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Sebaceous hyperplasia of the vulva: a clinicopathological case report with a review of the literature

Sebaceous hyperplasia consists of multiple asymptomatic small yellow papules with a central depression, occurring most commonly on the forehead and cheeks, but occasionally affecting the areola,¹ chest² or genital skin.³ The lesions are sometimes mistaken clinically for basal-cell carcinoma. Sebaceous hyperplasia belongs to the group of epidermal tumours with sebaceous differentiation. Farina *et al*⁴ suggested that hyperplasia in the sebaceous gland is analogous with trichofolliculoma. Although termed hyperplasia, they concluded that sebaceous hyperplasia is a benign neoplasm rather than hyperplasia as these lesions do not involute clinically. By contrast, the absence of significant enlargement of sebaceous lobules, and the sharp demarcation of the lesion distinguish it from hypertrophy. Thus, sebaceous hyperplasia is now considered as a hamartoma rather than a true neoplasm.^{5,6}

A universally accepted definition of sebaceous hyperplasia is not yet available. However, Barnhill and Crowson⁷ defined sebaceous hyperplasia by the presence of ≥ 4 sebaceous

Figure 1 (A) Photomicrograph showing lobules of mature sebaceous glands attached to central hair follicle (original magnification $\times 70$). (B) High-power view of sebaceous hyperplasia (original magnification $\times 250$). (C) H&E section showing the overlying lentiginous hyperplasia of melanocytes, centrally within the lesion (original magnification $\times 250$). (D) Melan A immunohistochemical stain demonstrating the melanocytic hyperplasia, (original magnification $\times 100$).

lobules attached to the infundibulum of each pilosebaceous unit.

Case report

A 31-year-old woman presented to the dermatology outpatients clinic with the appearance of two newly pigmented areas on the vulva, within the past 6 months. On examination, the lesions were darkly pigmented polypoidal papule (12 mm in diameter) and macule (5 mm in diameter) on the left labium minus and at the vestibule, respectively. They were non-tender without obvious textural change, and the surrounding skin was normal. Her gynaecological history was uncomplicated and she had had one normal pregnancy at the age of 20 years. Two biopsy specimens were taken. One was from the left vulva and the other one was from the mid-line region. Both lesions showed pigmented areas. The clinical diagnoses offered included melanocytic macule and benign tumour.

Methods

Sections were examined under routine light microscope using formalin-fixed, paraffin-wax-embedded tissue stained routinely with H&E. Immunohistochemical examination with a panel of stains, including antibodies to epithelial membrane antigen (1:50 dilution, Dako, Cambridgeshire, UK) and human milk fat globulin 1 (HMFG1; 1:25 dilution, Vector, Peterborough, UK) was performed on the

paraffin wax blocks. Appropriate positive controls were run concurrently for all antibodies tested. Mouse non-immune sera were substituted for negative controls. Tissue submitted for ultrastructural examination was retrieved from the processed paraffin wax block. This involved dewaxing in xylene, hydrating through graded alcohols, osmication, dehydrating through alcohol and propylene oxide, and infiltrating in TAAB EMIX epoxy resin (TAAB Laboratories, Aldermaston, Berkshire, UK). After polymerisation, sections were cut at 100 nm on a Reichert-Jung Ultracut E (Leica Microsystems, Buckinghamshire, UK) using a diamond knife; the sections were stained with alcoholic uranyl acetate and Reynold's lead citrate. Examination was on a Phillips 400T transmission electron microscope. Electron micrographs were taken using Kodak EM plate film (Agar Scientific Ltd, Stansted, UK).

Results

Microscopic examination of the first lesion showed an origin from sebaceous ducts and glands with a lobulated architecture. The lobules were composed of enlarged sebaceous glands (>4 around each pilosebaceous unit), which appeared to extend down into the dermis. The cells were predominantly mature sebocytes with a peripheral germinative layer, which was not prominent. Cytologically, the cells displayed a foamy, vesiculated cytoplasm and a central nucleolus with no atypical features (fig 1A,B). In addition, centrally, the

Figure 2 H&E-stained section of perivulval skin in the second biopsy specimen used as an internal control, original magnification $\times 100$.

epidermis displayed basal hyperpigmentation and mild lentiginous hyperplasia of basal melanocytes (fig 1C,D).

Immunohistochemical studies using monoclonal antibody against epithelial membrane antigen (1:50 dilution, Dako) and HMFG1 (1:25 dilution, Vector) were strongly positive.

Electron microscopic images showing features typical of sebaceous gland—that is, a multilobular gland lined by a simple squamous epithelium up to two cells deep. The squamous epithelial cells contained bundles of cytokeratin filaments, mitochondria, polyribosomes, rough endoplasmic reticulum and desmosome junctions.

