LENTIGO MALIGNA: REPORT OF ONE CASE TREATED WITH RADIUM

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Melanin pigmentation in its normal physiological relation to cell metabolism and its intimate relationship to many general and local conditions has been, and remains, the subject of much interest and investigation. The literature on any phase of this subject is voluminous, but reveals a wide divergence of opinion, and the conclusions of various workers are not in agreement. The relationship existing between pigment production and tumor cell proliferation has been studied extensively by many authors, more recently by Dawson (1925) (1), Miescher (1927) (2), and Becker (1930) (3). An important advance toward the solution of the pigment question has been made by Bloch (4) and his co-workers by a functional approach to the problem of melanin formation.

It is often impossible to make a fine distinction between pigmentation occurring normally as the result of a physiological process, and that occurring pathologically. The occurrence of freckles in a blonde individual as the result of a defensive reaction to exposure would be considered a normal reaction in most cases, but such a condition might be the early stage of xeroderma pigmentosum. Similarly, a small tan to brown macule on the face of a mature individual may be indistinguishable clinically from an ordinary freckle, yet such a spot might give rise to a malignant tumor.

This latter condition should be considered a precancerous melanosis. Hutchinson (5) was the first to describe the transformation from such a lesion to malignancy. In 1892 he reported three cases of pigmented carcinoma arising from long-standing aggressioning pigmented spots (senile freckles) in aged individuals; these he called "infective melanotic freckles" or "lentigo-melanosis." In 1894 Dubreuilh (6) described an identical condition in a report of four similar cases, which he termed "malignant
lentigo of the aged” or “precancerous circumscribed melanosis.” In the same year Bayet (7) reported a progressively enlarging black macule on the cheek of a woman of fifty-five, using the term “infective freckle of the aged.” In 1917 Pusey (8) illustrated the case of an elderly woman who presented a similar lesion which had developed in a period of a few years, and which he termed “pigmented senile patch.”

Cases of lentigo maligna have been reported in the literature occasionally since that time, but Miescher states that the condition occurs more frequently than has hitherto been assumed.

Piffard (quoted by Stelwagon) had previously assigned the name lentigo maligna to the dermatosis originally described by Kaposi in 1870, and generally referred to today as xeroderma pigmentosum. These affections, which might appear analogous, differ in the ages of the subjects, multiplicity of the lesions, the symmetrical and extensive distribution of the lesions, the factor of exposure as the immediate causative agent, the absence of a melanotic tumor, and the presence of telangiectases, atrophic areas, and dryness of the skin in xeroderma pigmentosum (Dubreuilh).

In 1904 Hutchinson (9) modified the lentigo maligna of Piffard (xeroderma pigmentosum) with juvenilis and the lentigo maligna of Dubreuilh with senilis. However, many writers since that time have used the term lentigo maligna synonymously with xeroderma pigmentosum (10, 11, 12, 13). Fig. 13 (p. 1568) shows a large pigmented macular lesion on the arm of a patient with xeroderma pigmentosum who has been under observation since 1914. This lesion has shown no tendency to enlarge; scattered in it are many points of atrophy the size of a pin head; around it are many telangiectases, atrophic spots, and the characteristic dryness of the skin. In modern literature the name of choice seems to be that originally given to it by Kaposi, and the condition of lentigo maligna described by Hutchinson, Dubreuilh and others should not be confused with it.

Darier (14) recognized the distinction between the two affections and classified lentigo maligna under the pigmented nevi. More recently Beeker (3) and Gans (15) have given this dermatosis a separate place under the cutaneous melanomata. A differential diagnosis between lentigo maligna and naevus pigmentosus rests upon the characteristic appearance, the irregular form, and the progressive and regressive growth in combination with other senile
dystrophic changes of lentigo maligna. The round-cell infiltration of the former does not occur in naevus pigmentosus (Gans).

