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Case report

Phyllodes tumor of the vulva: A case report and literature review highlighting a novel manifestation of Cowden syndrome

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ABSTRACT

Cowden syndrome is a rare hereditary cancer syndrome characterized by a germline *PTEN* mutation which results in an increased risk of developing breast, thyroid, and endometrial carcinoma, as well as widespread benign hamartomas. Phyllodes tumor (PT) is a rare fibroepithelial tumor that accounts for less than 1% of all breast tumors. As mammary-type glands can be found in the anogenital region, PTs can rarely arise in this location. We describe the presentation, workup and management of a PT of the vulva that developed in a patient with Cowden syndrome. This report represents the first time a vulvar PT has been described in association with Cowden syndrome and should be considered in the differential diagnosis of a slow-growing vulvar mass.

1. Introduction

Cowden Syndrome is an autosomal dominant hereditary cancer syndrome that belongs to the PTEN hamartoma tumor syndrome spectrum of disorders (Nelen et al., 1997). As a result of inheritance of a germline *PTEN* mutation, patients with Cowden syndrome are at an increased risk of developing breast, thyroid, and endometrial carcinomas, as well as benign hamartomas throughout the body (skin, colon, thyroid, etc.) (Nelen et al., 1997). Genetic analysis has revealed that the gene responsible for this disease is *PTEN*, a tumor suppressor located on chromosome 10q23 (Nelen et al., 1997).

Phyllodes tumors (PT) are fibroepithelial breast tumors that represent <1% of all breast neoplasms (Zhang and Kleer, 2016). These tumors are histologically characterized by intracanalicular growth, cleft-like spaces lined by epithelium, and hypercellular stroma resulting in a leaf-like architecture (Zhang and Kleer, 2016). Based on histologic features such as stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor border, PTs can be categorized as benign, borderline, or malignant. The majority of PTs are benign but have a 17% risk of local recurrence. In contrast, malignant PTs have a 27% risk of local recurrence and 22% risk of distant metastasis (Zhang and Kleer, 2016). Nonetheless, PTs can follow an unpredictable clinical course due to intra-tumoral morphological and genetic heterogeneity (Zhang and Kleer, 2016).

2. Case

This is a 41-year-old nulliparous female with a personal history of thyroid carcinoma treated with thyroidectomy and radioactive iodine, atypical hyperplasia/endometrial intraepithelial neoplasia treated with robotic-assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, and multiple benign breast biopsies. Her brother had been diagnosed with stage IV colon cancer, underwent genetic testing and was diagnosed with Cowden syndrome three years earlier. The patient herself underwent genetic testing and was also diagnosed with Cowden Syndrome (c.388C > T, p.Arg130*).

Five years prior to presentation, the patient had developed a right, and subsequently a left, labial mass that were excised and pathology was consistent with a papillary hidradenoma. One year after resection, she developed a small, non-erythematous, non-ulcerated left vulvar nodule. As she was asymptomatic, she opted for expectant management. Over the next 15 months, the mass gradually increased in size to approximately 3 cm and a second mass measuring approximately 2 cm developed adjacent to the first, resulting in intermittent burning pain. At this time, she elected for surgical removal and underwent another left partial vulvectomy.

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The partial vulvectomy specimen encompassed removal of two distinct nodules measuring 1.5 and 3.5 cm, both with a pink-tan, friable, and gritty cut surface. Histologically, the smaller nodule (designated as nodule 1) was hypocellular with intracanalicular growth, usual ductal hyperplasia, focal apocrine metaplasia, and focal pseudoangiomatous stromal hyperplasia (Fig. 1A and B). The larger nodule (designated as nodule 2) had prominent leaf-like growth and a hypocellular fibrotic stroma (Fig. 1C and D). Hypercellularity, cytologic atypia, increased mitotic activity, stromal overgrowth, and heterologous elements were not identified, and all margins were negative. These morphologic features were consistent with two benign PTs of the vulva.

Because breast cancer is known to be associated with Cowden Syndrome and the PTs appeared to arise in extramammary breast tissue, we sought to determine whether the etiology of these tumors could be due to a germline *PTEN* mutation. Next-generation sequencing using a targeted hybrid capture 1213-gene panel (Oncoplus at the University of Chicago) (Kadri et al., 2017) revealed that both nodules harbored the known *PTEN* germline mutation (p.Arg130*). Nodule 1 also had three additional *PTEN* somatic frameshift mutations with allele frequency ranging from 8% to 14% (Table 1). Due to the distance between the *PTEN* mutations, we are unable to distinguish whether these mutations were on the same allele (*in cis*) or on different alleles (*in trans*). No other pathogenic genetic alterations were identified in either nodule in the 1213 tested genes.