The central portion of the gland was composed of cells, the cytoplasm of which was full of lipid droplets. These lipid droplets were relatively monomorphic and typically $4.5\ \mu\text{m}$ in diameter; unfortunately, owing to the previous processing of paraffin wax block, it was impossible to comment on the proportion of saturated to unsaturated lipid. No cholesterol crystals were identified. In the cytoplasm between the lipid droplets, mitochondria, polyribosomes and short segments of rough endoplasmic reticulum were identified. Owing to paraffin processing, it was impossible to comment on smooth endoplasmic reticulum, or peroxisomes. Lysosomes were not prominent. Desmosomes were present between these cells. Nuclear morphology of both squamous and sebaceous cells was typically oval, smooth outlined, with medium-sized nucleoli, and contained mostly euchromatin. Between the glands, the connective tissue was composed of fibroblasts and fibrous collagen. Thus, confirming the sebaceous origin of these lobules.

The first lesion was diagnosed as benign vulval lentiginosis (genital melanotic macule) together with sebaceous hyperplasia of the vulva.

The second lesion showed mild hyperkeratosis and acanthosis with a central area displaying prominent basal hyperpigmentation. Melanocytic hyperplasia was not prominent and there was no evidence of dysplasia or malignancy, on multiple levels. No sebaceous lobules were present. This lesion was diagnosed as a genital benign melanotic macule. It also served as an internal control, as otherwise it showed the normal histological features of perivulval skin (fig 2).

Discussion and comments

Sebaceous glands are present throughout the skin, except on the palms and soles. Sebaceous glands are well developed a few weeks after birth, probably due to maternal hormones. They almost disappear during early childhood, especially within the first few months. As a direct result of increased androgen output, sebaceous glands enlarge during puberty and then remain constant until middle age, later tending to decrease slowly from around the 60s onwards.⁸

Sebaceous hyperplasia of the vulva is exceedingly rare, and only three cases have been reported in the literature^{6–9} so far. Table 1 lists the previous three, and includes the present case. The age range was between 19 and 37 (mean 29.7 and median 31) years. However, it is not only the remarkable rarity of this entity in the vulva that deserves mention but also the existence of some important differences that manifest in the lesions at this site when compared with the common facial lesions. The four cases (including our case) seemed to occur at young age (mean age 24.2 years) compared with a mean age of 61.2 years reported in some series of sebaceous hyperplasia of the face.^{7 10 11} In addition, the gross appearances of these lesions were polypoid in all cases and were remarkably larger (mean size 19.2 mm in maximum dimension) compared with the 2–3 mm usual size of sebaceous hyperplasia elsewhere in the body. Interestingly, all four cases were not diagnosed clinically, indicating the difficulty in recognising these lesions clinically. However, histologically, these lesions are distinct.

The clinical differential diagnoses offered in the four reported cases (including our case) were condyloma acuminata, inflammatory conditions such as furuncles and, most importantly, vulval neoplasms.

By contrast, the microscopically differential diagnoses include ectopic sebaceous glands (Fordyce's granules (FGs) or spots),¹² sebaceous adenoma and sebaceoma. It is important to differentiate sebaceous hyperplasia from FGs as the latter are normally present on the whole surface on the labia minora. FGs are

viewed as normal anatomical variation presenting on the buccal mucosa, upper and lower labial mucosa, lip and retromolar areas, although they have been rarely reported on other sites.^{12–17} FGs progressively involute after menopause, and they can sometimes be destroyed by inflammatory skin disorders such as lichen sclerosus. FGs are clinically seen as small yellow papules measuring 1–3 mm in diameter without central depression when labia minora are properly stretched; otherwise, they are not clinically visible. Importantly, FGs are, histologically, seen as ectopic sebaceous glands without attached follicles.^{7 12–17}

The pathogenesis of sebaceous hyperplasia is not fully understood. Sebaceous glands are holocrine glands that form secretion by total cellular disintegration and seem to be affected by both internal and external factors. For example, ultraviolet radiation possibly represents a cofactor.⁸ Prolonged ultraviolet radiation exposure has been shown to cause sebaceous hyperplasia in hairless mice.^{18 19} However, sebaceous hyperplasia also occurs in sun-protected sites like the vulval mucosa. Human papillomavirus has also been implicated in the development of sebaceous gland carcinoma.²⁰ In addition, mucus-secreting glands have been demonstrated to be associated with previous surgery and chronic inflammation.²⁰ Finally, de Berker *et al*²¹ reported that sebaceous hyperplasia occurred in 16% of immune-suppressed organ transplant recipients. Fortunately, none of these cofactors seemed to be present in our patient.

It is also noteworthy, that none of the four reported cases (including our case) recurred, and treatment was by simple excision. However, cryotherapy, cauterisation or topical medications have also been mentioned as valid therapeutic options.

In conclusion, we report a unique case of sebaceous hyperplasia of the vulva in association with benign lentiginosis. It is also important to biopsy any unusual-looking lesions in the vulva to exclude the possibility of intraepithelial neoplasia and malignancy. The presence of only four patients with sebaceous hyperplasia of the vulva to date showed that this entity is very rare.