This condition begins in a single or in multiple pigmented spots, usually, but not necessarily, on the face of old people. After periods of varying duration, these spots become confluent, and changes occur which can pass over into melanocarcinoma. These may or may not show pigment grossly. In their histologic structure, these growths closely resemble melanocarcinoma. In the transition stages, or at an aggressing border, there are found, under a thin epidermis, richly pigmented basal cells and ordinary cell elements in all stages of epithelial transformation. Very early in the process, apparently before these epithelial changes set in, the basal cells are transformed sporadically into extraordinarily large, irregularly shaped structures without the occurrence of any special augmentation of the dendritic cells (melanoblasts). In the cutis there are found, as a rule, numerous chromatophores (pigment-carrying cells) besides a pronounced subpapillary accumulation of round cells and plasma cells. In the areas that have become depigmented, there is a complete absence of epidermal pigment, but chromatophores (pigment-carrying cells) can be found in the dermis (Miescher).

Among 46,000 consecutive admissions to the Barnard Free Skin and Cancer Hospital since 1905 for treatment of all forms of skin diseases and cancer, there have been 103 cases of cutaneous melanomas, exclusive of a larger group of benign pigmented nevi. Of these melanomata there has been only one which can be classified properly under the head of lentigo maligna. In another case, in a woman of fifty-five who has been observed at intervals for the past ten years, there is a smooth black lesion over the right malar process, 3 cm. in diameter, which has been present for fifteen years. This lesion has trebled in size in the past five years. A definite diagnosis is precluded on account of the patient's unwillingness to co-operate, but this probably represents an earlier stage of lentigo maligna, namely senile freckle (Hutchinson) or pigmented senile patch (Pusey).

The following case is considered of sufficient interest to be recorded, not only because of the relative rarity of lentigo maligna, but also because of the uncertainty of the nosologic classification of this affection and its relationship to other of the cutaneous melanomata, and finally because of its notable response to radium therapy.
History: Mrs. L. K. (31982), a white female of seventy-nine years, was admitted to the service of Drs. M. F. Engman and W. H. Mook in August 1925, when she presented a pigmented lesion on the right cheek extending from the naso-labial fold backward to the zygomatic process, and from the external canthus downward to the level of the upper lip, covering an area 7 cm. wide and 5 cm. high. The outline of this area was irregular, the border was sharp and there was no elevation above the surrounding skin. The medial portion was black, but the color tended to become lighter in the lateral portion, this border having a sepia to dark brown color. Immediately over the malar process, in the center of the lesion, was a pigmented tumor 1 cm. in diameter, which was elevated about 2 mm. above the surrounding lesion. Lateral to this was a smaller tumor, not so darkly pigmented. Neither lesion was ulcerated.

The history of the lesion dates back for thirty-nine years. When the patient was forty years old she noticed a small brown freckle on the right cheek, about the size of a split pea. This spot was perfectly smooth and caused no symptoms. It slowly increased in size and deepened in color, until ten years later it had reached the size of a dime and had become coal-black. Except for the color, there was no appreciable difference between this lesion and the surrounding normal skin. During the course of the succeeding twenty years there was a slow, progressive extension of the lesion to involve the upper half of the right cheek; the border became irregular, and "satellite" freckles appeared at the lateral border, enlarged, and became confluent with the original lesion. In 1923, two years before her admission to the clinic, two small firm nodules began to develop in the center of the original lesion. These enlarged very slowly at the onset, but one month prior to her admission their growth became rapid. During the entire course, this lesion had caused no symptoms, and no treatment of any sort had been attempted. The history given by the patient was confirmed by members of her family.

The patient's past history is irrelevant to the dermatosis under consideration. Her health has always been excellent. In her youth she had a few freckles on the exposed parts, but these had disappeared in adult life. The hair had been a chestnut brown color until the age of forty-five, when it began to turn gray.

Except for the usual changes of old age, the findings in the general physical examination are normal. The patient is an exceptionally well preserved and active woman of seventy-nine. There were a few slightly scaly patches on the left temple on admission. No other lesions were present on the skin or mucous membranes.

Course and Treatment: In the six years that this patient has been under treatment she has been observed at frequent intervals and has been presented before several clinical conferences. In the interim of specific treatment of epitheliomatous lesions that have developed on the primary lesion, nothing but bland ointments has been used. The senile keratoses on the left temple were destroyed with the actual cautery.