Table 1
Comparison of *PTEN* Mutations in the Patient and Vulvar Phyllodes Tumors with Associated Allele Frequencies.

Patient	Nodule 1		Nodule 2	
p.Arg130*	p.Arg130*	47%	p.Arg130*	63%
	p.Ser287Argfs*10	14%	–	
	p.Asn212Metfs*6	13%	–	
	p.Arg335Profs*8	8%	–	

3. Discussion

Phyllodes tumor (PT) is an uncommon fibroepithelial breast neoplasm that was first described in 1838 (Zhang and Kleer, 2016) and is characterized by hypercellular stroma forming leaf-like intraluminal projections. Clinically, PT can mimic fibroadenomas. They are classified as benign, borderline, or malignant based on specific histologic features including stromal cellularity, stromal cell atypia, presence of stromal overgrowth (defined as at least one 4x microscopic field containing only stroma), mitotic activity, infiltrative tumor border, and the presence of malignant heterologous elements (Zhang and Kleer, 2016). Although PTs are primarily found in the breast, there have been rare reports described of these lesions arising in the vulva that are believed to originate from anogenital mammary-type glands (Mannan et al., 2010; Fu et al., 2011). Vulvar PTs typically present as a unilateral painless mass, most often involving the labia majora, labia minora, or inter-labial cleft (Mannan et al., 2010). Histologically these tumors show the same biphasic features seen in PTs of the breast and are graded similarly. However, there is inadequate data on long-term behavior after excision. Based on review of the literature, metastatic disease has not been reported.

Most (60–75%) PTs of the breast are benign, while a small subset (10–20%) are malignant with metastatic disease reported in greater than

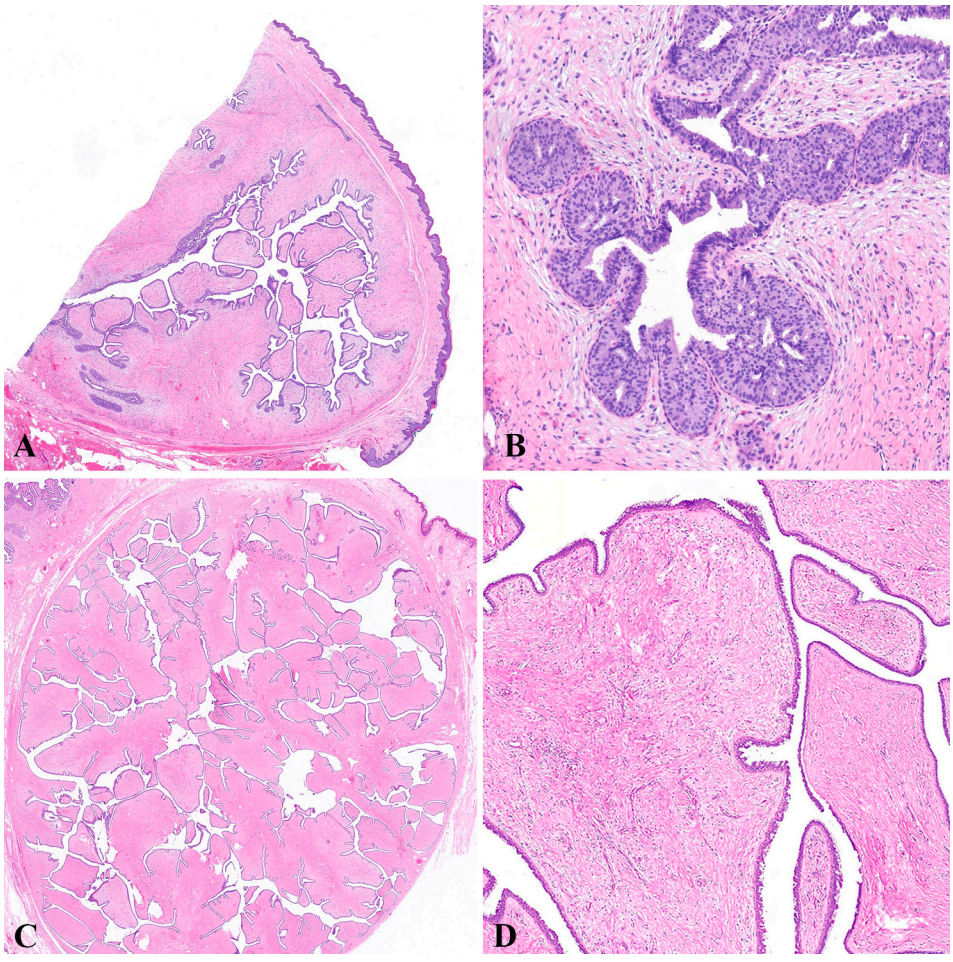

Fig. 1. Nodule 1 with intracanalicular growth (A) and usual ductal hyperplasia (B). Nodule 2 with prominent leaf-like architecture (C and D).

