Papillary hidradenoma: immunohistochemical analysis of steroid receptor profile with a focus on apocrine differentiation

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Abstract

Aim—To make a quantitative evaluation by image analysis of oestrogen receptors, progesterone receptors, and androgen receptors in papillary hidradenomas and anogenital sweat glands.

Methods—20 papillary hidradenomas and the anogenital sweat glands detected in surgical specimens selected from 10 vulvectomies for squamous carcinoma, eight haemorrhoidectomies, and one anal polypectomy, all from female patients, were investigated by the avidin–streptavidin peroxidase testing system.

Results—90% of papillary hidradenomas and almost all the anogenital sweat glands showed immunoreactivity for oestrogen receptor and, more weakly, for progesterone receptor, with immunolabelled nuclear area ranging from 10% to 90%. Conversely conventional sweat glands did not show any nuclear staining. Overexpression of androgen receptors occurred in 20% of papillary hidradenomas, with nuclear staining strictly bordering papillary epithelium with apocrine differentiation. There was no immunoreactivity for androgen receptors in anogenital sweat glands.

Conclusions—Oestrogen and progesterone receptors seem to represent reliable markers for differentiating between anogenital sweat glands and conventional sweat glands, and a further link to explain why papillary hidradenomas occur almost exclusively in the female anogenital region. Positivity for oestrogen/progesterone receptors suggests that epithelia either of anogenital sweat glands or of papillary hidradenomas are controlled by ovariand steroid hormones. Androgen receptor nuclear staining of the epithelium with apocrine differentiation in vulvar papillary hidradenoma strengthens its homology with breast duct papilloma.

Keywords: steroid receptors; anogenital sweat glands; papillary hidradenoma; apocrine differentiation

Oestrogen and progesterone receptors have recently been carefully investigated in both benign and malignant eccrine sweat gland tumours, primarily to identify a marker for differentiating breast cancer metastases from eccrine neoplasms. Syringoma, chondroid syringoma, eccrine hidradenoma, eccrine carcinoma, and microcystic adnexal carcinoma have sometimes been shown to express oestrogen receptors and progesterone receptors. However, there have been few reports on the steroid receptor profile of papillary hidradenoma, which has unique clinicopathological features as it develops only in postpuberal and post-menopausal women and is localised almost exclusively to vulvar, perineal, and perianal skin. Moreover in recent years several histological studies of the female anogenital region have carefully examined a new variant of cutaneous glands, the so called “anogenital sweat glands,” which are considered the most likely source of papillary hidradenomas. Our objective in this immunohistochemical study was to make a quantitative evaluation of oestrogen receptors, progesterone receptors, and androgen receptors. By focusing attention on the apocrine differentiation of papillary epithelium, we aimed to provide further immunohistochemical evidence for the supposed histogenetic linkage of papillary hidradenoma with anogenital sweat glands, as well its steroid hormone dependence.

Methods

The patient data and specimens used in this study were retrieved by AC from the files of the department of pathology and the dermatology clinic of the University of Ancona from 1986 to 1997. The investigation was performed on 19 excisional biopsies, including 20 papillary hidradenomas. In addition, anogenital sweat glands were analysed in the specimens from 10 vulvectomies performed for squamous carcinoma, eight hemmorhoidectomies, and one anal polypectomy, all from female patients. Sections from archival formalin fixed, paraffin embedded tissues were stained using conventional procedures, and by the alcian blue (pH 2.5) and periodic acid–Schiff (PAS) methods for mucus. Serial sections were also incubated with a panel of primary antibodies, all known to react with formaldehyde fixed, paraffin embedded tissue, against the following: low molecular weight keratins (CAM 5.2; Becton Dickinson), high molecular weight keratins (AE 1–3; Diagnostic Products Corporation), carcinoembryonic antigen (anti-CEA; Ylem), human milk fat globule protein (anti-HMFG 1 and 2; Oxoid), S 100 (anti-S protein; Dakopatts), actin (HHF 35; Dakopatts), vimentin (anti-vimentin; Dakopatts), lysozyme (anti-lysozyme; Dakopatts), EMA (anti-EMA; Dakopatts), and receptors for oestrogen (oestrogen receptor ID5; BioGenex), progesterone (PGR-1A6; BioGenex), and androgen
The avidin-streptavidin-alkaline peroxidase testing system was employed. All preparations of papillary hidradenomas were briefly counterstained with ethyl green and those of anogenital sweat glands with haematoxylin. Non-immune mouse and rabbit sera were substituted as negative controls. Appropriate positive controls were run concurrently for all the antibodies tested. Tissue samples from breast and prostate cancers, known to bear oestrogen/progesterone receptors and androgen receptors, acted as external controls. Stromal vimentin staining (fibroblasts, endothelium) was used as an internal control of antigenicity as its epitope shows a vulnerability to fixation or processing comparable to that shown by steroid receptor antigens. The oestrogen and progesterone receptors were quantified on slides with the Cell Analysis System 200 instrument (CAS 200). Information concerning clinical presentation, treatment, and outcome was sought for all patients. Complete excision of hidradenomas was easily accomplished and postoperative course was uneventful.

