THE RELATIONSHIP OF MALIGNANT AMELANOTIC MELANOMA (NAEVOCARCINOMA) TO EXTRAMAMMARY PAGET’S DISEASE

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Ever since Sir James Paget first described the disease of the nipple named after him and remarked that he had seen a lesion clinically resembling it on the glans penis, followed by cancer, reputed cases of extramammary Paget’s disease have been sporadically reported and their nature discussed. The debate has been ancillary to the related question of the nature of Paget’s disease, which is still not completely settled, although the great majority of writers now accept it as a malignant neoplasm and not a dyskeratosis which may only secondarily become neoplastic. In a recent very excellent analysis of 57 reported cases of extramammary Paget’s disease to which he added one more, Weiner rejected 32, accepted 16 (including his own) without qualification, and thought 10 more were probably acceptable but had insufficient data to be sure. The accepted cases were all either in the axilla, on the vulva, or on the penis and scrotum. Moreover, many of them were associated with underlying glandular carcinomas or had some relationship with sweat or sebaceous glands. Weiner pointed out that the apocrine glands, which have a genetic relationship with the mammary glands, are found only in these regions, and he felt it proper to conclude that extramammary Paget’s disease does exist and that it is an intradermal metastasis from an underlying carcinoma of the apocrine sweat glands.

After studying all of the case reports analyzed by Weiner and a few more which he failed to include, the writer is persuaded that his conclusions are well taken and that he has settled the question: Extramammary Paget’s disease does occur, and it consists of peculiar skin lesions which are clinically and microscopically similar to Paget’s disease of the nipple, are associated usually with an underlying apocrine sweat gland carcinoma, and are quite possibly secondary to it.

What, then, are all the rejected cases of reputed extramammary Paget’s disease in other regions of the skin surface? Some of them are manifestly superficial basal-cell epitheliomas (the pagetoid epithelioma of the French), Bowen’s disease, or squamous-cell epithelioma, and do not conform either to the clinical or microscopical criteria of Paget’s disease. This, however, does not dispose of all the cases; there remain a handful of lesions having the skin manifestations of Paget’s disease, with or without other evidences of malignancy, occurring on parts of the body where there are no apocrine glands.

An explanation of these cases has already been suggested, but as most of those making it thought that it explained all cases of extramammary Paget’s disease, the hypothesis has not received as much attention as it deserves. As long ago as 1911 Kreibich came to the conclusion that Paget cells are ana-
plastic melanoblasts with the lipoid function retained but with the pigment-making function lost. Twenty years later he changed his conception somewhat, suggesting that the Paget carcinoma comes from the Langerhans cells of the epidermis. The close resemblance of the Paget cell to naevus cells also impressed Darier, and in 1920 he expressed the opinion that naevocarcinomas, Paget's disease, and Bowen's disease are all analogous and that all of them are due to dysembryoplasia. When Civatte reported his case of apocrine sweat gland cancer of the axilla with Paget's disease of the skin, he was so impressed with the resemblance to naevocarcinoma that he added the subtitle: "Le cancer noevo-carcinoide de la maladie de Paget." Bloch discusses this similarity and very justifiably points out that the fact of naevi having been found associated with one or two cases resembling Paget's disease is no reason for supposing that all cases are naevocarcinomas.

The fact remains, nevertheless, that there are cases of non-pigmented melanoma of long duration and superficial spread which so closely simulate Paget's disease that they may easily be mistaken for it. It seems important to emphasize this observation by abstracting the few recorded cases of this nature and reporting a probable new one which has engaged our puzzled attention for several years.

The earliest case was reported by Hartzell in 1910. His patient was a sixty-four-year-old man who had had a mole on the outer side of his left forearm. Fifteen years before, it had been irritated, and subsequently there gradually formed a bright red, oval, smooth area, some 6 or 7 cm. in diameter, scaly in patches, with a few crusts and a superficial ulcer in the upper part. The epidermis showed Paget cell infiltration, and the ulcerated nodule was composed of cords of vacuolated cells with shrunken nuclei, which were believed to be a naevocarcinoma. Hartzell thought the two conditions were simply associated but, as Weiner points out, the case is probably altogether one of naevocarcinoma with intraepidermal spread.

