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Muinonen-Martin, AJ, O'Shea, SJ and Newton-Bishop, J orcid.org/0000-0001-9147-6802 (2018) Easily missed? Amelanotic melanoma. BMJ: British Medical Journal, 360 (8145). k826. ISSN 0959-8138

https://doi.org/10.1136/bmj.k826

Easily Missed: Amelanotic Melanoma

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Word count: 1181

A 50-year-old woman developed a bleeding nodule on the tip of the right index finger. She denied any history of trauma and said that the mass had developed spontaneously one month before. She was an avid gardener. Her GP diagnosed a pyogenic granuloma and cauterised it, which reduced its size but the lesion failed to clear. Further cautery was applied 12 weeks later. When this second treatment also failed to completely control the lesion, the woman was referred to the plastic surgery hand clinic, where a biopsy was carried out. A diagnosis of amelanotic malignant melanoma was made. Amputation of the terminal phalanx and a sentinel node biopsy were performed.

What is amelanotic melanoma?

An amelanotic melanoma is a melanoma in which most of the melanoma tumour cells are no longer manufacturing pigment (melanin) or are making so little melanin that it is not readily recognized. These melanomas are usually red or skin-coloured.

Amelanotic melanomas are rare overall, estimated to represent approximately 8% melanomas [1] and are more likely to be of nodular or acral subtypes rather than the most common form: superficial spreading melanoma. Fig 1A shows an example of an amelanotic melanoma occurring at an acral site, near the nail. Amelanotic melanomas are more likely to present with a more advanced stage of disease, compared to pigmented melanomas [1].

Why is it missed?

There are four main subtypes of cutaneous melanoma: superficial spreading, nodular, lentigo maligna and acral lentiginous. Melanoma of the skin is most commonly of the superficial spreading type (Fig 1B), which often arises in a melanocytic naevus but may arise *de novo*. These lesions develop over months or years. Various aids to diagnosis relate to this type of melanoma: both the 7-point checklist and the ABCDE rule (preferred in the US). Sensitivity and specificity for these algorithms have been reported to vary according to the level of training[2-5], with some estimating a specificity of about 40% for the 7-point checklist[3]. These "classical" melanomas are usually asymmetrical and irregularly pigmented (usually with black, brown, grey, sometimes red areas). The variation in colour results from melanoma cells synthesizing pigment (brown to black), areas where the tumour has died or regressed (grey), areas that are inflamed or have induced new blood vessels (pink). When the melanoma cells have no capacity to synthesize pigment the tumours often look red as the blood vessels and the inflammatory changes then dominate.

Most healthcare professionals, and indeed patients most easily recognise superficial spreading melanomas: irregular in shape, size and colour. Amelanotic melanomas are often missed because:

- they are usually red or skin-coloured rather than pigmented.
- being "nodular", amelanotic melanomas tend to be more symmetrical than "classical" melanomas.
- acral melanomas may mimic fungal infections, diabetic foot ulcers or even plantar or periungual warts.

Put simply, we recognize superficial spreading melanomas more easily and generally earlier because the classic signs are relatively easily described by educators, and remembered whereas amelanotic melanomas are less readily described and have fewer distinguishing characteristics.

Why does it matter?

Melanoma is curable in the majority of patients, if diagnosed early enough. Late diagnosis is associated with an increased risk of metastases and although the therapeutic options have improved considerably for metastatic disease in recent years, the mortality is still considerable.

The best chance the patient has is early surgery.

The single most important thing that one can do to reduce the risk of developing melanoma is to avoid sunburn. This can be achieved by seeking the shade, covering up with clothing and using a sunscreen with high broad-spectrum protection (e.g. at least SPF 30 and 4 star UVA protection) if pale skinned and the sun is strong.

How is it diagnosed?

The diagnosis is clinical. The first step is examination with the naked eye. This is followed by examination with a dermatoscope, which allows a x10 magnification and improved illumination. This allows the interpretation of specific morphologic patterns which are not readily recognised by the naked eye.

Confirmation is made by a specialist pathologist after excision. The preference is always to excise the lesion in its entirety[6], but in some sites, e.g. acral, it may be necessary to carry out an incisional biopsy first (especially if definitive surgery involves amputation of part of a digit or would impact on mobility). The decision to carry out an incisional biopsy should be made by a pigmented lesion clinic. Surgery involving acral sites often requires an experienced surgeon, in order to sample sufficient tissue.

Clinical features.

Red to skin-coloured lesions tend to develop over a matter of weeks or months. Examples of nodular melanomas are shown in Fig 2. They are often friable and bleed readily. Bleeding may indicate ulceration, which is a poor prognostic sign.

In acral sites, these lumps may develop in, or may be associated with, quite subtle pigmented macules, particularly in the periphery. The latter represent the *in situ* precursor

of the invasive tumour and these change so slowly that patients are often lulled into a false sense of security and don't recognize the macules as being associated with risk.

The differential diagnosis includes that made by the GP in this case: a pyogenic granuloma. Pyogenic granulomas are comprised of masses of friable blood vessels and therefore, like amelanotic melanomas (especially in acral sites), grow quickly and bleed readily.

The principal second differential diagnosis is non-melanoma skin cancer: either a basal cell or squamous cell carcinoma (Fig 3). This is a powerful argument in support of a 2-week wait referral for all new lumps and bumps where the diagnosis is unclear.

Investigations

The histopathologist reviewing the primary tumour will stage the melanoma based upon its thickness in the skin (Breslow thickness) and the presence of a number of key features, including surface ulceration. The AJCC staging system is used.

An additional staging procedure, called a sentinel node biopsy, may also be offered to patients with tumours thicker than 1mm, but there is as yet no evidence for a survival benefit for this procedure. The NICE Clinical Melanoma Guideline[7] includes tables designed to help the melanoma team to explain the pros and cons of sentinel node biopsy to the patient. These are available to everyone via the Option Grid webpage ***optiongrid***.*org*.

How is it managed?

The treatment is complete excision in the first instance. This is required to give the pathologist the best chance to make the correct diagnosis: melanoma pathology can be very difficult. Furthermore, removing the entire lesion reduces the risk to the patient if the histology is falsely reassuring.

After confirmation of the diagnosis and discussion at the Multidisciplinary Team Meeting, a wider excision is arranged. This is normally carried out by plastic surgeons and the width of the surgical margins is proportional to the thickness of the primary tumour[7].

Patients with thicker tumours are offered sentinel node biopsy staging as above.

There is as yet no adjuvant therapy available in the clinical setting outside of clinical trials (that is treatment designed to reduce the risk of further recurrence). However, due to promising trial data, it is very likely, that licensed adjuvant treatments will shortly become available.

Acknowledgements

JNB is funded by Cancer Research UK (Program grant C588/A19167 and Clinical Research Fellowship Grant C37059/A17894).

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Contribution statement
AMM was involved in revisions of the manuscript and collected patient feedback.
SOS was involved in revisions of the manuscript and provided clinical images.
JNB wrote the manuscript and provided a clinical image.

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