An attempt is made with the aid of the accompanying diagram and
photographs to illustrate the progress of the lesion and the effect of treatment. On Aug. 27, 1925, radium was applied to the two pigmented warty tumors in the following dosages: to the larger tumor, 100 mg. for four hours; to the smaller tumor, 50 mg. for four hours (Fig. 1: areas 1 and 2 respectively). Three weeks later, a reaction began to manifest itself by edema and moderate pain in the treated areas and ulceration of the tumors. Three weeks after the beginning of the reaction, it had apparently reached its height and the tumors began to retrogress. With the subsiding of the reaction, the skin in the exposed areas began to lose its pigment. Six months after the application, the tumors had disappeared entirely and the irradiated areas were relatively pigment-free (Figs. 2 and 3).

There was a continuous peripheral extension of the lesion, and two years after admission it had enlarged about 1.5 cm. in each direction,
FIGS. 2 AND 3. OCTOBER 15, 1926. FOURTEEN MONTHS AFTER THE APPLICATION OF
RADIUM TO AREAS 1 AND 2

The exposed areas have lost considerable pigment. The medial portion and the
nasal border remain deeply pigmented.

FIGS. 4 AND 5. MARCH 12, 1928. TWO AND ONE-HALF YEARS AFTER THE
FIRST RADIUM APPLICATION

The lesion has shown an irregular peripheral extension, and the previously brownish
areas in the lateral portion have become black. Pigment has reappeared along the
margins of the irradiated areas. Three pigmented epitheliomas have arisen in the
untreated areas. Specimens at a and b were excised for histologic examination.
and pigment had begun to reappear at the edge of the previously depigmented area. The lateral and lower borders of this aggressing lesion were preceded by a zone of light brown to dark brown pigmentation, which became darker as the lesion progressed. The medial border was very sharp, and there was no fading of the lesion as the normal skin was approached. The medial portion of this area was black, and the surface was smooth and shiny; the lateral portion was of a somewhat lighter color, and the surface was not so smooth to the touch.

Figs. 6 and 7. Fig. 6 (Left), September 17, 1928: Six Months After Application of Radium to Area 3. Fig. 7 (Right), August 12, 1929: Nine Months After the Application of Radium to Areas 4 and 5

In Fig. 6 the large epithelioma at the lower portion has retrogressed completely, and the pigment is disappearing from this area. The two untreated epitheliomas have doubled in size. Fig. 7 shows complete retrogression of the warty growths and complete depigmentation of the irradiated areas.

By February 1928 a small nodular pigmented growth the size of a pea just medial to the treated area (Area 1) had developed. Just above this area there was a group of three small warty tumors, which showed little gross pigmentation. At the lower portion, there was a raised, indurated, warty growth 1.5 cm. in diameter, the surface of which appeared brown (Figs. 4 and 5); 100 mg. of radium was applied to the largest tumor for six hours on March 18, 1928 (Fig. 1, area 3). One of the warty growths was removed with the electric cautery (Fig. 5, b); and a portion of the smooth black lesion at the lower lateral border (Fig. 5, a) was removed for biopsy. The course of the radium reaction was essentially like that following the former applications. Six months later the tumor had disappeared; the area irradiated had lost most of its pigment; and the two untreated tumors had doubled in size (Fig. 6).
On Oct. 14, 1928, 100 mg. of radium was applied to the lower portion of the smooth black lesion (Fig. 1, area 4). On Dec. 6, 1928, the same dosage was applied to the tumors on the upper portion of the lesion (Fig. 1, area 5). The usual reaction to the radiation was noted. Nine months later, the tumors had disappeared, and the entire area treated with radium was free of pigment, slightly atrophic and pink in color. The lateral portion of the lesion, which had become much darker, and an area about 2 cm. square, involving the lower lid, remained (Fig. 7).

