Fibroadenoma in vulval ectopic breast tissue in a patient with *PTEN* Hamartoma Tumour Syndrome

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Abstract

PTEN is a tumour suppressor gene involved in regulating cell division. Pathogenic germline variants in *PTEN* predispose to benign and malignant growths of numerous organs, including of the breast. In the following report, we describe the first documented case of a fibroadenoma developing in ectopic breast tissue of the vulva in a patient with a germline pathogenic variant in *PTEN*. This highlights the risk of proliferative hyperplasia developing in any breast tissue, including rare ectopic sites, particularly in patients with underlying germline variants in cancer susceptibility genes.

Introduction

Germline pathogenic *PTEN* variants are associated with the overlapping clinical phenotypes Cowden Syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome and PTEN-related Proteous Syndrome, which are variably associated with overgrowth, developmental delay and risks of cancer. The umbrella term for these conditions is PTEN Hamartoma Tumor Syndrome (PHTS)(1) (2) (3) (4). PHTS is an autosomal dominant condition with a general population prevalence of roughly 1 in 200,000

The clinical phenotype of PHTS includes increased risk of malignancies such as breast, endometrial, thyroid, renal, skin and colorectal cancers (2, 3, 5, 6). Benign lesions are almost universal among affected patients; and include hamartomatous overgrowth of various tissues.

The estimated lifetime breast cancer risk in patients with CS is reported to be between 67-85% (2, 7, 8) and women have an 87% chance of developing at least one malignancy before the age of 60 (9). Benign breast disease is more common in patients with PTEN pathogenic variants; 76% of patients with CS have breast fibroadenomas/ fibrocystic disease compared with up to 60% of the normal population(10).

Vulval fibroadenomas are rare neoplasms, but have been reported in otherwise healthy females (11-13). The origin of these lesions has been debated with some considering them to originate from ectopic breast tissue, whilst others theorise that they arise from anogenital mammary-like glands(14-18).

In 2016, Hedayat *et al*. reported a case of a 27-year-old woman with Cowden syndrome with a perianal lesion demonstrating proliferative changes strikingly similar to those commonly seen in breast tissue(19).

Herein we report, to the best of our knowledge, the first case of a vulval fibroadenoma occurring in ectopic breast tissue in a patient with underlying PTEN Hamartoma Tumour Syndrome.

Case

A 41-year-old non-smoking female presented to her dentist with diffuse gum hypertrophy. She had a preceding history of a multinodular goitre in her 20s, benign breast lesions and a prior history of resection of a vascular malformation from her wrist, and a large lipoma from her back. On clinical examination, the patient was also noted to have macrocephaly, with head circumference of 63.5cm. There was a strong family history of breast cancer on her maternal side, with her mother sadly dying of breast cancer aged 49 years, and her maternal aunt developing breast cancer in her early 60s. Her mother also had a reported history of benign thyroid disease. The patient's Cleveland Clinic Score was estimated to be 20 at the time of testing, corresponding to a 29% probability of carrying a pathogenic constitutional variant in *PTEN* (20).

Subsequent constitutional genetic testing identified a heterozygous missense variant in exon 5 of *PTEN:* c.407G>A, (p.Cys136Tyr). With a z-score of 3.49, *PTEN* is highly constrained against missense variation, and missense variation in this gene is a common mechanism of disease. The cysteine residue at this position is highly conserved across species, and located in the phosphatase domain and ATP binding motif. This variant has been shown in vitro to lead to inactivation of phosphatase activity(21). This variant is absent from the gnomAD database(22), but has been reported in other individuals with features of PHTS(23, 24), and has been reported by multiple commercial laboratories on ClinVar(25). Another variant (p.Cys136Arg) at this position has also been reported as pathogenic by multiple laboratories(26). All things considered, this variant has been classified as pathogenic by the ClinGen *PTEN* variant Curation Expert Panel, using gene-specific criteria for variant classification(27). Following molecular confirmation of PHTS, the patient thereafter commenced cancer surveillance in line with contemporary departmental guidelines, and cascade testing was offered to at-risk family members.