In discussion of Hartzell's case Winfield recalled that he had seen a woman who for eight years had had a peculiar raw red area typical of Paget's disease of the nipple over a portion of the scapula irritated by a corset. This lesion and a large congenital pigmented mole of the mammary region were both removed. "The patch over the scapula gave the typical picture of Paget's disease, and the mole also showed the same histological appearance." It seems probable that the scapula lesion represented the intraepidermal spread of a malignant melanoma without obvious pigmentation.

Another possible case is that of Satani. A seventy-four-year-old man had always had a "wart" the size of a pea in the axilla. Six years earlier it became red and swollen, and after one year there was a discharge from it. The lesion sometimes itched and burned and finally attained a diameter of 7 cm., forming a red, moist patch with a nipple-like nodule in the center. The patient also had condylomata covering the penis and scrotum. The axillary lesion was excised and the condylomata treated with x-ray and ointments. There was no evidence of disease after three weeks. The tumor was composed of cords of cells, and the skin lesion was characteristic of Paget's disease. This case is accepted by Weiner as an apocrine sweat gland tumor, but
with the history of having started in a "wart" it seems much more probable that it is an amelanotic melanoma.

In Taylor's case also, the lesion commenced in a "wart" on the lower third of the buttock and gradually spread until after seven years it formed an area $5 \times 8$ inches, surrounding the anus and involving the perineum. It had a slightly red, moist, granular surface with an ulcer at the site of the original "wart." It was stated that biopsy showed Paget's disease. When the report was made, the case was being treated with radium. The age and sex of the patient are not given, and the report is brief. It seems a proper inference that the case is probably one of superficial amelanotic melanoma.

Werther reported briefly the occurrence, in a woman sixty-nine years old, of a lesion resembling seborrhoeic eczema, of one year's duration, situated just below the left knee. It was of a brownish color with sharply defined borders, and in the center was a red, moist nodule; otherwise it was smooth and dry. Grossly it recalled Paget's disease, and a biopsy showed carcinoma with large clumped nuclei and vacuoles in the cytoplasm. A subsequent report, two years later, states that the patient was successfully treated with radium. Obviously the case cannot be evaluated from such meager data, but it seems more probable that it is amelanotic melanoma of the superficial type.

In 1924 Grutz described three skin lesions as manifestations of Bowen's disease. The third case is that of a sixty-eight-year-old man who had had a slightly elevated, light brown fleck on his right eyebrow for three years, with sudden growth over a period of three months. Without any other gross description Grutz states that the lesion was excised. Examination showed that the tumor was a malignant melanoma, and note is made of the presence of atypical cells and cell nests in the epidermis. This is obviously a case of malignant melanoma with epidermal infiltration which microscopically resembled Paget's disease. There is nothing in the report to warrant the diagnosis of Bowen's disease.

**Case Report**

A seventy-one-year-old housewife was admitted to Vanderbilt Clinic April 24, 1933. She stated that twelve years before, a small crusting lesion appeared in the left popliteal space. This gradually increased until it covered an area $3 \times 4$ cm. and was covered with crusts from constant exudation. It occasionally bled. Four years before admission, the patient went to another hospital, where a diagnosis of "chronic inflammatory tissue" was made on a piece removed by biopsy, and x-ray therapy was instituted. The dosage was not ascertained. After this treatment the condition healed for the most part, but the area was never entirely free from the presence of at least one small crusting lesion. Seven and a half months before admission a mass appeared in the left femoral region which increased painlessly and became hard.

When the patient was examined, two small, rounded, crusted lesions were found in the popliteal space, the larger of which was only $5 \text{ mm}$ in diameter. There was no hyperkeratosis, and when the crusts were removed, the underlying surface was moist and red. Reddened areolae surrounded the lesions. There was some thickening but no true induration. In the left femoral region was a single, firm node, $5 \times 4$ cm.

