CLINICAL VIGNETTE

Multi-Organ Tumors in a Classic Case of Cowden Syndrome

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Introduction

Cowden syndrome is a rare genetic disorder characterized by multiple hamartomas throughout the body and an increased risk for certain malignancies such as breast and thyroid cancers. Cowden syndrome is caused by mutations in the *PTEN* gene, which regulates cell growth and division.[1] We describe the clinical presentation and management of a patient with Cowden syndrome, who presented classically with a variety of medical conditions including chronic vertigo due to cerebellar tumors, goiter, anal lesions, and breast cancer. Subsequent germline genetic testing confirmed the diagnosis of Cowden syndrome, with further genomic profiling revealing a somatic *BRCA1* re-arrangement and mutations in several other genes.

Presentation

A 49-year-old female initially presented to an outside hospital with chronic dizziness. Bilateral cerebellar tumors were identified and she underwent a right suboccipital craniectomy with resection of the right cerebellar tumor. The pathologic diagnosis was dysplastic ganglioglioma. A year later, MRI at her initial presentation to our institution revealed postsurgical changes in the right cerebellum, a cavernous malformation in the left parietal lobe, and two T2/FLAIR hyperintense areas in the left cerebellar hemisphere (Figure 1a-c), representing the remaining left-sided tumors.

Over the following year, she developed infrequent episodes of vertigo that were well-controlled with meclizine. She was also found to have hyperthyroidism, controlled with methimazole, and neck enlargement with tracheal deviation. Ultrasound demonstrated a 67 mm substernal goiter, which was resected with a left hemithyroidectomy. Pathology demonstrated an adenomatoid nodule with a background of multinodular thyroid.

This patient later presented to our ED with pain, itchiness, and bleeding with defecation. A 3-4 cm pedunculated external peri-anal mass was noted on exam. Colorectal surgery was consulted and resected the right-sided mass. Intra-operative anoscopy demonstrated diffuse circumferential polyposis deep into the rectum, in addition to polyp-like lesions in the posterior vagina. Biopsy of the resected anal mass demonstrated fibroepithelial proliferation with a GATA3+/GCDFP15+/ER+/PR+ pattern that was consistent with a benign phyllodes tumor. Three months later, the patient developed another anal mass which was subsequently excised and pathology revealing another phyllodes tumor. Screening colonoscopy identified numerous hyperplastic polyps throughout the colon and rectum with pseudopolyposis and ulcers in the terminal ileum.

At the time of colonoscopy, the patient underwent a routine screening mammogram that revealed bilateral masses in the breasts, deemed BI-RADS-0. This was followed up with diagnostic mammography, revealing benign-appearing masses and cysts, diagnosed as BI-RADS-3 (Figure 2a-b). The patient was instructed to return for follow-up imaging in 6 months. Unfortunately, the patient did not return until more than 18 months with a palpable mass in the right breast. Follow-up diagnostic mammogram showed a new complex mass in the right breast, measuring 6 x 5 x 6 cm with central necrosis and cystic changes (Figure 2c-d). A 1.5 cm right axillary lymph node with focal nodular cortical thickening was also discovered on ultrasound (Figure 2e). Biopsy of the mass was consistent with a poorly differentiated epithelioid malignant neoplasm with necrosis, favoring a poorly differentiated carcinoma. Staging CT of the thorax with contrast demonstrated a 10.7 x 8.3 cm mass with central cystic changes and necrosis, in addition to enlarged right axillary and subpectoral lymph nodes measuring up to 1.0 cm (Figure 3a-b). On biopsy and pathology, immunochemistry of the mass was negative for *GATA3, ER, PR,* and *HER 2*, deeming it unlikely to be a lobular carcinoma. The origin of the carcinoma may not have been the breast. The patient was started on CARBOPLATIN-TAXOL, but the mass enlarged to 15 x 13 x 10 cm, and the chemotherapy regimen was changed to Dose-Dense Adjuvant Doxorubicin and Cyclophosphamide (ddAC). Follow up PET/CT showed no evidence of metastatic disease, and the patient underwent a successful modified radical mastectomy to excise the carcinoma. The patient was placed on adjuvant chemotherapy and which she has since completed and is now on surveillance.

