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Pathology

Histopathologic Findings in a Patient with Cowden Syndrome Undergoing Prophylactic Bilateral Mastectomy

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Abstract | **Case Report**

PTEN hamartoma tumor syndrome (PHTS) is a spectrum of disorders caused by the PTEN mutation that include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN Related Proteus-like syndrome, adult Lhermitte-Duclos disease (LDD), and autism spectrum disorders with macrocephaly. In female patients, this syndrome is associated with up to a 50% lifetime risk of developing breast cancer, and current National Comprehensive Cancer Network (NCCN) Guidelines state that depending on the personal/family history, the option of risk-reducing bilateral mastectomy should be discussed with patients. However, there is little current literature regarding expected mammary histopathologic findings in these patients. Here, we present the histopathologic findings in a patient with Cowden Syndrome undergoing bilateral prophylactic mastectomy. Numerous benign lesions are seen with no evidence of malignancy, raising the question of a need for more rigorous risk assessment and clearer guidelines regarding management of these patients.

Keywords: Cowden Syndrome; Histopathology; Prophylactic Mastectomy.

INTRODUCTION

PTEN (Phosphatase and Tensin homolog) is a tumor suppressor gene that plays a crucial role in regulating cell growth, proliferation, and survival. Germline mutations of the PTEN lead to the cancer predisposition syndrome of PTEN hamartoma tumor syndrome (PHTS), which is a spectrum of disorders that include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN Related Proteus-like syndrome, adult Lhermitte-Duclos disease (LDD), and autism spectrum disorders with macrocephaly [1]. These syndromes, namely, Cowden syndrome, have been associated with various cancers, including breast cancer, the most common malignancy involving women with CS [2,3]. Individuals with germline PTEN mutations are at an increased risk of developing breast cancer, frequently reported between 25-50%, though some studies report as high as a 90% incidence [4]. For this reason, prophylactic mastectomies have been considered as a risk-reducing strategy [5].

In female patients, Cowden syndrome is associated with up to 50% lifetime risk of developing breast cancer, 5-10% risk of developing endometrial cancer, and 10% lifetime risk of developing follicular thyroid cancer [4]. Several studies have investigated the prognostic factors in breast cancer patients with PTEN mutations. Loss of PTEN expression has been linked to adverse prognostic factors, such as lymph node metastasis, higher tumor grade, and decreased overall survival [6,7].

Regarding breast histopathology, 74% of patients with Cowden syndrome who undergo a diagnostic procedure have malignant breast disease. Ductal carcinoma is the most common pathology, with 86% having in situ and/or invasive disease [7]. Other histological subtypes, such as lobular carcinoma and additional rare subtypes, have also been observed [2]. Furthermore, studies have suggested that PTEN mutations may be more prevalent in certain breast cancer subtypes, such as triple-negative breast cancer [8]. Benign breast histopathological findings have been reported in CS, such as usual ductal hyperplasia, intraductal papilloma, sclerosing adenosis, lobular atrophy, fibroadenoma, and densely fibrotic hyalinized nodules [7]. However, there is a paucity of literature

examining the histopathologic findings in CS after a bilateral prophylactic mastectomy. Here, we present a unique case of a CS patient with a spectrum of benign breast lesions but no malignant lesions found after bilateral prophylactic mastectomy.

Case Report

This is a 42-year-old female with a history of phyllodes tumor of the vulva status post resection, bilateral fibroadenomas biopsied seven years prior, papillary thyroid cancer diagnosed 24 years prior (status post total thyroidectomy), and epilepsy secondary to cortical dysplasia. She was found to have a positive monoallelic mutation in the gene PTEN (identified as c.395G>A (p.G132D)) on the Ambry Genetics Cancer Next-Expanded Panel. The PTEN c.395G>A (p.G132D) mutation was consistent with a diagnosis of PTEN hamartoma tumor syndrome (PHTS), and along with her clinical criteria, a diagnosis of Cowden Syndrome was made. Of note, the panel was negative for BRCA1 and BRCA2 gene mutations. The patient underwent mammography, which revealed multiple waxing and waning circumscribed masses throughout both breasts. Additionally, there was an ovoid mass with a biopsy clip in the lower inner quadrant at middle depth. Benign calcifications were present. No evidence of a suspicious mass, architectural distortion or clustered calcifications were appreciated.

