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Case report

Lhermitte-Duclos Disease in association with Cowden Syndrome

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Abstract

Cowden syndrome (CS) is a rare genetic disorder with autosomal dominant inheritance, linked to germline mutations in the PTEN tumor suppressor gene on chromosome 10. Cowden syndrome often co-exists with Lhermitte–Duclos disease (LDD), with LDD included as a major criterion in CD diagnosis. This case involves a woman presenting with many of the classic diagnostic criteria and associations of CD, as well as with several comorbidities and unique objective findings.

Keywords: Cowden syndrome, Lhermitte-Duclos disease, verrucous keratoses

Introduction

Cowden syndrome (CS) is a rare genetic disorder with autosomal dominant inheritance [1], linked to germline mutations in the PTEN tumor suppressor gene on chromosome 10 [2]. Initially considered a mainly dermatologic disease, over time, the phenotypic spectrum has broadened to include neurological and cancer disorders. Notably, Cowden syndrome often co-exists with Lhermitte–Duclos disease (LDD). Lhermitte-Duclos disease is a non-neoplastic mass composed of cerebellar folia expanded by hypertrophic neurons of the internal granule cell layer and is now included as a major criterion in Cowden syndrome diagnosis by the International Cowden syndrome Consortium [8]. We describe a woman with many of the classic diagnostic criteria and associations of Cowden syndrome, as well as with several comorbidities and unique objective findings.

Case Synopsis

A 47-year-old woman with a significant past medical history of Cowden syndrome, complicated by breast cancer and a benign cerebellar hamartoma, presented to the clinic with a five-year history of a pruritic eruption bilaterally over her hands and feet and asymptomatic “bumps” on her cheeks and jawline since her mid-20s. The patient was seen by a member of the genetic counseling team several years prior and the diagnosis of Cowden syndrome was confirmed through DNA analysis of the PTEN gene. The final report showed a nonsense mutation of the PTEN gene.

The patient's surgical history was significant for bilateral mastectomy with reconstructive breast implants inserted, right salpingo-oophorectomy and left salpingectomy, and prophylactic thyroid removal. Family history included Cowden syndrome without brain involvement in her mother. The patient described an array of pertinent neurological review of systems positives including dizziness, tremors, speech difficulty, weakness, light-headedness, numbness, headaches, confusion, decreased sleep, agitation, and anxiety.

Radiological imaging of the cerebellar lesion was first performed at an outside hospital. The lesion was diagnosed as a benign gangliocytoma of the cerebellum classified as WHO stage I (Figure 1). The patient was asymptomatic and conservative management was recommended. Given the specificity of the cerebellar lesion in association with known Cowden syndrome, the patient was further diagnosed with Lhermitte-Duclos disease in association with Cowden syndrome. A neurosurgery consultant ultimately recommended conservative management with annual follow-up as long as the patient remained asymptomatic.



Figure 1. Axial T2 hyper-intensity within the medial right cerebellar hemisphere with prominent cerebellar folia, consistent with cerebellar gangliocytoma.

Dermatologic exam revealed verrucous papules and plaques of bilateral palmar hands (Figure 2) and left medial foot (Figure 3). Flesh-colored papules were present bilaterally on her cheeks and jawline (Figure 4).



Figure 2. Verrucous papules and plaque of R palmar hand **Figure 3.** Verrucous papules of the left medial foot. **Figure 4.** Flesh-colored papules on the cheek and jawline

A well-healed scar was also evident on the anterior neck corresponding to the site of her thyroidectomy scar (Figure 5).



Figure 5. Prophylactic thyroidectomy scar over the anterior neck

Clinical differential diagnosis of the palmoplantar lesions originally included verruca vulgaris, but was narrowed to palmoplantar verrucous keratosis in association with Cowden syndrome. The flesh-colored papules on her cheeks were consistent with trichilemmomas. Liquid nitrogen was utilized initially for the destruction of the palmoplantar keratoses using a pair of 10-second

treatments on each lesion. Upon follow-up with residual keratosis, topical 40% urea cream was prescribed and utilized successfully. The patient was not bothered by the trichilemmomas and chose not to pursue treatment. Given the diagnosis of Cowden syndrome with Lhermitte-Duclos disease, our patient continues to be followed by the Neurosurgery service. Surgery was not indicated for the stable gangliocytoma of the cerebellum.

Discussion

Cowden syndrome (CS) is a dominantly inherited multi-system disorder characterized by hamartomas across many tissues, which increase the risk of developing benign and malignant lesions [1-5]. The International Cowden syndrome Consortium defined the most updated criteria for diagnosis of Cowden syndrome in 2000. These criteria include the mucocutaneous lesions as well as major criteria like breast/thyroid carcinomas or macrocephaly and minor criteria including thyroid lesions, lipomas, or fibromas (table 1) [5-8].