Screening ultrasound of a clinically goitrous thyroid revealed goitre with multiple nodules. FNA of the most suspicious nodule identified a Thy3f lesion, for which hemithyroidectomy was undertaken, with histology ultimately showing a unifocal papillary microcarcinoma on a background of patchy but florid nodular lymphocytic thyroiditis, with some background nodules demonstrating considerable Hurthle cell differentiation. In view of this background pathology and her underlying genotype, a completion thyroidectomy was undertaken – revealing a further focus of papillary carcinoma with adjacent multifocal atypical follicular lesions thought to represent Follicular/Hurthle cell variant papillary carcinoma.

Breast screening also identified multiple benign lesions. The patient ultimately elected to undergo risk-reducing bilateral mastectomies with immediate DIEP (Deep Inferior Epigastric Perforator) autologous reconstruction. Final histology showed a plethora of benign breast changes, including fibrocystic disease, intraductal papilloma, fibroadenomatoid and apocrine change, and periductal mastitis. No malignant features were identified. Baseline colonoscopic assessment identified a single sigmoid polyp, which was resected endoscopically, and determined to be a hamartomatous lesion. Follow up colonoscopy did not detect any new lesions. Renal imaging did not detect any sinister lesions. Dermatological assessment identified a number of seborrheic keratoses, suspected actinic keratosis treated with cryotherapy, and a number of benign-looking naevi.

Initial gynaecological assessment identified an endometrial polyp and a long-standing vulval lesion, suspected to represent a Bartholin's cyst. Based on contemporary UK Cancer Genetics Group *PTEN* management guidelines(28), the patient elected to undergo risk-reducing total laparoscopic hysterectomy with opportunistic bilateral salpingectomy. The vulval lesion was also excised at the same time, at the patient's request. Histological examination of the hysterectomy specimen identified benign functional endometrial polyps but otherwise no sinister features.

Histological examination of the vulval lesion identified a benign neoplasm, consistent with a fibroadenoma developing within ectopic breast-like tissue in the vulva (Figure 1). Immunohistochemistry showed negative immunoreactivity for PAX-8, while GATA-3 showed diffuse positive reactivity within the acinar and ductular

structures of breast-like tissue and the fibroadenoma. Patchy PTEN loss by immunohistochemistry was seen, consistent with the underlying genomic aberration.

Discussion

The ectodermal primitive milk streaks are formed during the fifth week of embryologic development and run bilaterally between the axillae and inguinal regions. Normally, the majority of the primitive milk line undergoes regression with only a small section persisting forming two ridges on the thorax; later developing into breast tissue. Occasionally, when there is incomplete involution, ectopic breast tissue can occur anywhere along the embryological milk line (16, 17). Ectopic breast tissue has a reported incidence of 1-6% amongst the general population, most commonly found in the axilla and rarely in the vulva (16, 17, 29), and rarely mammae erraticae have been reported in locations outside the milk line, including thigh (30), foot(31), back (32) and face(33). Ectopic breast tissue is hormonally responsive and can undergo benign and malignant transformations, similar to those found in normal breast tissue. (16, 34). Although the exact origin of vulval mammary-like lesions remains unclear, it is well documented that these tissues behave pathologically like breast tissue(35). Notably, the histology of the tissue surrounding the fibroadenoma in our patient was consistent with that of breast tissue. As ectopic breast tissue undergoes the same hormonal processes as normal breast tissue and can undergo the same physiological and pathological changes (16, 34), it is also possible for breast cancer to develop in ectopic breast tissue. This is very rare, with only approximately 30 reported cases of primary breast cancer developing in the vulva; while patients are often treated along a breast cancer paradigm, the disease is often aggressive with a poor prognosis (17, 36-38). Loss of PTEN expression is rarer in benign breast neoplasms than in breast cancers(39, 40), indicating a key role in mammary oncogenesis.

PTEN germline pathogenic variants lead to an inability to arrest the cell cycle and undergo apoptosis, leading to a much-increased risk of multiple heterogenous benign and malignant neoplasms of the breast, thyroid, uterus, kidney, gastrointestinal tract, brain, skin as part of PHTS. Characteristic non-malignant features of PHTS include macrocephaly, with occipito-frontal circumference in excess of the 97th centile, and mucocutaneous lesions such as trichilemmomas, acral keratoses, and mucosal hyperplasia. Developmental delay and features of autistic spectrum disorders are also part of the phenotypic spectrum, which may prompt *PTEN* testing in childhood. Gingival hypertrophy has also been reported as a feature of PHTS(41-43), and this rare feature in our patient prompted referral to Clinical Genetics.