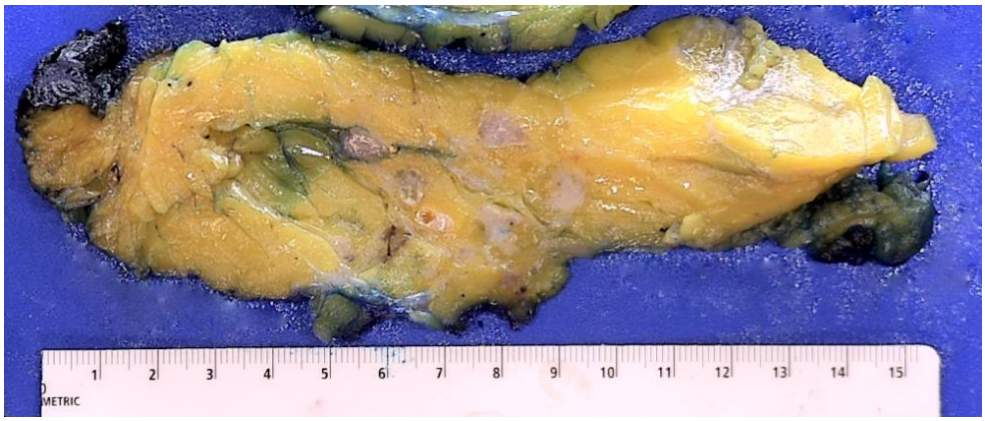

Figure 1: Gross photograph of a representative area of the breast specimen showing multiple ovoid-round, firm, and rubbery brown-tan lesions ranging in size from 0.2 cm to 0.7 cm in greatest dimension

