

MALIGNANT MELANOMA IN PREGNANCY

A. M. E. PICHANICK, *Fifth-year Medical Student, University of Cape Town*

It is rare for malignant melanoma to arise during or soon after pregnancy. When it does occur, however, it presents a particularly tragic picture because of the young age of the patient, the rapidity of the clinical course, and the tremendous shock to the patient's family and to the medical attendants. The young husband becomes a widower, and young children lose their mother, for, once established, there is little that can be done for a malignant melanoma beyond palliative treatment. Yet the disease is a preventable one, to some extent, if only doctors and laymen knew a bit more about it and exercised more care when dealing with naevi and moles. It is the purpose of this article to focus some attention on the problem.

CASE REPORT

History and Examination

A 29-year-old White woman was admitted to hospital 4 weeks after delivery of a premature baby in Stellenbosch. Her complaints were loss of appetite, malaise, and intermittent abdominal pain with a sensation of abdominal distension, especially in the right hypochondrium. She was slightly pyrexial (99 - 100°F) and had an enlarged firm lymph node at the apex of the left axilla. The cardiovascular, respiratory, and central nervous systems were all normal. Abdominal examination showed the liver to be enlarged four-fingers below the costal margin; the organ was firm, not tender, and had an irregular surface. The haemoglobin level was 10 G/100 ml.; ESR 15 mm./hour; WBC 16,500/cu.mm.—67% polymorphs and 33% lymphocytes. Estimates of blood electrolytes and liver-function tests showed little of note except for a high serum alkaline phosphatase level of 37 King-Armstrong units; this was evidence of parenchymal liver damage. Biopsy of the liver showed no abnormality except for some cellular infiltration in the portal tracts.

Diagnosis

The clue to the disease was found when a routine urine examination with Benedict's solution gave a dark black colour in the test tube; other oxidizing agents also turned the urine black, showing that melanin was present. Confirmation was obtained from biopsy of the axillary lymph node—it had black-and-white 'crossword-puzzle' macroscopic appearance, and histological examination showed a typical metastatic deposit from a malignant melanoma. Interrogation of the patient elicited the fact that she had had a black mole removed from her back in 1956 for cosmetic reasons and that this had presumably been the primary lesion. The patient was given hormonal and palliative treatment but died several months later.

DISCUSSION

Types of Moles

It has been stated in the literature¹ that by the time the average person reaches adulthood he will show 20 moles,

of different sizes, on his skin. All white-skinned people have at least one pigmented mole, and some have over 100. These may occur anywhere on the body and are of 4 main types:

1. *The junctional naevus* is situated at the dermo-epidermal junction and is generally flat and hairless. It exhibits all variations of size and colour, and may occur anywhere on the skin; naevi on the palms, soles and genitalia are always of this type. Few of them become malignant, but 90% of malignant melanomata arise from them.

2. *The intradermal naevus*, which is the common mole seen in adults. It may be flat and smooth or papillary and warty. Hairy naevi are always of this type. It never undergoes malignant change. It is never seen on the palms, soles, or genitalia, and is rarely seen before puberty.

3. *The compound naevus*. This has junctional and dermal elements in it and is commonly seen in children (98% of all naevi in children, 12% of adult naevi).² Because of the junctional element there is a risk of malignancy, and 10% of malignant melanomas arise from this type.

4. *The blue naevus* or 'beauty spot', which may be blue, black, or brown, and which is seen on the face, dorsum of hands and feet, and buttock. It is smooth and hairless, and malignancy is very rare.

To summarize: all malignant melanomata arise from junctional or compound naevi; and hairy naevi do not become malignant.³ Many naevi are not evident until after puberty, at which time they may suddenly appear in sites where they were previously unrecognized. Another feature of pubescence is that naevi which are already present become larger, darker, and more elevated. This phenomenon is well documented in the literature;^{1,3} Spitz, for instance, reported a small series of cases of growth of pigmented cutaneous lesions occurring 3-4 months after the menarche. An associated feature is that a true malignant melanoma hardly ever occurs before puberty, even though the patient has moles which are histologically indistinguishable from malignant melanoma. This is the condition of 'juvenile' or 'prepubertal melanoma', which is well known.¹ Many of these cases which have been left untreated go on to develop a full-blown malignant melanoma soon after puberty, with rapid growth and wide dissemination.^{4,5}

In Pregnancy

The pigmentary changes of pregnancy on the breasts,

abdomen, and face are of course well known. Not so well known is the fact that there is increased growth and darkening of existing naevi at the same time, and occasionally the appearance of new ones. This has been noticed by many women, and is sometimes a source of concern. These changes in naevi which occur at puberty and pregnancy suggest a hormonal influence, and this has been borne out by animal experiments.⁶ Ovariectomy performed on guinea-pigs produces varying degrees of deformities in melanocytes and inhibition of melanogenesis. Oestrogen given to such ovariectomized animals produces marked increase in melanogenesis, but progesterone does not give such a marked response. Orchidectomy, with or without subsequent testosterone administration, appears to have no effect on the melanocytes.