The standard incidence ratio for breast cancer in carriers of a pathogenic constitutional *PTEN* variant is estimated to be 39.1(7), with absolute lifetime risks up to 85%(4). Current guidelines recommend that carriers of pathogenic *PTEN* variants be offered the same breast cancer surveillance and risk-reduction surgical options as carriers of pathogenic *BRCA1/BRCA2* variants. Recommended surveillance comprises a combination of magnetic resonance imaging and/or mammography depending on patient age and breast density, starting from the age of 30. Risk-reducing bilateral mastectomies, usually with immediate reconstruction, should also be offered(9). Benign breast disease is also very common among women with PHTS, with fibroadenomas and mammary hamartomas being particularly prevalent(44). Histopathological assessment of the breast tissue taken from our patient at the time of bilateral mastectomy demonstrated florid benign changes consistent with her genotype.

Lifetime risk estimates for endometrial cancer in PHTS are variable but are reported to be as high as 28%(4, 7-9, 45). There is weak evidence to support the role of endometrial cancer surveillance in female carriers of pathogenic *PTEN* variants, and at present such screening is not recommended outside of a research setting. Although risk-reducing hysterectomy is not recommended as part of the most recent ERN GENTURIS PHTS guideline(46), the UK Cancer Genetics Group guideline used at the time of the patient's surgery included risk-reducing hysterectomy as an option in carriers of pathogenic *PTEN* variants. Many women with PHTS develop benign endometrial issues and may require therapeutic surgical intervention. Opportunistic bilateral salpingectomy at the time of routine hysterectomy for benign indications has been endorsed by the Royal College of Obstetricians and Gynaecologists, as a means to minimise the background risk of non-uterine pelvic

high-grade serous cancers for which reason bilateral salpingectomy with preservation of the ovaries was undertaken in our patient.

Recommended cancer surveillance for carriers of pathogenic *PTEN* variants otherwise involves yearly thyroid ultrasound starting from the age of 18 and 1-2 yearly renal imaging starting from the age of 40(28, 46). Baseline skin examination at 30 years of age, and colonoscopy at 35 years of age are recommended, with onward follow-up thereafter guided by findings.

Vulval fibroadenomas are rare entities, with only a handful of reported cases in the medical literature. Such lesions are perhaps under-recognised considering they may be misdiagnosed as any one of a number of other benign vulval lesions such as epidermal, follicular or Bartholin's gland cysts, or lipoma. The diagnosis of such lesions often falls to histological analysis, but diagnostic clues may include timing of enlargement of the mass, and lactogenesis(47).

Conclusion:
We believe this case represents the first reported vulval fibroadenoma in a patient with PHTS, and this case, in addition to the report of a proliferative lesion of anogenital mammary-like glands in a patient with PHTS reported by Hedayat et al, increases the likelihood of an association between PHTS and neoplasia within ectopic mammary-like tissue. Diagnosis of rare neoplastic lesions arising within ectopic breast tissue should prompt consideration of an underlying genetic predisposition. Treating clinicians should be alert to other clinical stigmata of PHTS in such cases, particularly if immunohistochemistry suggests loss of PTEN expression. Considering the high risk of benign and malignant neoplasia in PHTS, clinicians should have a low threshold to biopsy and/or excise any abnormal lesions in affected patients, particularly in the axillae and vulva where ectopic breast tissue and associated pathological changes may be seen.

Declarations

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References

1. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. Nature Reviews Cancer. 2011;11(4):289-301.
2. Nelen MR, Kremer H, Konings IB, et al. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype–phenotype correlations. European Journal of Human Genetics. 1999;7(3):267-73.
3. Pilarski R, Burt R, Kohlman W, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. Journal of the National Cancer Institute. 2013;105(21):1607-16.
4. Pilarski R. PTEN hamartoma tumor syndrome: A clinical overview. Cancers. 2019;11(6):844.