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Table 1 Previous reports and current report of sebaceous hyperplasia of the vulva

Author (year)	Age (years)	Site	Clinical diagnosis	Gross appearances	Size (mm)	Immunohisto-chemistry
Ortiz-Rey JA <i>et al</i> , ⁵ 2002	19	Left labia majus	None offered	Polypoidal lesion covered by normal skin	25	Androgen receptors and EMA
Rocamoro A <i>et al</i> , ⁶ 1986	32	Labia majus (both) and mons veneris	Condyloma accuminata/soft fibroma	Three polypoidal lesion covered by normal skin present for 8 years	15	Not done
Bakaris S <i>et al</i> , ⁹ 2003	37	Both labia minora	Irregular cycle/none offered	Polypoidal, slightly tender masses	25×20×10	EMA
Present case	31	Left vulva and mid-line region	Pigmented areas benign tumour	Polypoid	12×6×3	EMA and EM studies

EM, electron microscopy; EMA, epithelial membrane antigen.

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Neuroendocrine tumour cells in the wall of a splenic artery aneurysm

Neuroendocrine tumours are reported from the alimentary and respiratory tracts. A case of a 57-year-old man with an unsuspected histopathological finding of neuroendocrine tumour

cells in the wall of a splenic artery aneurysm is reported.

Visceral artery aneurysms are uncommon but clinically important owing to the risk of rupture and of intra-abdominal bleeding.¹ There are several possible aetiologies, atherosclerosis being one, and often the cause is unknown or at least not stated.¹ The case of a patient with two visceral artery aneurysms and unsuspected histopathological finding is reported.

Case report

A 57-year-old man presented with a 24 h history of increasingly severe upper abdominal pain. As an infant, he was operated on for an open Botalli duct. At the age of 20 years, he was conservatively treated for a pyloric ulcer. For the previous 2 years, he had been taking drugs for depression. On admission to hospital, his abdomen was tender with general guarding. A contrast-enhanced CT scan showed a splenic artery aneurysm and a mass in the pyloric region suspected as a ruptured visceral aneurysm. Both lesions were about 7 cm in diameter. An emergency laparotomy showed free blood in the peritoneal cavity and an upper right retroperitoneal haematoma.

A ruptured aneurysm of the right gastropiploic artery was resected en bloc with a part of the antrum and colon. Histopathological examination showed atherosclerosis in the wall of the aneurysm and chronic gastritis in the antrum. An elective operation was performed 4 months later and the splenic artery aneurysm repaired by proximal and distal ligation. A representative part of the splenic artery aneurysm was resected and fixed in formalin for histopathological examination.

Blood and urine samples were obtained postoperatively for hormonal and polypeptide evaluation (table 1). Values for plasma chromogranin A and urinary 5-hydroxyindoleacetic acid were slightly increased. The increased level of serum gastrin was explained by the patient's chronic gastritis.

Further investigations, including upper gastrointestinal endoscopy, colonoscopy, contrast x ray investigation of the small intestine and MRI (Octrescan)-somatostatin receptor scintigraphy were performed and found to be normal.

A capsule endoscopy showed two polypoid tumours located in the jejunum. A third laparotomy was performed 10 months after the first operation with peroperative endoscopy of the small intestine. The polypoid tumours were benign lymphangiomas. The appendix was normal at inspection.

Figure 1 Discrete finding of some divergent cells in small groups and rows in the muscularis layer of the splenic artery aneurysm wall, suggesting tumour impression.

Figure 2 Chromogranin staining of tumour cells in the wall of a splenic artery aneurysm.

Pathological findings

The histopathological examination of the resected part of the splenic artery aneurysm showed atherosclerosis, fibrosis and chronic inflammation. Furthermore, the microscopical examination showed a discrete finding of some divergent cells in small groups and rows in the muscularis layer of the aneurysm wall, suggesting tumour impression (fig 1).

Immunohistochemical staining of the tumour cells showed positivity for cytokeratin AE1/AE3 (DakoCytomation, Glostrup, Denmark), synaptophysin (DakoCytomation) and chromogranin (Ventana Medical Systems, Arizona, USA, fig 2), supporting the diagnosis of a neuroendocrine foregut type tumour. Immunohistochemical staining of tumour cells was negative for serotonin (DakoCytomation) and therefore the cells were not classic carcinoid tumour cells.

Table 1 Biochemical tumour markers

Samples	Observed value	Reference value
s-CEA	<0.5 µg/l	<5 µg/l
s-Insulin	79.2 pmol/l	<206 pmol/l
s-C-peptide	0.5 nmol/l	0.36–1.7 nmol/l
s-Gastrin	166 pmol/l	12–53 pmol/l
p-Glucagon	40 pmol/l	<60 pmol/l
p-VIP	<5 pmol/l	<15 pmol/l
Fp-chromogranin A	7.3 nmol/l	<4 nmol/l
Fp-chromogranin B	1.5 nmol/l	<2 nmol/l
tu-5-HIAA	47 µmol/day	2–33 µmol/day

p-VIP, p-vasoactive intestinal peptide; s-CEA, s-carcinoembryonic antigen; tu-5-HIAA, total urinary 5-hydroxyindoleacetic acid.