A very interesting report in the literature is the production of junctional naevi through the administration of ACTH,¹⁶ especially when it is remembered that 90% of malignant melanomata arise from junctional naevi. It is also known that MSH, the pituitary melanocyte-stimulating hormone, is increased in pregnancy, and it will be remembered that MSH is thought to be the hormone for the pigmentation of Addison's disease. It is clear from clinical and experimental evidence, then, that hormones, especially the female sex hormones, have marked effects on melanogenesis.¹ This must account for the changes described in pigmented moles at puberty and pregnancy. But can such hormonal influences be linked with the rapid development of malignant melanoma which takes place at these times? The answer is not clear yet but clinical evidence seems to indicate that this hypothesis is true. We have already described how malignant melanoma may arise after puberty in previously quiescent moles: 'There is a precipitous rise in the capacity of melanomas to metastasize after puberty despite the histological similarity to the non-metastasizing juvenile melanoma'.²

Pack and Scharnagel¹ report 32 cases of malignant melanomata associated with pregnancy. These arose mostly from junctional naevi, as one would expect, but were characterized by extremely rapid growth, early dissemination, and a very poor prognosis. The patients developed their melanomata during or shortly after pregnancy; in some cases a melanoma had been surgically removed several years before pregnancy ensued and the malignant condition developed during the pregnancy, as occurred in the case outlined in this article. The inference is that some melanomatous cells had been left and the malignant condition had been highlighted or brought out by the hormonal changes of the pregnancy. Of these 32 cases the primary lesion was on the trunk in 14 cases, upper limb in 3, lower limb in 8, head and neck in 4, choroid in 1, and one case had generalized lesions. Fourteen patients were in their twenties, and 16 in the thirties. Fourteen patients died within 3 years, despite radical surgery and other measures: 15 of the patients had been treated too recently (within two years of the report) for their follow-up observation to be significant. Only 2 patients are recorded as surviving a reasonable length of time—8 years and 13 years, after radical surgery. Most patients died within 20 months of parturition. This testifies to the extraordinary degree of malignancy which the pregnancy-induced tumour seems to have.

Another report⁷ described a typical case of malignant melanoma arising in the eye of a woman who was 5-months pregnant. There was rapid destruction of the eye with lethal metastases, a huge liver, and death 4 months after delivery, when the patient would normally have been expected to survive another 3-4 years. The melanoma may become so malignant that the placenta is seeded with metastatic deposits, and the foetus is infected with melanoma *in utero*. This is a rare occurrence but it has been recorded.^{2,8,9}

Regression. The prognosis is not uniformly bad, for on occasions spontaneous regression of a malignant melanoma may occur in the puerperium, presumably from withdrawal of the hormonal stimulus. Allen¹⁰ reports such a case, a woman with metastatic melanoma deposits on the abdomen, arm, scapular and inguinal areas, which regressed in the 11th week of the puerperium, and caused no further trouble. Spontaneous regressions of malignant melanomata have occurred even without pregnancy.^{11,12}

Incidence

Fortunately malignant melanoma is not a common condition; it constitutes only 3% of all skin cancer, and pregnancy is associated with only a minute fraction of these. The common sites, in order of frequency, are the leg and foot, the head and neck, the trunk, and lastly the upper extremity. It can also occur on internal mucous membranes; melanoma of the eye is a separate entity. The lesions are generally of the low warty type with a macular edge. They are often insignificant and their removal may be forgotten by the patient when metastases occur. The signs of malignant change are increase in size, darkening, peripheral spread, nodularity, oozing of serum which crusts, spontaneous bleeding, or bleeding from slight trauma, and the appearance of satellite spots. The tumour spreads by lymphatic and blood-vessels, in a quite unpredictable way, to any tissue or organ of the body. No other tumour gives such widespread metastases.