**Results**

**CLINICAL FEATURES**

All patients were in postpuberal and postmenopausal age groups: the youngest was 26 years old and the oldest 92 (mean 51 years). One patient had two hidradenomas. Nine of the 19 patients were asymptomatic; in three, the tumour was a fortuitous finding in specimens from haemorrhoidectomies. Bleeding and ulcerated lesions had occurred in three patients. Four patients reported fluctuation in size of the tumour with the menstrual cycle. The clinical diagnosis of the lesion was correct in five cases; misdiagnoses included cysts in nine, haemorrhoids in three, and melanoma and carcinoma in one case each. Tumour sizes ranged from 0.3 cm to 4 cm (mean: 1.2 cm).

**HISTOPATHOLOGY**

All 20 tumours fulfilled the diagnostic criteria of papillary hidradenoma, as reported in standard textbooks of dermatopathology. In five cases we detected areas of apocrine differentiation of papillary epithelium where lining cells appeared columnar, cuboidal, or flattened, depending entirely on the location of the lesion on papillary folds or in tension cysts. These cells were equipped with dome shaped, abundant, granular, and strongly cosinophilic cytoplasm and pale, globoid nuclei with one or two nucleoli. Anogenital sweat glands were selected according to the morphological description provided by van der Putte.

**IMMUNOHISTOCHEMISTRY**

The epithelium of both papillary hidradenomas and anogenital sweat glands rested on a outer layer of myoepithelial cells that gave a strong reaction with antibodies directed against smooth muscle actin (HHF35), S100 protein, and, more weakly, CAM 5.2. The inner luminal layer of columnar cells, mainly with apical “snouts,” expressed distinct reactivity for antibodies against low molecular weight keratin, human milk fat globules (HMFG), and lysozyme but not for those against carcinoembryonic antigen (CEA). The cells with apocrine differentiation were distinctly immunoreactive to epithelial membrane antigen, keratin, and lysozyme, but not to carcinoembryonic antigen.

**RECEPTORS**

Anogenital sweat glands reacted strongly with antibodies to oestrogen receptor and moderately to progesterone receptor, whereas there was no immunoreactivity to androgen receptor. Interestingly, in glands with an intermediate morphology encompassing anogenital sweat glands with “a small segment of typical eccrine epithelium”, only nuclei of anogenital epithelium stained with oestrogen receptor and progesterone receptor antibodies.

Eighteen papillary hidradenomas (90%) showed immunoreactivity for oestrogen/progesterone receptor which was scored according to per cent positive nuclear surface: 0, negative (two cases); 1, less than 1–10% positive (no cases); 2, 1–10% positive (no cases); 3, 10–33% positive (five cases); 4, 34–66% positive (seven cases); 5, 67–100% positive (six cases). We chose a score of 10% as the cut off to include borderline positive cases in the positive category. The staining intensity was calculated on the basis of 1, weak; 2, moderate; and 3, intense nuclear staining. The oestrogen receptor score staining was 3 in all positive cases, whereas progesterone receptor staining score was 2 in 13 cases and 1 in five cases. There was no relation between staining degree and the age of the patients. No immunostaining was obtained for oestrogen and progesterone receptors in epithelium with apocrine differentiation; in contrast, it showed overexpression of androgen receptors as almost all the nuclei were immunolabelled. Two papillary hidradenomas did not show any staining for either steroid receptors or vimentin filaments.

**Discussion**

Although an unusual lesion, papillary hidradenoma represents the most common benign adnexal tumour of vulvar skin. The hypothesis that this tumour originates directly from apocrine sweat glands conflicts with its main clinicopathological features: it has not been reported in men, it does not develop in the axillary regions, and it does not appear to occur in black women. The common factor in these exceptions is the presence of high concentrations of apocrine sweat glands. Several recent studies of the microscopic anatomy of the female anogenital region have examined in detail a new variant of cutaneous glands, the so called anogenital sweat glands, which are considered to be the most likely source of papillary hidradenomas (fig 1). In this immunohistochemical investigation, we evaluated oestrogen receptors, progesterone receptors, and androgen receptors in a large series of anogenital sweat glands in which the epithelial cells were distinctly immunoreactive to oestrogen receptors (fig 2) and to a lesser degree to progesterone receptor, but not to androgen receptor.
Interestingly, in anogenital sweat glands of intermediate type equipped with both “ano-
genital” and typical eccrine epithelium, only
the former was immunoreactive to oestrogen and
progesterone receptors. There was no cor-
relation between number of nuclei expressing
oestrogen/progesterone receptor and age of the
patients. Typical eccrine and apocrine sweat
glands included in specimens selected were
devoid of either oestrogen receptors or proges-
terone receptors, while immunoreactivity for
androgen receptor was detected in eccrine
secretory coils and apocrine luminal cells.
These results agree with those previously
reported.13–15 Thus oestrogen and progesterone
receptors seem reliable markers for differenti-
ating female anogenital glands from conven-
tional sweat glands.

