CASE REPORT

Missed opportunity to diagnose subungual melanoma: potential pitfalls!

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SUMMARY

Subungual melanoma, an uncommon form of acral melanoma that arises within the nail matrix, accounts for 1%–3% of all cutaneous melanoma in Caucasians. As subungual melanoma presents in a more disguised manner than cutaneous lesions, increased vigilance is required. It most commonly presents as a discolouration of the nail, nail splitting or nail-bed bleeding. Black pigmentation of the adjacent nail fold, termed Hutchinson's sign, may be a diagnostic clue. Treatment of subungual melanoma remains surgical with wide local excision and amputation primary modalities. We present the case of a 61-year-old man with an 18-month history of a left thumb nail-bed abnormality and a 6-week history of left axillary lymphadenopathy. One year earlier, he presented to the emergency department with a purulent discharge from his left thumb but declined nail-bed ablation. He was referred to the 'Hand and Plastic Injuries Clinic' by his general practitioner and diagnosed with a chronic traumatic-induced nail-bed injury. As his symptoms did not improve, he was referred to the 2-week wait Skin Cancer Clinic. The left thumb nail-bed was excised as a nail unit down to bone, and the diagnosis of melanoma was rendered. Left axillary lymphadenopathy was confirmed as metastatic melanoma. He underwent amputation of his left thumb at the interproximal phalangeal joint, and a left axillary node dissection was performed. No residual melanoma was identified in his thumb. Microscopically, his left axillary dissection confirmed 9 out of 36 positive nodes for metastatic melanoma with extracapsular spread. He was staged at IIIC disease. This case report demonstrates missed opportunities to diagnose subungual melanoma and acts as a cautionary tale in considering this pathology in the differential diagnosis of nail-bed lesions with prompt referral for further investigation.

CASE PRESENTATION

A 62-year-old male UK resident was referred to the 2-week wait Skin Cancer Clinic, with an 18-month history of a left thumb nail-bed abnormality and a 6-week history of left axillary lymphadenopathy. He reported a rapidly spreading darkly pigmented patch of the nail-bed in the form of bands with an irregular border after hitting his thumbnail with a hammer (figure 1). This discolouration progressed to thickening, splitting and full destruction of the nail with a purulent discharge. Seven months later, his left thumbnail fell off. He attended the emergency department with an abnormally growing nail and a purulent discharge from the dorsal aspect of

his thumb. No erythema was evident, and it was not tender on palpation. He was reviewed by the Orthopaedic Registrar. Nail-bed ablation was declined. He was referred by his general practitioner to the 'Hand and Plastic Injuries Clinic' as his symptoms failed to improve. The working diagnosis was of an acute bruise and a chronic traumatic-induced nail-bed injury. The left thumb nail-bed was excised as a nail unit down to bone. Discolouration was observed intraoperatively. The diagnosis of melanoma was confirmed histologically. The Breslow thickness was 5.95 mm, ulcerated, 16 mitoses/mm² and incompletely excised at the deep aspect. Left axillary lymphadenopathy was confirmed to be metastatic melanoma on core biopsy. His medical history included hypertension treated with ramipril 5 mg once per day. He had no recorded drug allergies. He was a non-smoker and did not consume alcohol. He was referred urgently to the Department of Plastic Surgery.

Examination of this right-hand dominant man's left thumb revealed a large exophytic swelling of his left thumb nail plate. It was difficult to discern a discrete lesion, but it appeared scaly with a very unusual contour to the nail-bed. The differential diagnosis included squamous cell carcinoma, pyogenic granuloma or melanoma.

INVESTIGATIONS

A radiograph of his left thumb was unremarkable (figure 2). Further investigation with an ultrasound scan of his left axilla showed a large hypoechoic axillary node, measuring 5×4.3 cm and a further subcentimetre node superomedially. Under ultrasound guidance, a core biopsy was performed (figure 3). Microscopically, highly pleomorphic malignant cells with prominent eosinophilic nucleoli and abundant amphophilic cytoplasm were noted (figure 4). Fragments of lymphoid tissue widely infiltrated by pleomorphic cells with a plasmacytoid morphology and loosely cohesive architecture were observed. Microsatellites were not observed. Invasive tumour was 5 mm from the distal margin. The neoplastic cells were immune-positive for S-100, Melan-A and HMB-45 and immune-negative for MNF116 and AE1/3. The appearances were those of a metastatic melanoma. Macroscopically, the excision specimen of his left thumb nail unit showed an ulcerating tumour, and microscopically, the entire nail-bed was replaced by ulcerating melanoma (figures 5 and 6). Distinction between acral lentiginous and superficial spreading melanoma was hindered by

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Figure 1 Clinical photograph of his left thumb. Clinical examination of his thumb demonstrated a spreading darkly pigmented patch of the nail-bed appearing in the form of bands with an irregular border.