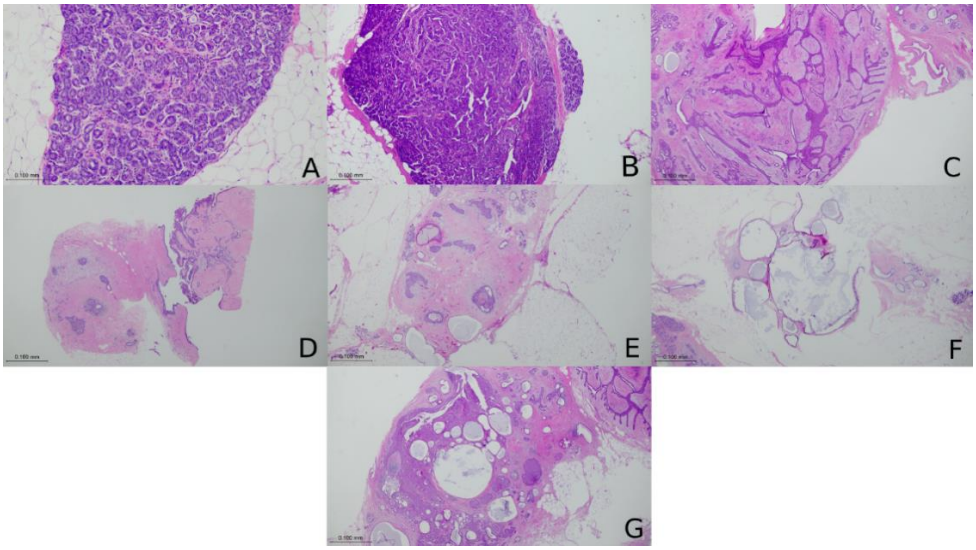

Figure 2. Histopathology of the bilateral breast lesions. A: Small, uniform, closely packed round tubules diagnostic of tubular adenoma. B: Benign intraductal glandular proliferation with sclerotic stroma consistent with ductal adenoma. C: Complex fibroadenoma with intracanalicular pattern highlighted by branching structures with proliferating stroma. D: Intraductal papilloma with florid ductal hyperplasia and focal sclerosis. D: Fibroadenomatoid nodule with pseudoangiomatous stromal hyperplasia and fibrocystic changes. F: Cysts and dilated ducts filled with mucin, consistent with mucocele-like lesion. G: Sclerosing adenomyoepithelioma with fibrocystic change. Hematoxylin and eosin stain. All objectives are 2x, except for A which is 4x

The patient was then recommended for bilateral prophylactic mastectomy after multidisciplinary discussion with surgery and genetic counseling providers given her previous history of multiple benign breast findings and increased surveillance for her other medical conditions. Gross examination findings of the

mastectomy specimens were remarkable for ill-defined areas of fibrous tissue measuring 2.1 cm in greatest dimension and multiple ovoid-round, firm, and rubbery brown-tan lesions ranging in size from 0.2 cm to 0.7 cm in greatest dimension (Fig 1). Representative sections were sampled for histologic evaluation and fixed in 10% formalin solution, then stained with Hematoxylin and Eosin (H&E). Histopathologic examination revealed numerous benign lesions in both breasts, including tubular and ductal adenomas in the right breast, and a complex fibroadenoma, intraductal papilloma with florid ductal hyperplasia, fibroadenomatoid nodule with pseudangiomatous stromal hyperplasia and fibrocystic changes, mucocele like lesion, and sclerosing adenomyoepithelioma in the left breast (Fig 2). No malignant lesions were identified. She has done well post-operatively and was recommended for a six month follow up visit.

DISCUSSION

This case highlights the histopathological findings in a patient with CS undergoing bilateral prophylactic mastectomy, which has not been previously reported in the literature to our knowledge. Female patients with a mutation in the PTEN gene have been shown to have a 50% lifetime risk of breast cancer [4]. Our patient's breast tissue showed a wide spectrum of benign lesions with no malignancy identified. These findings suggest that patients with CS may only have benign findings after undergoing a prophylactic mastectomy. Another notable finding from this case was the patient's history of a phyllodes tumor of the vulva, which is a rare fibroepithelial tumor that accounts for less than 1% of all breast tumors, but can arise in any location. Interestingly, there have been very few case reports in the literature for CS patients with a phyllodes tumor of the vulva [8].

The absence of malignant lesions raises questions about potential overestimation of risk for patients with PHTS/CS due to the lack of studies on risk-reducing mastectomy for women with a PTEN mutation. While bilateral risk-reducing mastectomy has been shown to reduce breast cancer risk by up to 90% in women with BRCA1 and BRCA2 [9,10], this patient was negative for those gene mutations. The National Comprehensive Cancer Network (NCCN) Guidelines state that depending on the personal/family history, the option of risk-reducing bilateral mastectomy can also be discussed in those with PTEN mutations. This case highlights the variability of findings that can be seen in these patients. It is important to thoroughly evaluate the histopathologic findings because PHTS can lead to a wide variety of both benign and malignant tumors [11]. Additionally, more research is needed in this area to form clearer guidelines for these patients. Personalized risk assessment can further be improved to ensure patients are provided with adequate and accurate information in order to inform their best treatment strategy.

CONCLUSION

To conclude, this case reports benign histopathological findings in a patient with CS undergoing prophylactic bilateral mastectomy. The findings of multiple benign lesions along with the patient's reported clinical history of a phyllodes tumor of the vulva, highlights the wide spectrum of lesions seen in CS. These results shed light on the need for a more rigorous risk assessment, comprehensive histopathological evaluation, and personalized management strategies.

Ethics: Our local institutional review board has determined this manuscript to not be human research.

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