Given the patient's extensive oncological history, genetics was consulted, and genomic profiling was ordered through Foundation One. The patient was found to be positive for somatic *BRCA1* rearrangement on exon 10, in addition to *MSI-I, TMB 4muts/mb*, and mutations in *CCNE1, KDR, PDGFRA, PTEN, AKT2, TP53, and KDR*. Germline assays also showed a PTEN mutation, confirming the diagnosis of Cowden syndrome. After careful consideration, and given the patient did not desire fertility, she underwent prophylactic hysterectomy.

Diagnosis and Management

The patient's clinical presentation, including the presence of cerebellar tumors, goiter, multiple anal masses, and the development of breast cancer, raise concerns for Cowden syndrome. This suspicion was confirmed through genetic testing, which revealed a *PTEN* gene mutation, the underlying cause of Cowden syndrome. Further genomic profiling also identified somatic *BRCA1* rearrangement and mutations in several other genes.

The International Cowden Syndrome Consortium established diagnostic criteria based on patient presentation, including two major criteria: cerebellar gangliocytoma, thyroid carcinoma, breast cancer, or macrocephaly, or one major and three minor criteria[2] (Table 1). Our patient also qualifies for diagnosis based on these criteria, as she had bilateral cerebellar tumors, at least one of which was a ganglioglioma, and breast cancer, in addition to minor criteria such as goiter and genitourinary tumors.

The patient underwent surgery and chemotherapy for breast cancer and will require ongoing surveillance and management for the various medical conditions associated with Cowden syndrome. This includes close monitoring and treatment if additional cancers develop.

Discussion

Cowden syndrome is a rare genetic disorder caused by mutations in the *PTEN* gene, most often inherited in an autosomal dominant fashion.[1] The *PTEN* gene is responsible for a phosphatase enzyme with functions in cell movement, cell adhesion, angiogenesis, tumor suppression and apoptosis pathways. The dysfunction of these enzymes leads to "PTEN-opathies", such as Cowden disease, characterized by various benign and malignant tumors, in addition to neurodevelopmental disorders such as autism.[3] The clinical presentation of Cowden syndrome can vary greatly, with individuals experiencing a wide range of medical conditions, including cerebellar tumors, goiter, and anal masses, as well as an increased risk for the development of cancers such as breast and follicular thyroid carcinoma.

Gangliocytomas and gangliogliomas are both well-differentiated, benign neuroepithelial tumors which include mature ganglion cells, in addition to glial cells in the case of gangliogliomas.[4] On MRI, these tumors are classically described as cerebellar lesions with a tigroid/striated appearance. Outside hospital records from our patient's resected cerebellar tumor indicated a ganglioglioma, although we were unable to obtain and confirm the specific pathology report. The dysplastic gangliocytoma of the cerebellum, also known as called Lhermitte-Duclos disease (LDD), is pathognomonic with Cowden disease.[5] Our patient's resected tumor may have had a glial component, distinguishing it from the pure gangliocytoma which defines LDD; the association between cerebellar ganglioglioma and Cowden syndrome, and the overlap between the two tumor types remains unclear.

The risk of breast cancer is significantly elevated in females with Cowden disease, with rates reported up to 85% of developing breast carcinoma in their lifetime.[6] This study reports that even males with Cowden disease have increased rates of breast carcinoma. Finally, thyroid carcinoma risk is also reported to be elevated by 30% in Cowden syndrome, which increased the pretest probability in the large goiter observed in our patient.[7,8]

In this case, the patient presented with various medical conditions and ultimately received a diagnosis of Cowden syndrome through genetic testing. An important learning point of this case is the necessity of vigilant surveillance in patients with past history of tumors or suspicion of a genetic disorders which increase cancer risk. At the time of our patient's initial screening and diagnostic mammograms, she was found to have BI-RADS-3 lesions, and a history of cerebellar tumors and goiter. She was advised to return in 6 months for follow-up imaging, but she may have benefitted from additional guidance and caution about its importance. When she returned with a palpable breast mass after 18 months, the carcinoma had grown to considerable size. Fortunately, the patient underwent successful surgery and chemotherapy for her breast cancer, and will continue ongoing surveillance and management for the various medical conditions associated with her Cowden syndrome.