5. Orloff M, Eng C. Genetic and phenotypic heterogeneity in the PTEN hamartoma tumour syndrome. Oncogene. 2008;27(41):5387-97.
6. Ngeow J, Sesock K, Eng C. Breast cancer risk and clinical implications for germline PTEN mutation carriers. Breast cancer research and treatment. 2017;165(1):1-8.
7. Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. Journal of medical genetics. 2013;50(4):255-63.
8. Tan M-H, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clinical Cancer Research. 2012;18(2):400-7.
9. Nieuwenhuis MH, Kets CM, Murphy-Ryan M, et al. Cancer risk and genotype–phenotype correlations in PTEN hamartoma tumor syndrome. Familial cancer. 2014;13(1):57-63.
10. Pilarski R. Cowden syndrome: a critical review of the clinical literature. Journal of genetic counseling. 2009;18(1):13-27.
11. Baisre A, Heller DS, Lee J, et al. Fibroadenoma of the vulva. A report of two cases. The Journal of reproductive medicine. 2002;47(11):949.
12. Carter JE, Mizell KN, Tucker JA. Mammary-type fibroepithelial neoplasms of the vulva: a case report and review of the literature. Journal of cutaneous pathology. 2008;35(2):246-9.
13. Kalyani R, Srinivas MV, Veda P. Vulval fibroadenoma—a report of two cases with review of literature. International journal of biomedical science: IJBS. 2014;10(2):143.
14. Donati P, Amantea A. Adenoma of anogenital mammary-like glands. The American journal of dermatopathology. 1996;18(1):73-6.
15. van der Putte R. Anogenital “sweat” glands: histology and pathology of a gland that may mimic mammary glands. The American journal of dermatopathology. 1991;13(6):557-67.
16. Đorđević M, Jovanović B, Mitrović S, et al. Ectopic mammary tissue in vulva. Vojnosanitetski pregled. 2008;65(5):407-9.
17. Fracchioli S, Puopolo M, De La Longrais IR, et al. Primary “breast-like” cancer of the vulva: a case report and critical review of the literature. International Journal of Gynecologic Cancer. 2006;16(Suppl 1).
18. Assor D, Davis JB. Multiple apocrine fibroadenomas of the anal skin. American journal of clinical pathology. 1977;68(3):397-9.
19. Hedayat AA, Pettus JR, Marotti JD, et al. Proliferative lesion of anogenital mammary-like glands in the setting of Cowden syndrome: case report and review of the literature. Journal of cutaneous pathology. 2016;43(8):707-10.
20. Cleveland Clinic Genomic Medicine Institute PTEN risk calculator [Available from: https://www.lerner.ccf.org/gmi/ccscore/.
21. Han SY, Kato H, Kato S, et al. Functional evaluation of PTEN missense mutations using in vitro phosphoinositide phosphatase assay. Cancer research. 2000;60(12):3147-51.
22. gnomAD - PTEN [Available from: https://gnomad.broadinstitute.org/gene/ENSG00000171862?dataset=gnomad_r2_1.
23. Heald B, Mester J, Rybicki L, et al. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010;139(6):1927-33.
24. Scala S, Bruni P, Lo Muzio L, et al. Novel mutation of the PTEN gene in an Italian Cowden's disease kindred. International journal of oncology. 1998;13(4):665-8.
25. National Center for Biotechnology Information. ClinVar; [VCV000189406.6] [Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000189406.6
26. National Center for Biotechnology Information. ClinVar; [VCV000183726.8] [Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000183726.8
27. Mester JL, Ghosh R, Pesaran T, et al. Gene-specific criteria for PTEN variant curation: Recommendations from the ClinGen PTEN Expert Panel. Human mutation. 2018;39(11):1581-92.

