Cowden syndrome diagnosed by Lhermitte–Duclos disease

Yuan-Shao Chen, Yoon Bin Chong, Chih-Hung Lin, Ann-Shung Lieu
Department of Surgery, Division of Neurosurgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

Abstract
Cowden syndrome (CS) is a rare genetic disease which puts patients at an increased risk of developing mucocutaneous lesion, multiple hamartomas, breast cancer, thyroid cancer, and Lhermitte–Duclos disease (LDD). This article reviews the role of LDD in the diagnosis of CS. It is important for all clinicians to identify these patients due to the high risk of other associated malignancies.

Keywords: Cowden syndrome, dysplastic cerebellar gangliocytoma, Lhermitte–Duclos disease

INTRODUCTION
Cowden syndrome (CS) is mostly related to the mutation of phosphatase and tensin homolog (PTEN) gene, a tumor suppressor gene on chromosome 10. CS was first noted by Lloyd and Dennis in 1962 when a 20-year-old female presented with breast tumor, thyroid tumor, brain tumor, and oral mucosal papillomatosis, and her family history revealed similar diseases.[1] CS is a spectrum of disease which consists of breast tumor, thyroid tumor, oral mucosal papillomatosis, and Lhermitte–Duclos disease (LDD). LDD is also referred to as a dysplastic cerebellar gangliocytoma which is a rare genetic disease first introduced by Lhermitte and Duclos in 1920.[2] It is typically characterized by a unilateral slowly enlarging hamartomatous mass arising from the cerebellar cortex and is often associated with CS. Thus, we present a patient diagnosed with CS after LDD was previously noted.

CASE REPORT
A 39-year-old female was initially diagnosed with left breast tumor, and then, she underwent left nipple-sparing and skin-sparing mastectomy with sentinel lymph node dissection. The pathology report confirmed the diagnosis of left breast invasive ductal carcinoma (pT2N0M0, stage: 2A, ER[+], PR[+], HER2[−], and Ki-67[10%]). Postoperative therapy included chemotherapy and hormone therapy with tamoxifen. She also had a nontoxic multinodular goiter, multiple cavernous hemangiomas in the liver (S4, S6, and S7), and arteriovenous malformation in her right upper back. Tracing back the patient’s medical history, she underwent resection surgery for the hemangioma on her back. Her family history was inconspicuous concerning CS and neurological syndromes. Approximately 5 months later during a follow-up, she presented with severe dizziness and headache. She denied nausea and vomiting, unsteady gait and ataxia, visual disturbances, nor vertigo. The neurological examination did not demonstrate any cerebellar sign. Magnetic resonance imaging (MRI) of the brain showed a 3.8-cm mass in the right cerebellar hemisphere [Figure 1]. The patient underwent right suboccipital craniectomy for the near-total resection of the lesion. Histopathological evaluation suggested a glioneuronal origin which was consistent with dysplastic cerebellar gangliocytoma [Figure 2] and

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compatible with the previous radiographic diagnosis. Subsequent testing of PTEN mutation was negative result. The postoperative course was uneventful. She recovered very well and was discharged later on.

Further investigations for additional clinical features related to CS proceeded. Thorough inspection and examination of the whole body were carried out. Multiple trichilemmomas were noticed over her face and both hands. Computed tomography showed multiple thyroid nodules bilaterally and arteriovenous malformation in her right posterior neck and right upper back. Fine-needle aspiration of the thyroid mass revealed benign colloid cystic goiter. Three major criteria (breast cancer, LDD, and multiple mucocutaneous lesions) and two minor criteria (thyroid structural lesions and vascular anomalies) of the revised diagnostic criteria were fulfilled which were sufficient to make the diagnosis of CS. To date, no symptom and sign indicating the recurrence of LDD has been observed during the subsequent 2 years of follow-up.

**DISCUSSION**

LDD was first introduced by Lhermitte and Duclos in 1920. Many researchers had also described different cases and strived to clarify the fundamental nature of this highly unusual entity inclusive of the first surgical attempt by Bielschowsky and Simons in 1930, the first successful surgery performed by Christensen in 1937, Duncan and Snodgrass in 1943, and the first familial cluster of LDD reported by Ambler in 1969. Padberg pointed out the coexistence of LDD and CS in 1991. In 1996, the International Cowden Consortium proposed a set of operational diagnostic criteria in which LDD was included as a major criterion. CS is an autosomal dominant inherited hamartomatous syndrome, mostly caused by the mutation of PTEN gene, a tumor suppressor gene. Hamartomas can be the characteristic mucocutaneous lesions on the skin (papillomas and trichilemmomas) and mucous membranes (mouth, nose, and gastrointestinal tract) or the other parts of the body such as thyroid and breast. CS is also associated with macrocephaly and increased risk of developing cancers of the breast, thyroid, endometrium, and kidney. Recently, LDD is considered to be a part of CS as a true single phakomatosis spectrum in a variety of investigations. Robinson and Cohen put forward a new phakomatosis named “Cowden and Lhermitte–Duclos disease complex” in 2000. In 2013, Pilarski included additional clinical features and set forth revised diagnostic criteria to increase the positive predictive value. The reported PTEN mutation rates ranged widely from 11% to 81% in early studies before 2000 which were considered inaccurate. More recently, in much larger cohort studies in 2011, PTEN mutations had only been found in 30%–35% of patients meeting consortium criteria. Moreover, genetic changes involving succinate dehydrogenase complex subunit B (SDHB) and subunit D (SDHD) and KLLN genes could also lead to CS. Despite a plenty of studies had been carried out, the exact etiology and pathogenesis of LDD remain unknown.