Conclusion

Cowden syndrome is a rare genetic disorder caused by mutations in the PTEN gene. As a such, the clinical presentation of Cowden syndrome can vary greatly but always involves benign or malignant tumor growths. In the present case, our patient presented with classic signs and symptoms of Cowden disease, in addition to some unique learning points. Cerebellar gangliocytoma, called Lhermitte-Duclos disease, are highly linked to Cowden syndrome. While we were unable to confirm the pathology of our patient's reported ganglioglioma, it would present a similar, but previously unreported, association with Cowden syndrome. Further cases need to be studied and reported to understand the overlap between these two entities and Cowden syndrome. The development of breast cancer in our patient, 18 months after her prior BI-RADS-3 diagnosis, highlights the importance of vigilant surveillance in patients with prior tumors.

Figures

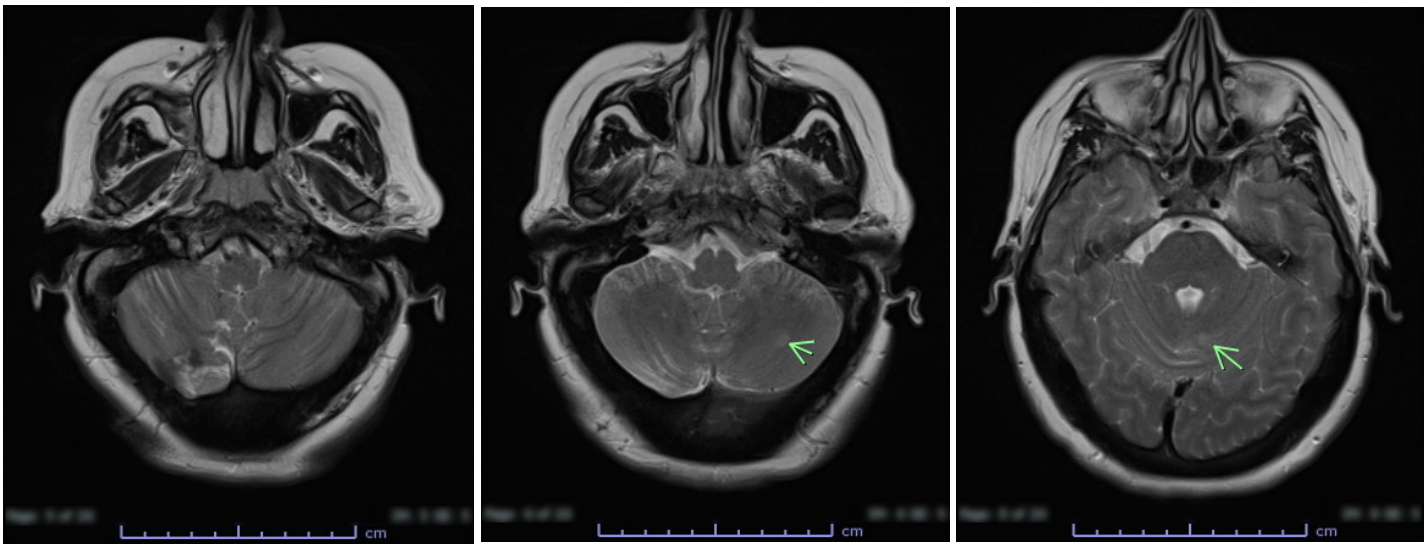

Figure 1. Axial planes of brain MRI from 2016. (a) Postsurgical findings in the right cerebellum after resection of ganglioglioma. Mild FLAIR hyperintensity surrounding the resection cavity is unchanged. (b) Area of T2 hyperintensity within the left cerebellum within the superior cerebellar hemisphere adjacent to the vermis and (c) area of T2 hyperintensity within inferior cerebellar hemisphere, that are unchanged and nonspecific.