28. Group UCG. Guidelines for management of tumour risk in PTEN hamartoma syndrome UKMay 2017 [Available from: https://www.ukcgg.org/media/10879/pten_management_-_cgg_4may2017.pdf.
29. da Costa ATMD, Coelho AM, Lourenço AV, et al. Primary breast cancer of the vulva: a case report. Journal of lower genital tract disease. 2012;16(2):155-7.
30. Camisa C. Accessory breast on the posterior thigh of a man. Journal of the American Academy of Dermatology. 1980;3(5):467-9.
31. Conde DM, Kashimoto E, Torresan RZ, et al. Pseudomamma on the foot: an unusual presentation of supernumerary breast tissue. Dermatology online journal. 2006;12(4).
32. Babuccu O, Kalayci M, Turhan E, et al. Mammae erraticae: A case report and reappraisal of the related theories. Aesthetic plastic surgery. 2012;36(3):607-10.
33. Koltuksuz U, Aydin E. Supernumerary breast tissue: a case of pseudomamma on the face. Journal of pediatric surgery. 1997;32(9):1377-8.
34. Dhaoui A, Nfoussi H, Kchir N, et al. Vulvar lactating adenoma associated to a fibroadenoma: common neoplasms in an uncommon site. Pan African Medical Journal. 2012;13(1).
35. Kazakov DV, Spagnolo DV, Kacerovska D, et al. Lesions of anogenital mammary-like glands: an update. Advances in anatomic pathology. 2011;18(1):1-28.
36. Nihon-Yanagi Y, Ueda T, Kameda N, et al. A case of ectopic breast cancer with a literature review. Surgical oncology. 2011;20(1):35-42.
37. Lopes A, St Louis J, Balancin ML, et al. A Rare Presentation of Primary Breast Carcinoma in the Vulva: A Case Report and Literature Review. Clinical breast cancer. 2018;18(3):e291.
38. Butler B, Leath III CA, Barnett JC. Primary invasive breast carcinoma arising in mammary-like glands of the vulva managed with excision and sentinel lymph node biopsy. Gynecologic oncology case reports. 2014;7:7.
39. Bazzichetto C, Conciatori F, Pallocca M, et al. PTEN as a prognostic/predictive biomarker in cancer: an unfulfilled promise? Cancers. 2019;11(4):435.
40. Golmohammadi R, Rakhshani MH, Moslem AR, et al. Prognostic role of PTEN gene expression and length of survival of breast cancer patients in the north east of Iran. Asian Pacific Journal of Cancer Prevention. 2016;17(sup3):305-9.
41. Masmoudi A, Chermi ZM, Marrekchi S, et al. Cowden syndrome. Journal of dermatological case reports. 2011;5(1):8-13.
42. Delannoy P, Debray FG, Verloes A, et al. How to recognize Cowden syndrome: A novel PTEN mutation description. Annales d'endocrinologie. 2017;78(3):188-90.
43. Seol JE, Park IH, Lee W, et al. Cowden Syndrome with a Novel Germline PTEN Mutation and an Unusual Clinical Course. Ann Dermatol. 2015;27(3):306-9.
44. Marsh DJ, Kum JB, Lunetta KL, et al. PTEN Mutation Spectrum and Genotype-Phenotype Correlations in Bannayan-Riley-Ruvalcaba Syndrome Suggest a Single Entity With Cowden Syndrome. Human Molecular Genetics. 1999;8(8):1461-72.
45. Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hereditary cancer in clinical practice. 2010;8(1):1-7.
46. Tischkowitz M, Colas C, Pouwels S, et al. Cancer Surveillance Guideline for individuals with PTEN hamartoma tumour syndrome. European Journal of Human Genetics. 2020;28(10):1387-93.
47. Hernandez Lopez AL, Manandhar S, Dubow L. Pregnancy-unrelated fibroadenoma in ectopic breast tissue in the axilla and vulva: A case report. Case Rep Womens Health. 2020;28:e00255-e.