Table 1. Diagnosis of Cowden Syndrome

<u><i>Pathognomonic Criteria</i></u>	<u><i>Major Criteria</i></u>	<u><i>Minor Criteria</i></u>
Trichilemmomas	Macrocephaly	Lipomas
	Lhermitte-Duclos disease	Fibromas
Association with: cutaneous facial papules, oral papillomas acral keratoses	Breast Cancer	Mental Retardation (IQ<75)
		GU tumors or malformations
	Thyroid Cancer	Fibrocystic disease of the breast
		Multi-nodular goiter
		Thyroid Lesions

In 1991, Padberg recognized that Lhermitte–Duclos disease (LDD) is strongly associated with Cowden syndrome [5-7]. The number of cases associating LDD with Cowden syndrome is probably underestimated, as this association is often misdiagnosed [5-7]. Thus an exact number describing their relationship remains unclear. However LDD is now included as a major criterion in Cowden syndrome diagnosis [8].

The identification of the *PTEN* gene in 1997 led to the ability to molecularly define the syndrome. The gene, located at chromosome 10q23-3, is a tumor suppressor gene that encodes a protein with phosphatase activity [6-8]. The percentage of *PTEN* mutations leading to Cowden syndrome has been reported to be anywhere from 30%-80% [5]. Whether Cowden or another disease is diagnosed, risk of malignancy is always greatly increased in the presence of a *PTEN* mutation [5]. Cowden syndrome represents one of several disorders in the spectrum of *PTEN* hamartoma-tumor syndromes, also including Bannayan-Riley-Ruvalcaba syndrome and Proteus-like syndromes [1-3]. In patients with germline *PTEN* mutations, three studies to date have examined risks for malignancy [5]. The largest by Tan et al., identified greatly increased lifetime risks for breast (85%), thyroid (35%), renal (34%), and endometrial cancers (28%), with slightly elevated risks for colorectal cancers (9%) and melanoma (9%). Management guidelines for *PTEN*-mutation positive patients have been developed in an attempt to identify tumors at the earliest and most treatable stages (table 2) [5-8].

Table 2. Monitoring for Cowden related malignancy

<u><i>Cancer</i></u>	<u><i>Age</i></u>	<u><i>Recommendation</i></u>
Female Breast	30	Annual mammogram; consider MRI for dense breasts. (<i>Consider prophylactic mastectomy</i>)
Thyroid	Age of Dx	Annual ultrasound
Renal	40	Imaging every two years
Endometrial	30	Annual endometrial biopsy or transvaginal ultrasound. (<i>Consider prophylactic hysterectomy-oophorectomy unnecessary</i>)
Colorectal	35-40	Colonoscopy with follow-up depending on results
Melanoma	Age of Dx	Annual dermatologic exam

More than 90% of Cowden syndrome patients exhibit mucocutaneous lesions [5-7]. These lesions include trichilemmomas, papillomatous papules, mucosal lesions, and palmoplantar keratosis [7-10]. Many cases also exhibit skin manifestations on the neck, hands, feet, and inside the mouth [9]. Skin signs most often develop in the 20s and 30s, but age of onset greatly varies [11]. These dermatological symptoms usually appear prior to internal malignancy and can be used as diagnostic markers and clues to other potential cancerous tumors associated with the disease [9].

Treatment of Cowden syndrome facial papules is accomplished by 5-fluorouracil, laser ablation, or surgical excision [4]. The palmoplantar keratoses have multiple treatment options, including topical keratolytics, topical retinoids, topical corticosteroids, nitrogen cryosurgery, or photodynamic therapy [12, 13]. Rapamycin is an mTOR inhibitor, and has been a successful treatment in promoting the rapid regression of advanced mucocutaneous lesions [14].

LDD is diagnosed by MRI and is a non-neoplastic mass composed of cerebellar folia expanded by hypertrophic neurons of the internal granule cell layer [14-16]. This lesion can be visualized as widened cerebellar folia with the unique tiger-like striated appearance [15, 16]. Histologically, this lesion is usually considered to be benign, with undetectable or very low proliferative activity. Recurrence is not rare, but no malignant transformation has been reported to date [14-17]. Therefore, treatment is usually not needed in asymptomatic patients. Symptomatic patients may benefit from surgical debulking of the tumor [14-17]. Symptoms include headaches, vision and hearing problems, ataxia, and cranial nerve palsies, attributed to increased intracranial pressure [18].

Conclusions

In summary, PTEN germline mutations, Lhermitte-Duclos disease, and the pathognomonic criteria of trichilemmomas and/or cutaneous facial papules are strongly associated with Cowden syndrome. When the diagnosis of either of the above is established, it is critical to consider a diagnosis of Cowden syndrome. Early screening and prophylactic surgeries are available to detect and prevent early malignant lesions in Cowden syndrome. When Cowden syndrome is diagnosed, long-term screening and thorough examination of family members are necessary.

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