the abnormally thickened leaflets. In spectroscopy, a decrease in N-acetylaspartate and an increase in lactate are detected, which are characteristic features.^{x-xii} Finally, on perfusion imaging, elevated local perfusion is usually observed.^{viii}

In this case, the cerebellar lesion identified on MR showed the typical appearance described in the medical literature, which was relevant to reach the diagnosis.

LDD and CS are related since approximately 35 % of patients with CS characteristically present cerebellar dysplastic gangliocytoma.ⁱⁱⁱ This connection has led it

to be known as Cowden-Lhermitte-Duclos syndrome (COLD syndrome).ⁱⁱⁱ Detection of one of these disorders may require further evaluation and follow-up.

Cowden syndrome (also known as Cowden disease or multiple hamartoma syndrome, OMIM 158350) is a rare genetic disorder with a highly variable autosomal dominant pattern of inheritance. It was first described in 1963 by Lloyd and Dennis in a patient named Rachel Cowden.^{vi,xv} Its characteristics are the presence of multiple hamartomas of ectodermal, mesodermal, and endodermal origin.^{vii} Loss of PTEN gene function contributes to benign hamartomatous tissue overgrowth, especially in the skin and mucous membranes, as well as in the gastrointestinal tract, breast, thyroid, and brain, thus increasing the risk of malignant neoplasms, especially breast cancer, thyroid cancer, and uterine cancer.^{iv} It is a typical young adult disease, presenting in the second or third decade of life, with an average age at diagnosis of 39 years (between 40 to 75 years). It is slightly more common in women.^{xv}

In 1997, it was discovered that CS is related to mutations in the PTEN gene, present on chromosome 10q23.^{xv} Approximately 80 % of patients have an identifiable mutation in this gene. PTEN is a tumor suppressor gene that encodes a phosphatase and negatively regulates the PI3K/AKT and mTOR signaling pathways. It controls cell proliferation, cell cycle progression, and apoptosis. Loss of PTEN function contributes to cellular transformation and increases the risk of developing cancer in multiple organs.^{iv,xv}

Benign manifestations include multiple gastrointestinal polyps (93 %, with 44 % as hamartomas), dermatological features (98 %), macrocephaly (93 %), benign breast lesions (74 %), thyroid lesions (71 %) and vascular malformations (18 to 35 %).^{xvi} Patients have a lifetime risk of breast cancer (85 %), thyroid cancer (38 %), endometrial cancer (28 %), colorectal cancer (9 %), and melanoma (6 %).^{vi,xv}

The updated diagnostic criteria for CS were developed by Pilarski *et al.* in 2013,^{viii} and recognized by the National Comprehensive Cancer Network. According to the NCCN guidelines (Table 1),^{viii,ix} the diagnosis is based on the presence of a pathogenic/likely pathogenic variant in the PTEN gene and, or specific clinical criteria: three or more major criteria (one of which must be macrocephaly, ELD or gastrointestinal hamartomas) or two major and three minor criteria.

These guidelines recommend imaging surveillance in patients with CS for early detection of possible cancers, allowing timely

resection of neoplasms.^{ix} This intentional screening approach aims to identify and treat any malignancy early, thus improving prognosis and clinical outcomes in patients.^{xv}

The recommended treatment for LDD is observation with symptom control unless mass effect symptoms are sufficiently problematic to warrant surgery. Complete surgical resection is associated with low recurrence rates.ⁱⁱⁱ However, during surgery, the main technical challenge is the lack of a clear margin between the tumor and normal brain tissue. Complete resection of the lesion is difficult due to the slow growth of the tumor and diffuse boundaries with the adjacent cerebellum.^x Intraoperative ultrasound has been described as a useful tool for real-time evaluation during neurosurgical operations.^{xiv}

Ethical aspects

In the case presented, the patient's confidentiality was respected and the informed consent of the person responsible for the patient was obtained.

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