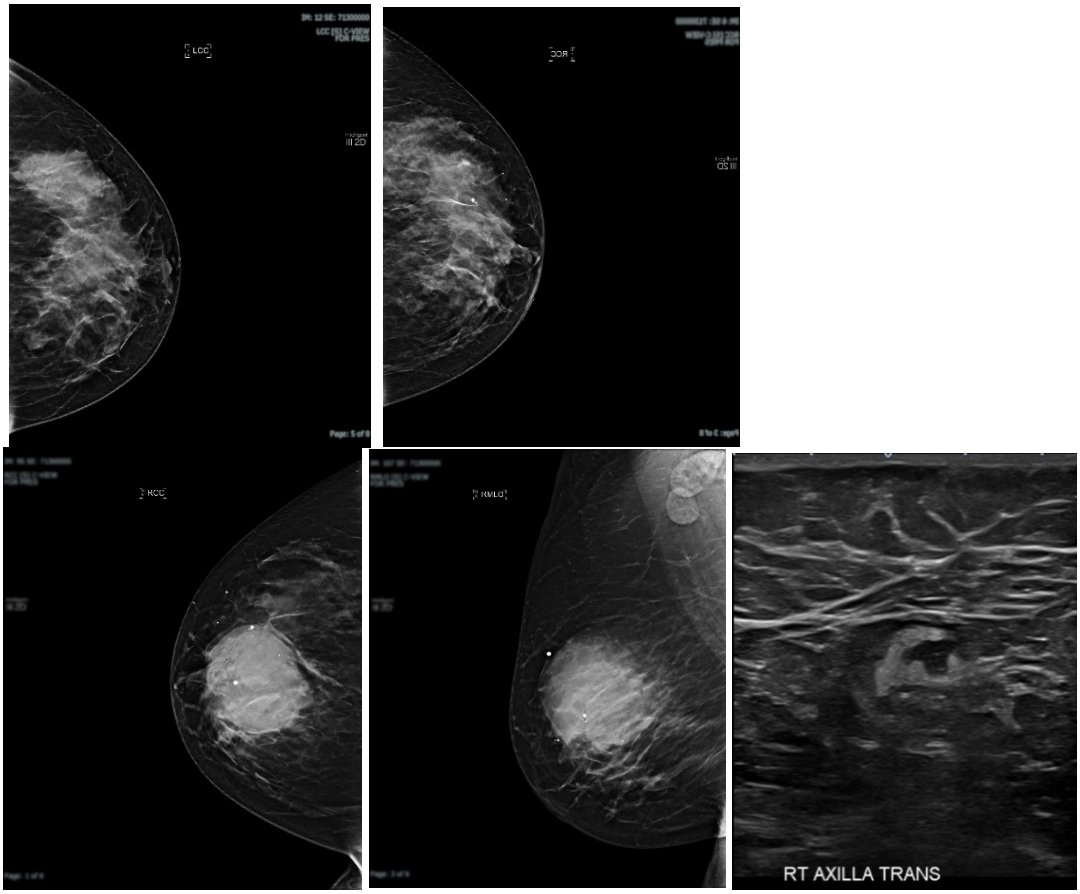

Figure 2: Imaging of breast lesions in patient with Cowden syndrome. Initial screening mammography from 2019 demonstrating multiple bilateral partially circumscribed, partially obscured masses (BI-RADS Category 0) in the (a) left and (b) right breasts. Follow-up diagnostic mammography in 2021 of the patient's new round mass 6.5cm with angular margins and complexity in the (c) CC view and (d) MLO view of the right breast. (e) Ultrasound of a right axilla lymph node demonstrating focal nodular cortical thickening at the same time.