In June 1930 a small ulcer developed in the mid-portion of the cheek. This enlarged rapidly, and upon it a warty growth developed. Three months later this had reached one centimeter in diameter, was indurated and raised 3 mm. above the surrounding skin. Fig. 8 shows the increase in depth of color of this portion, and the slight spread of the pigmented portion involving the lower lid. On Sept. 25, 1930, 100 mg. of radium was applied to this tumor for six hours (Fig. 1, area 6). There was no change in the character of the reaction. In December 1930, the patient began to notice an itching of the right eye. When examined one month later, the lower lid was found to be thickened and indurated, but neither the skin surface or the palpebral conjunctiva was found to be affected. On Jan. 19, 1931, 95 mg. of radium was applied over the lower lid for four hours (Fig. 1, area 7). Six weeks after this last application (March 4, 1931), the reaction following the irradiation of Area 7 is at its height. The lesion under the eye is beginning to lose its pigment, and the induration noted in December 1930 is beginning to subside. The pigmentation of the entire lesion is much less.
1931) the reaction had reached its height, the pigment had begun to disappear from the periphery toward the center, and the lid became less indurated. The large area treated in September 1930 had become much lighter in color, and the tumor had retrogressed completely (Fig. 9).

At this observation, all that remained was a subsiding radium reaction of the lower lid and infra-orbital region, with evidence of regression of the pigment. The mid-portion of the cheek (Fig. 1, area 6) presents a diffuse light tan appearance with a few brownish macules at the periphery.

In each radium application, the radiation was filtered with one-half millimeter of silver and one millimeter of rubber.

![Histologic Features: In a study of the section removed from the pigmented skin there is noted a quite marked variation in the thickness of the epithelium, from one to many cell layers. In the thicker portions the basal layer and the lower portions of the stratum mucosum give a frayed appearance, and an occasional mitotic figure is demonstrated (Fig. 10). The pigment is finely granular in the subepithelial layer, and structures such as those described as dendritic cells are fairly well demonstrated under the higher magnifications when proper stain is used. Deep in the corium, and especially surrounding the glandular elements of the skin, the pigment is clumped into masses, the granular appearance being lost (Fig. 11). The striking histologic features of the verrucous growth that was removed are the marked increase in cell content, sparseness of vessels, a definite irregularity in staining quality, the presence of mitotic figures, and occasionally an attempt at pearl formation. Even though the histologic picture is rather indistinct, this tumor is no doubt...](image-url)
malignant and is most probably of the basal-cell type with a squamous-cell anaplasia. In other words, it is a tumor of low-grade malignancy (Fig. 12).

A case of a slowly progressing pigmented lesion of long duration, giving rise to seven pigmented epitheliomas during the past six years of observation, has been reported. The interesting features of this case are: the prompt response of the epitheliomas to radium therapy; complete de-pigmentation of the irradiated areas, which is apparently temporary, the pigment tending to reappear at the periphery of such an area and spreading slowly inward after about a year of decoloration; absence of recurrences of the epitheliomas, even after six years in the cases of the first ones treated. Epitheliomas have developed only in the black portions of the melanoma, and never from the tan to brown portions.

The term "lentigo maligna" is used to describe the process from its onset. The formation of melanocarcinomas seems to be
The richly cellular structure is made up of basal cells, squamous cells, some with mitotic figures, a definite hyperchromatism throughout, and a quite marked irregularity in size.
the end result of the early aggressive macular lesion (senile freckle, Hutchinson).

From the histologic study, clinical appearance, and clinical course of the case reported, one would infer that we were dealing with an increased activity of the melanoblasts of the basal layer. The relationship of this increased function of melanin production to cell proliferation and tumor growth cannot be explained on the basis of this one case. In this case tumors have developed in an area only after it had remained fully pigmented (black) for many years. This seems to indicate that the cells began to proliferate only after pigment production had ceased and the pigmentation had remained stationary for many years.

The impossibility of removing fresh tissue at this time precludes the study of the pigment-forming ability of the cells at the border of the original lesion or in the depigmented area. After the early treatments, pigment was noted to reappear in the depigmented...
areas. It is possible that the few remaining brown macules (Fig. 9) will enlarge; and at this time one cannot evaluate accurately the cosmetic result of treatment in so far as the permanency of the decolorization is concerned. These matters will form the basis of a future report.

The complete and apparently permanent retrogression of every epithelioma treated with radium has been very gratifying in this case. This form of therapy should be considered in the treatment of lentigo maligna.

BIBLIOGRAPHY