The femoral node was first excised May 15, 1933, and ten days later the two popliteal lesions were separately excised and the denuded area Thiersch-grafted. When the wounds had healed, x-ray treatment was instituted, 3600 r being given in two different courses to a $15 \times 15$ cm. field in the left femoral and inguinal regions between June 14 and Sept. 22, 1933. The factors were 190 kv., 8 ma., 50 cm. target skin distance, and 1.86 mm. copper +
1.0 mm. aluminum filtration. The popliteal region was treated through three $10 \times 15$ cm. lateral, mesial, and posterior fields between June 21 and Dec. 29, 1933, a total of 6300 $r$ being given. The factors were the same except that the filtration was 0.56 mm. copper + 1.0 mm. aluminum.

The patient remained well for nineteen months after operation, at the end of which time pain and swelling of the left lower extremity developed, due to lymphatic invasion of the inguinal, femoral, and iliac regions. From Jan. 11 to Jan. 18, 1935, 600 $r$ were given to the left femoral and iliac regions through a $15 \times 20$ cm. field, but the patient could not come for further treatments. She was admitted to a home for incurables, and died Jan. 9, 1936, thirty-one months after operation and nearly fifteen years after onset of the disease, with evidence of extensive pulmonary metastases. No autopsy was obtained.

**FIG. 1. THE LARGER POPLITEAL LESION**

This shows the lengthening and thickening of the rete pegs, the small amount of hyperkeratinization, the marked inflammatory cell infiltration beneath the epidermis, the absence of tumor invasion beneath the epidermis, and the intact corium with its sweat glands.

**Histopathology:** The popliteal lesions (S.P. 51429) both show the same features (Fig. 1). The epidermal layer is intact. It is thickened chiefly because of the great elongation of the rete pegs, which extend downward for three times the normal distance and are broadened. The basement membrane is, however, intact, and nowhere is there any invasion. The cause of the thickening and elongation is the presence of rounded or elongated tumor cells which have hyperchromatic nuclei with clearly defined nuclear markings and usually one distinct nucleolus. Mitoses average one in every five high-power fields. The cytoplasm is finely granular and neutrophilic and the cell membrane distinct. In some areas these cells have completely replaced the entire thickness of the epidermis. In other areas the epidermis is relatively well preserved, but the tumor cells lie within it either as isolated units or in small packets (Fig. 2). These cells have very pale-staining, finely granular cytoplasm, and this, together with their rounded shape, makes them stand out in sharp contrast to the surrounding epidermal cells of the stratum mucosum, which have fibrillar and
more deeply stained cytoplasm and are connected by filaments of union. The epidermis is covered in part by a thin keratinized layer, and the tumor cells extend up to and sometimes into this. The Fontana stain shows no trace of melanin in any of the tumor cells, although in the surrounding intact epidermis both basal and dendritic melanoblasts are found in considerable numbers. In one or two places intraepidermal lysis has occurred with the formation of microscopic blebs filled with tumor cells and fluid. The papillary layer and the superficial part of the corium are heavily infiltrated with many lymphocytes and some plasma cells. This zone also shows increased vascularity. The sweat glands and their ducts show no evidence of epithelial activity, and there is nothing to suggest that they play any part in the tumor formation. At its margins the tumor ceases quite abruptly in the epidermis.

The femoral lymph node (S.P. 51317) has been almost entirely replaced by tumor.
tissue, only traces of lymphoid tissue being found near the capsule at one point. The tumor cells are arranged in thick cords separated by slender collagen bands near the capsule and by thick fibrous strands toward the center (Fig. 3). The tumor cells are large and rounded except where pressure from neighboring cells has moulded them. The nuclei are large, rounded, centrally placed, and hyperchromatic, with sharply defined nuclear markings but no larger nucleoli. Mitoses average one in every high-power field, and many of them are bizarre. The cytoplasm is finely granular, neutrophilic, and often vacuolated. No trace of pigmentation is visible grossly, nor are there any blackened granules found with the Fontana stain. Nowhere do the tumor cells show any epidermoid differentiation: there is no keratinization, pearl formation, or stratification, nor are there any intercellular bridges or intercellular fibrils.