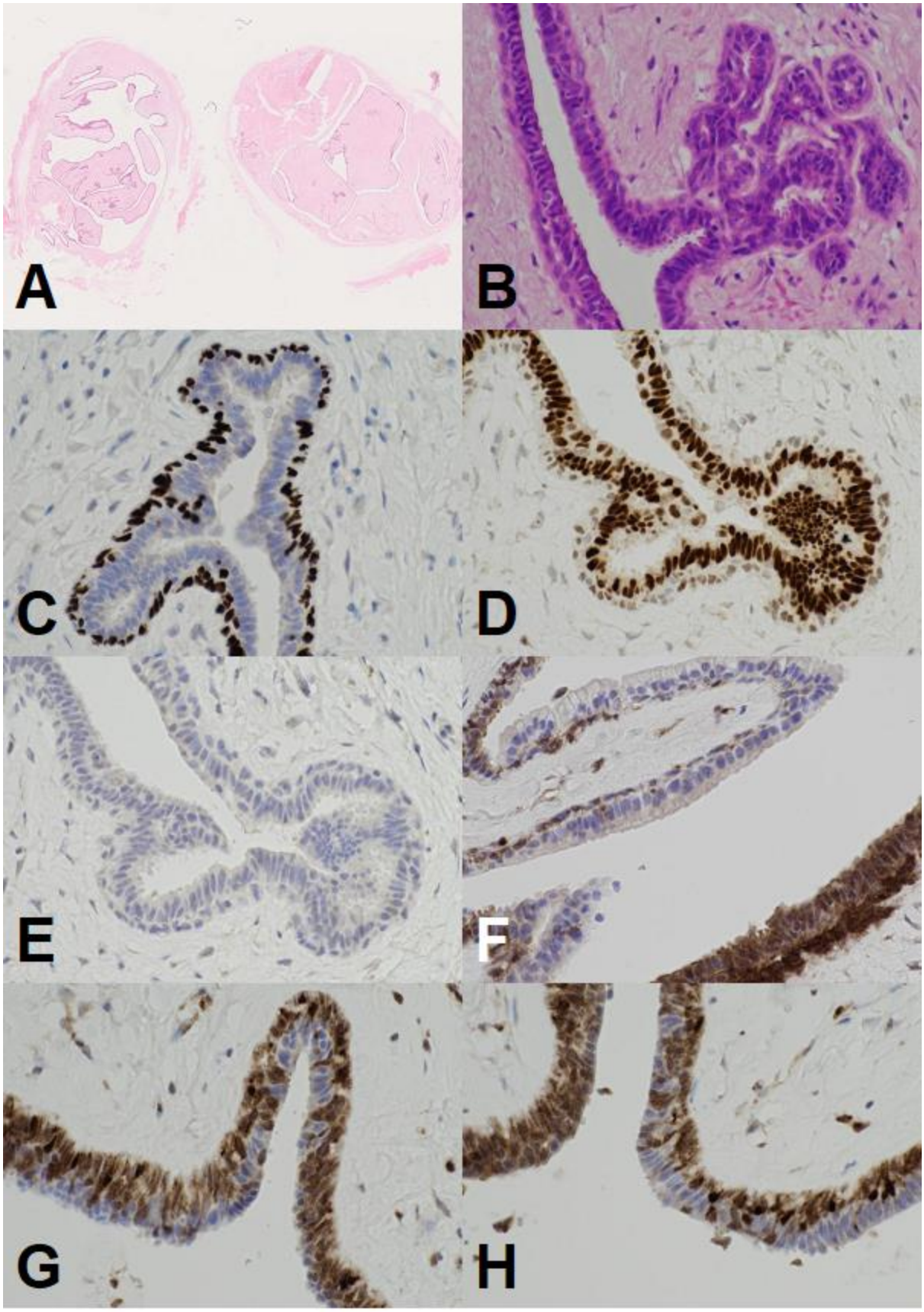

Figure 1: Histopathology of the vulvar lesion.

(A) Whole mount, H&E stain, 1.25x objective. Histology shows a well-circumscribed fibroepithelial lesion with an intracanalicular pattern of growth and an even balance of epithelial and stromal elements.
(B) H&E, 40x objective. A high magnification view of the lesion shows bilayered ducts composed of a mixture of myoepithelial and luminal cells, virtually identical to the appearances seen in fibroadenoma of the breast.
(C-G) Immunohistochemistry, 40x objective. Immunohistochemistry for p63 (C) confirms the presence of a myoepithelial cell layer around the ductular epithelium. GATA-3 (D) is positive, and PAX-8 (E) is negative, in keeping with origin from ectopic breast-like tissue. PTEN is heterogeneous with areas showing block positivity (F), loss of expression (F) and variable expression (G, H).