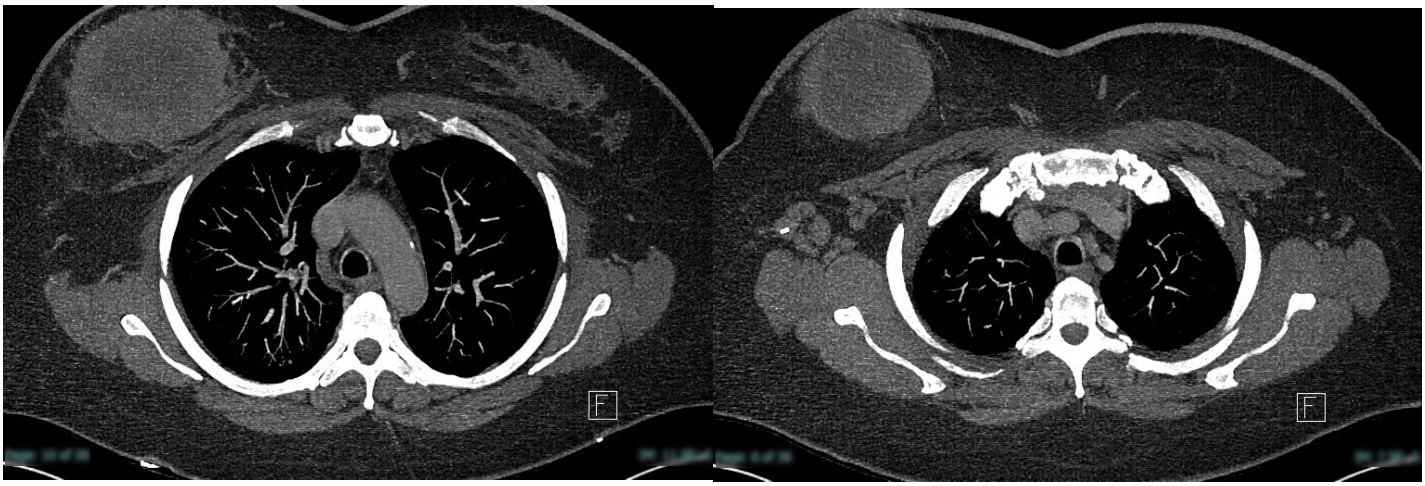

Figure 3: 2021 CT Thorax with Contrast for staging of newly diagnosed breast cancer with (a) large heterogeneous right breast mass and (b) enlarged right axillary and subpectoral lymph nodes, demonstrating asymmetry to left side. Otherwise no CT evidence of distant metastatic disease within chest, abdomen or pelvis.

International Cowden Syndrome Consortium Diagnostic Criteria	
Major Criteria	**Minor Criteria**
Lhermitte-Duclos disease*	Genitourinary tumors/malformations
Thyroid carcinoma	Lipomas
Macrocephaly*	Fibromas
Breast cancer	Mental retardation
	Fibrocystic disease of the breast
	Thyroid lesions (goiter)
Patients need to have two major criteria to be diagnosed with Cowden disease, including one of Lhermitte-Duclos disease or macrophaly OR	
Patients with one major and three of the minor criteria	

Table 1. Clinical criteria for diagnosis of Cowden syndrome, as outlined by the International Cowden Syndrome Consortium.

REFERENCES

1. **Barax CN, Lebwohl M, Phelps RG**. Multiple hamartoma syndrome. *J Am Acad Dermatol*. 1987 Aug;17(2 Pt 2):342-6. doi: 10.1016/s0190-9622(87)70209-6. PMID: 3624577.
2. **Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E**. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst*. 2013 Nov 6;105(21):1607-16. doi: 10.1093/jnci/djt277. Epub 2013 Oct 17. PMID: 24136893.
3. **Yehia L, Ngeow J, Eng C**. PTEN-opathies: from biological insights to evidence-based precision medicine. *J Clin Invest*. 2019 Feb 1;129(2):452-464. doi: 10.1172/JCI121277. Epub 2019 Jan 7. PMID: 30614812; PMCID: PMC6355220.
4. **Odia Y**. Gangliocytomas and Gangliogliomas: Review of Clinical, Pathologic and Genetic Features. *Clinics in Oncology*. 2016;1. [Internet] Available at: https://www.clinicsinoncology.com/open-

access/pgangliocytomas-and-gangliogliomas-review-of-clinical-pathologic-and-genetic-featuresp-1187.pdf.

5. **Khandpur U, Huntoon K, Smith-Cohn M, Shaw A, Elder JB**. Bilateral Recurrent Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos Disease) in Cowden Syndrome: A Case Report and Literature Review. *World Neurosurg*. 2019 Jul;127:319-325. doi: 10.1016/j.wneu.2019.03.131. Epub 2019 Mar 21. PMID: 30905649.
6. **Fackenthal JD, Marsh DJ, Richardson AL, Cummings SA, Eng C, Robinson BG, Olopade OI**. Male breast cancer in Cowden syndrome patients with germline PTEN mutations. *J Med Genet*. 2001 Mar;38(3):159-64. doi: 10.1136/jmg.38.3.159. PMID: 11238682; PMCID: PMC1734834.
7. **Garofola C, Jamal Z, Gross GP**. Cowden Disease. 2022 Jul 24. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 30252240.
8. **Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C**. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res*. 2012 Jan 15;18(2):400-7. doi: 10.1158/1078-0432.CCR-11-2283. PMID: 22252256; PMCID: PMC3261579.