TREATMENT

The treatment of malignant melanoma is difficult and disappointing. The best treatment is obviously prevention; ideally this consists of removal of all suspicious moles before puberty, while the prognosis is still good. In particular all moles on the palms, soles, or genitalia should be excised, and all moles which are subject to repeated trauma.^{1,4,12} It is dangerous to leave 'benign moles' until they 'bother' the patient—by then it may be too late. Pack puts forward a strong argument for routine histological examination of all moles excised. Minor excisions and biopsies are not permitted; the advocated treatment^{1,4,12} is local wide excision of all skin 3-5 cm. around the lesion, down to and including the fascial structures, with the least possible manipulation, followed by a skin graft. Safety is more important than cosmetic appearances. The prognosis is much worse if there is involvement of lymph nodes, and the fallibility of clinical assessment of lymphadenopathy has been recorded by Lane *et al.*¹⁵ A prophylactic block dissection of the lymph nodes is therefore ideal in all cases. 42% of clinically 'benign' nodes removed prophylactically have been found to have metastatic deposits already and the 60% 5-year cure rate of the procedure outlined above is in marked contrast to the 10% cure rate which is

found if the nodes are not dissected. The importance of early detection and removal is brought out by the fact that for lesions under 2 cm. in size the 5-year cure rate is 61%, while it is only 16% for larger tumours.

X-ray treatment was formerly thought to be of no value but recent reports¹³ indicate that there is a place for post-operative irradiation combined with wide excisional surgery. Cytotoxic drugs have no effect on the condition.

One might think that in view of the hormonal influence outlined above, the condition could be controlled by hormone therapy. Various procedures have been tried; oophorectomy, irradiation of the ovaries, massive doses of testosterone, pituitary irradiation, and bilateral adrenalectomy. But none of these has altered the course of an established malignant melanoma.^{1,4} It would seem that, as with many other tumours, the factors concerned in their induction are different from those which control their growth. For this reason therapeutic abortion is not indicated.¹ By the time the malignancy is diagnosed it is too late and abortion will not halt its growth or spread. It is advised, therefore, that women who have been recently treated for melanomata should avoid pregnancy for 3-5 years, but sterilization is not considered necessary. In recent years a more optimistic approach to the prognosis in malignant melanoma has arisen, and some reported series claim 5-year cure rates of up to 50%.¹⁴

Prevention

The best treatment is prevention, and so the first antenatal examination of the pregnant woman should include a survey of her pigmented moles.¹ Those on the palms, soles, genitalia, and in traumatized areas should be excised.

SUMMARY AND CONCLUSIONS

1. An outline of the 4 types of pigmented naevi is given, with a discussion of the effects of hormones, puberty, and pregnancy upon them.
2. A case of malignant melanoma arising in pregnancy is reported, with a survey of the literature on the condition.
3. The treatment and prognosis of malignant melanoma is outlined.
4. It is recommended that all moles presenting in childhood should be removed before puberty.
5. Antenatal care should include a survey of all naevi, and the wide excision of all those on the palms, soles, genitalia, and in traumatized areas.
6. Prophylactic block dissection of lymph nodes, and histological examination of all specimens removed, should be done as a routine procedure.
7. All moles should be watched for signs of darkening, enlargement, bleeding, ulceration, or pain.
8. Women recently treated for melanoma should avoid pregnancy for at least 3-5 years. Therapeutic abortion, however, is not considered necessary.

I wish to thank Dr. H. Edelstein and Prof. J. H. Louw for their encouragement and assistance.

REFERENCES

1. Pack, G. T. and Scharnagel, I. M. (1951): *Cancer (Philad.)*, **4**, 324.
2. Spitz, S. (1948): *Amer. J. Path.*, **24**, 591.
3. Pack, G. T. and Davis, J. (1961): *S. Afr. Cancer Bull.*, **5**, 30.
4. Cade, S. (1957): *Brit. Med. J.*, **1**, 119.
5. Pack, G. T. (1948): *Surg. Gynec. Obstet.*, **86**, 374.
6. Bischoff, P. G. and Snell, R. S. (1958): *Nature (Lond.)*, **187**, 1413.
7. Siegel, R. S. and Ainslie, W. H. (1963): *J. Amer. Med. Assoc.*, **185**, 542.
8. Hoiland, L. (1933): *Gynec. and Obstet.*, **18**, 524.
9. Weber, F. P., Schwartz, E. and Hellenschied, R. (1930): *Brit. Med. J.*, **1**, 537.
10. Allen, E. P. (1955): *Ibid.*, **2**, 1067.
11. Sumner, W. C. and Foraker, A. G. (1960): *Cancer (Philad.)*, **13**, 79.
12. Volger, W. R., Perdue, G. D. and Wilkins, S. A. (1958): *Surg. Gynec. Obstet.*, **106**, 586.
13. Dickson, R. J. (1958): *Amer. J. Roentgenol.*, **79**, 1063.
14. Daland, E. M. (1959): *New Engl. J. Med.*, **260**, 453.
15. Lane, N., Lattes, R. and Malm, J. (1958): *Bull. N.Y. Acad. Med.*, **34**, 824.
16. Goldman, L. and Richfield, D. F. (1951): *J. Amer. Med. Assoc.*, **147**, 941.