This report, based on the quantitative evalu-
ation by image analysis of oestrogen, proges-
terone, and androgen receptors in 20 papillary
hidradenomas, is one of the most complete, as
other reports have included fewer cases,16 or
have involved testing for oestrogen receptor
alone. Ninety per cent of papillary hidradeno-
mas showed immunoreactivity for oestrogen
receptor and more weakly for progesterone
receptor (fig 3), and labelling ranged from 90%
to 10% of nuclear area. We think that the nega-
tivity in two cases was caused by loss of
antigenicity during fixation and processing
rather than because of a true lack of steroid
receptors.

Thus the presence of oestrogen and proges-
terone receptors tends to support the assump-
tion that papillary hidradenoma is derived from
anogenital epithelium expressing these recep-
tors rather than from conventional apocrine
glands.

In 20% of our papillary hidradenomas,
immunoreactivity for androgen receptor was
present but was strictly limited to luminal cells
bearing the phenomenon of so-called “apocrine
differentiation” (fig 4), in the same way as in
breast proliferative disorders, where it has been
investigated in detail.17 18

This finding, in combination with the
morphological features, underscores the ho-
mology between papillary hidradenoma and
breast duct papilloma and supports the view
that papillary hidradenoma originates from
ectopic breast tissue, which may occur any-
where along the embryonic milk line. The vulva
lies in this line and is rich in apocrine glands,
modification of which may give rise to
accessory well developed breast tissue. Never-
theless this occurrence is exceedingly rare, since only 35 cases had been documented
in published reports up to 1988.19 We did not
find any well formed breast tissue in our speci-
mens, and papillary hidradenomas were mainly
found in the neighbourhood of anogenital
sweat glands. Moreover they were also located
in perianal skin, which is considered to be out
of the milk line and, on the average, they were
of smaller size than ectopic breast tissue. In
addition, no patients in our series described
vulvar symptoms during pregnancy and lacta-
tion, which might be expected as ectopic breast
tissue is capable of behaving in a similar way to
the normal breast and responds to the hormo-
nal influences.20 The presence of oestrogen
receptors, and even more so of progesterone
receptors, which are a phenotypical markers of
hormonal action,21 22 suggests that the luminal
cells of anogenital sweat glands and papillary

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**Figure 1** Anogenital sweat gland with characteristic
localisation in vulvar sulcus interlabialis: coiled duct is lined
by columnar cells with intraluminal snouts and apocrine
type secretion. Haematoxylin and eosin stain.

**Figure 2** Anogenital sweat gland: immunohistochemical
detection of oestrogen receptor on formalin fixed, para-
affin embedded tissue. Nuclear area was strongly stained up to
95% with anti-oestrogen receptor antibody (ER-ID5).
Immunoperoxidase staining counterstained with
haematoxylin.
formalin fixed, para

ey

n embedded tissue. Only cells with apocrine differentiation did not show any reactivity. Immunoperoxidase staining weakly counterstained with ethyl green.

Figure 3 Papillary hidradenoma: immunohistochemical detection of progesterone receptor on formalin fixed, paraffin embedded tissue. Almost all nuclei lining papillary folds were positive for progesterone receptor. Immunoperoxidase staining weakly counterstained with ethyl green.

Figure 4 Papillary hidradenoma: immunohistochemical detection of androgen receptor on formalin fixed, paraffin embedded tissue. Only cells with apocrine differentiation did not show any reactivity. Immunoperoxidase staining weakly counterstained with ethyl green.

Figures 3 and 4 show immunohistochemical staining for progesterone and androgen receptors, respectively, in papillary hidradenomas. The papillary epithelium tends to support the assumption that papillary hidradenomas are derived from these glands, rather than directly from conventional apocrine sweat glands, the latter being devoid of oestrogen and progesterone receptors. Finally the coexpression of steroid receptors has enabled us to classify the papillary hidradenoma in the group of hormone related tumours.

1 Wallace ML, Longacre TA, Smoller BR. Estrogen and progestosterone receptors and anti-gross cystic disease fluid protein 15 (BRST-2) fail to distinguish metastatic breast carcinoma from eccrine neoplasms. Mod Pathol 1995;8:987–901.


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