The patients can be asymptomatic at first. As the tumor grows larger, they frequently demonstrate the symptoms of increased intracranial pressure, cerebellar ataxia, upper limbs ataxia, dysmetria, visual disturbances, and cranial nerve palsies resulting from the mass effects in the posterior
fossa as well as the symptoms of occlusive hydrocephalus. LDD mostly presents in the 3rd–4th decade of life, but the age of onset can range from birth to the 6th decade. There is no obvious sex preponderance.[3,4] To date, >220 cases of LDD have been reported in the literature.[2]

MRI is certainly the diagnostic modality of choice today. It revealed the lesion to be a cortical origin with a distinct gyriform pattern corresponding to the enlarged and thickened but preserved cerebellar folia. The lesions are hypointense on T1-weighted images with rare enhancement following the injection of gadolinium-diethylenetriamine pentaacetic acid. On T2-weighted images, they demonstrate well-circumscribed hyperintense lesions with alternating isointense bands among which turn out to be the characteristic “tiger-stripped” appearance. MR spectroscopy (MRS) revealed elevated lactate, decreased myo-inositol, N-acetylaspartate, and choline.[7] Nagaraja recounted the MRS findings of two patients demonstrating reduced ratios of both N-acetylaspartate/choline and N-acetylaspartate/creatine in relation to the controls. Peaks attributed to lactate were also present. The low ratios could result from the apparent lack of neuronal architecture and the presence of embryonic neural tissue which does not express N-acetylaspartate, indicating the hamartomatous nature of the lesions.[8]

Derangement of the normal laminar organization of the cerebellar cortex is presented with the central white matter reduced greatly. Thickening of the outer molecular layer, loss of the middle Purkinje cell layer, and expansion of the internal granular layer are also noted. The principal histopathological abnormality is the massive expansion of the internal granular layer occupied densely by hypertrophied neurons with vesicular nuclei and prominent nucleoli. The molecular layer is broadened by abundant, enlarged and irregularly myelinated axons which belong to the abnormal hypertrophied neurons, composing the internal granular layer. Calcareous deposits are frequently seen in the molecular layer associated with capillary-sized blood vessels.[2] The immunohistochemistry of dysplastic ganglion cells reveals positive staining for synaptophysin. The absence of mitotic figures and the lack of proliferation activity in staining with monoclonal antibodies to proliferating cell nuclear antigen, measuring cell DNA index, and ploidy with a cell image analyzer all indicate the benign character of LDD instead of neoplasm.[9]

Surgical resection is preferable and often curative for symptomatic patients. Complete remission can be achieved compared to the poor outcome of the patients not surgically treated. Only a few cases of recurrence after total resection were reported.[10] The prognosis of the patients with LDD has improved significantly with the tremendous advances of surgical techniques and modern neuroimaging.

LDD is a rare disease entity. It can be an isolated condition or associated with CS. Thus, patients with LDD, oral papillomatosis, extreme macrocephaly, gastrointestinal polyps, and penile freckling often prompt surgeons to suspect the coexistence of CS. It is very important for a surgeon to identify these patients and proceed other cancer screening for them and family members due to the high risk of other associated malignancies, as it can facilitate the early detection and prompt treatment.

Ethical approval
This study was approved by the IRB of Kaohsiung Medical University Chung-Ho Memorial Hospital, approval no. KMUHIRB(E)-I-20190278 obtained on October 17, 2019.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Mester J, Eng C. Cowden syndrome: Recognizing and managing a not-so-rare hereditary cancer syndrome. J Surg Oncol 2015;111:125–30.
2. Nowak DA, Trost HA. Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma): A malformation, hamartoma or neoplasm? Acta Neurol Scand 2002;105:137–45.
3. Eng C. Will the real Cowden syndrome please stand up: Revised diagnostic criteria. J Med Genet 2000;37:828–30.
4. Robinson S, Cohen AR. Cowden disease and Lhermitte-Duclos disease: Characterization of a new phakomatosis. Neurosurgery 2000;46:371–83.
5. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607–16.
6. Rainbow NG, Holzhauzen HJ, Burkett W. Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease). Clin Neurol Neurosurg 1995;97:175–80.
7. Klisch J, Juengling F, Spreer J, Koch D, Thiel T, Büchert M, et al. Lhermitte-Duclos disease: Assessment with MR imaging, positron emission tomography, single-photon emission CT, and MR spectroscopy. AJNR Am J Neuroradiol 2001;22:824–30.
8. Nagaraja S, Powell T, Griffiths PD, Wilkinson ID. MR imaging and spectroscopy in Lhermitte-Duclos disease. Neurology 2004;63:355–8.
9. Hair LS, Symmans F, Powers JM, Carmel P. Immunohistochemistry and proliferative activity in Lhermitte-Duclos disease. Acta Neuropathol 1992;84:570–7.
10. Kulkantrakorn K, Awwad EE, Levy B, Selhorst JB, Cole HO, Leake D, et al. MRI in Lhermitte-Duclos disease. Neurology 1997;48:725–31.