The original biopsy, taken four years before, was obtained for inspection from the hospital where it was made. The preparation was poorly fixed and stained, but, so far as could be observed, the process was exactly the same at that time as it was when the lesions persisting after x-ray treatment were excised.

**DISCUSSION**

It is quite obvious that this lesion can be one of only two conditions: either extramammary Paget's disease or intraepidermal melanoma without evidence...
of pigment formation. It is possible for both to be of very long duration, during which time the primary tumor displays only intraepidermal spread, with eventual metastasis and death. Unless there is pigment formation or the cells are Dopa-positive, it is impossible to distinguish between the Paget cell in the epidermis and the cells of malignant melanoma (Fig. 4). In this instance

![Image](image_url)

**Fig. 4. Detail of the Epidermis Covering a Malignant Melanoma of the Foot, Showing Intraepidermal Invasion**

At the right a group of cells has penetrated the stratum corneum. Above, solitary tumor cells are seen in the stratum mucosum. It is evident that this is the same type of epidermal invasion as occurs in Paget's disease. × 345.

no Dopa test was done on the fresh tissue, and no pigment was found after treatment with ammoniacal silver. There was no history of a preceding mole or pigmented spot to aid in the diagnosis. The chief factor which enables one to choose between the two is the primary site. Every unquestioned case of extramammary Paget's disease has occurred in the male and female genital
areas or the axillae, where there are apocrine glands, while every reported case from the rest of the skin is either not Paget's disease or is doubtful. On the other hand, melanomas can arise anywhere in the skin; it is not uncommon to find no evidence of pigment formation (Miescher, Horwitz), and metastasis may manifest itself after a delay as long as twenty-seven years (Miescher), while the primary tumor remains insignificant. The second fact which aids in differential diagnosis is the morphology of the metastases. In the few cases of extramammary Paget's disease where the metastases were studied there was usually some tendency to form tubes or acini (Weiner). That never occurs in malignant melanoma. On the contrary, the melanoma metastases assume usually the cordiform arrangement separated by fibrous strands seen in the metastases in this case (Fig. 3).

The present case and the six others here reviewed have certain features in common. They are all superficial, of relatively long duration (one to fifteen years), all of them had exudative reddish lesions which crusted, and many of which became superficially ulcerated. The cases of Hartzell, Satani, Taylor, and Grütz developed from or around primary nodules described as moles or warts. Examination of all seven showed intraepidermal invasion by cells resembling Paget cells, while the cases of Hartzell, Satani, Werther and Grütz showed, in addition, superficial invasion of the tissues beneath the epidermis. The writer's case is the only one which metastasized.

If these cases are accepted as malignant melanomas without demonstrated pigmentation, they must then be recognized as specialized and unusual forms of that tumor in which, contrary to the rule, growth is exceedingly slow and metastasis may be expected to manifest itself only after a long quiescent period. When a Paget-like lesion occurs on the surface of the body outside of the mammary, axillary, and genital zones, one of these pigment-free melanomas may be suspected. If the lesion is in any of the zones where Paget's disease is known to occur, it may be impossible to distinguish clinically between the two.

**Summary**

A case is reported of a tumor believed to be a pigment-free malignant melanoma of the popliteal region, the primary manifestation of which was indistinguishable from Paget’s disease. It was of long duration and apparently limited to the epidermis, yet it metastasized and resulted in death. The anatomical situation and the morphology of the metastases determined the diagnosis of melanoma rather than Paget's disease. Six comparable cases are reviewed. It is suggested that these cases form a group of superficial, slow-growing naevocarcinomas with Paget-like characteristics which distinguish them from other melanomas.

**Bibliography**

Winfield: in discussion of Hartzell's case (see above).