20% of patients (Zhang and Kleer, 2016). Prognosis is poor due to limited treatment options. The standard of care for malignant PT of the breast is surgery with or without radiation therapy, while the role of chemotherapy is unclear other than for disease palliation (Zhang and Kleer, 2016). Studies have been performed evaluating the genomic features of PTs which highlight recurrent alterations in *TERT* and *MED12* (Pareja et al., 2017). Two distinct pathways for malignant progression of fibroepithelial lesions have been proposed based on sequencing data (Pareja et al., 2017). In the first, referred to as the *MED12*-mutant pathway, a pre-existing fibroadenoma with a *MED12* mutation may progress to a borderline or malignant PT due to accumulation of alterations in cancer genes such as *TERT*. In contrast, in the *MED12*-independent pathway, malignant PTs (without fibroadenoma-like areas) may develop de novo secondary to early alterations in cancer genes including *EGFR, RB1,* or *TP53*. Alterations in *RARA* and *ZNF703* have been implicated in PTs showing local recurrence, while *SETD2*, *BRCA2,* and *TSC1* have been detected in those with distant metastases (Kim et al., 2018). To our knowledge, only one study examined molecular alterations in vulvar fibroepithelial tumors (Konstantinova et al., 2017). Using a panel of 50 genes, mutations were detected in 1/5 (20%) papillary hidradenomas, 2/7 (29%) fibroadenomas, and 1/2 (50%) borderline PTs. No *PTEN* alterations were identified.

Alterations in *PTEN* are infrequent in PTs of the breast, with rare malignant PTs harboring copy number deletions (Kim et al., 2018), missense mutations (Pareja et al., 2017), or a frameshift mutation (Mitus et al., 2020). In one report, a malignant PT harboring *PTEN* and *RB1* copy number deletions had rapid disease progression despite surgery and chemoradiation (Kim et al., 2018). In another study, a *PTEN* truncating mutation was found in both the primary and locally recurrent malignant PT (Mitus et al., 2020). All reported malignant PTs with *PTEN* alterations also harbored alterations in other genes such as *TERT, FGFR1, CDKN2A/B, EGFR, MED12, RB1,* and/or *TP53* (Mitus et al., 2020).

Several case reports suggest an association of PT with hereditary conditions including Li-Fraumeni syndrome and hereditary breast and ovarian cancer syndrome (Rosenberger et al., 2020). To our knowledge, prior to this report, there have been no known descriptions of PTs of the breast or vulva associated with Cowden Syndrome.

In our patient, both tumors harbored the known germline *PTEN* mutation (p.Arg130*) and nodule 1 also had three additional somatic *PTEN* mutations (p.Ser287Argfs*10, p.Asn212Metfs*6, p.Arg335Profs*8). The presence of the germline mutation in both tumors confirms their association with Cowden syndrome, while the lack of somatic *PTEN* mutations in nodule 2 confirms they are two independent tumors. This germline mutation has been described in other patients with Cowden syndrome, none of which developed a PT.

4. Conclusion

Although PTs are primarily breast neoplasms, they may occasionally arise in the vulva. PTs of the breast are uncommon neoplasms, and their vulvar counterparts are exceedingly rare making it difficult to study or understand tumor behavior, disease course, and management. To our knowledge, this is the first report of PTs in a patient with Cowden syndrome. Next-generation sequencing proved that both PTs harbored the known germline *PTEN* mutation. Despite the presence of at least one *PTEN* mutation in her tumors, the low-grade morphology and lack of additional pathogenic alterations makes it unlikely that it will behave like a malignant PT with a *PTEN* mutation.

Author contributions

Sahana Somasegar: Conducted all literature review, result analysis and conclusions. Composed manuscript.

Lisa Han: Performed histologic analysis and next-generation sequencing of tumor samples. Contributed to composition of manuscript.

Aaron Miller: Performed histologic analysis and next-generation sequencing of tumor samples. Contributed to composition of manuscript.

Pankhuri Wanjuri: Performed histologic analysis and next-generation sequencing of tumor samples. Contributed to composition of manuscript.

Peng Wang: Performed histologic analysis and next-generation sequencing of tumor samples. Contributed to composition of manuscript.

Jennifer A. Bennett: Performed histologic analysis and next-generation sequencing of tumor samples. Edited manuscript.

S. Diane Yamada: Diagnosed and interacted with patient directly. Supervised literature review and guided manuscript writing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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