Figure 2 Radiograph of the left thumb. A radiograph of his left thumb demonstrated no evidence of a destructive process.

Figure 3 Ultrasound scan of the left axilla. An ultrasound scan of his left axilla showed a large hypoechoic mass, and a core biopsy was performed.

excessive ulceration, although the superficial spreading type was favoured.

The Breslow thickness was 5.95 mm. He was staged at Clark level 5, pT4b. The mitotic count was 16/mm². The growth phase was vertical. Infiltrating lymphocytes were absent. There was no evidence of lymphovascular or perineural invasion. A full cancer panel was performed.

Mutations of potential clinical significance were not detected in the following nine genes: TP53, PTEN, PIK3CA, PDGFRA, KRAS, NRAS, KIT, EGFR and BRAF. A staging CT chest, abdomen and pelvis with contrast showed no significant mediastinal, hilar lymphadenopathy or lung metastases. The large axillary node, already described on ultrasound scan was noted

Figure 4 Histology slide showing pleomorphism. Highly pleomorphic malignant cells with prominent eosinophilic nucleoli and abundant amphophilic cytoplasm. A mitotic figure is present in the lower left-hand side (magnification 40×).

Figure 5 Histology slide of ulcerated malignant melanoma. Scanning view of ulcerated malignant melanoma (magnification 1×).

(figure 7). No right axillary, abdominal or pelvic lymphadenopathy was evident. The liver, spleen, kidneys and adrenals were normal, with no evidence of bone metastases.

TREATMENT

His left thumb was amputated with a 1 cm margin around the tumour at the interproximal phalangeal joint. A left level 3 axillary node dissection was performed, and a large mass of tumour closely adherent to the brachial plexus and axillary vein was observed. Two drains were inserted, and the wound was closed primarily. His postoperative recovery was uneventful.

Macroscopically, the thumb nail was ill-defined, irregular and merged into a focally pigmented and scarred area. The sections showed skin and underlying bone together with a broad area of postsurgical change microscopically. No residual melanoma was identified. The left axillary dissection contained multiple enlarged nodes including macroscopically identifiable metastatic deposits, the largest measuring 15 mm in maximum dimension. Microscopically, 36 nodes were identified, 9 of which contained metastatic melanoma with extensive extracapsular spread, extending up to 1.8 mm from the closest peripheral margin.

OUTCOME AND FOLLOW-UP

He was diagnosed with stage IIIC acral melanoma of his left thumb. He has a high risk of recurrence, and the standard of care presently in the UK is close observation. He will be reviewed every 3 months by both the plastic surgeons and the oncologists.

Figure 6 Histology slide demonstrating an in situ component. Malignant melanoma with ulceration and adjacent in situ component (magnification 5×).

Figure 7 Staging CT chest, abdomen and pelvis with contrast. A very large left axillary node, measuring 5×4.3 cm and a further subcentimetre node superomedially, was noted.

He will also receive a CT scan in the first year and then in a further 12 months. Although radiotherapy is not routinely indicated for melanoma, given the degree of extracapsular spread, he will be discussed at the Oncology Multidisciplinary Team meeting to obtain further advice.

DISCUSSION

In the UK, melanoma ranks as the third most common skin cancer, accounting for more deaths than all other skin cancers combined.¹ In the UK alone, 900 adults less than 35 years are diagnosed annually, and it is now the second most common cancer in adults between 25 and 49 years. In 1834, Boyer described the first case of subungual melanoma involving the fifth digit of a man's hand in his paper 'Fungus hematode du petit doigt'.²

This was followed by Hutchinson in 1886, describing melanoma of the nail-bed as melanotic whitlow, 'melanosis often not black' owing to its resemblance to herpetic infection of the hand.³

Subungual melanoma is rare, accounting for 1%–3% of all cutaneous melanoma in Caucasians, but interestingly, it occurs in 8%–33% of cases in black, Asian, Native American and Hispanic populations.^{4,5} No gender predilection is observed. It occurs most commonly between the ages of 50 and 70 years. As in our reported case, it has a preponderance for the thumb and great toe, followed by the index finger, accounting for 75%–90% of cases. As subungual melanoma presents with non-specific symptoms, it is often diagnosed late resulting in a poor prognosis, with 5–10 year survival rates of 30% and 13%, respectively.⁶ Melanoma is defined as a malignant tumour arising from the pigment producing cell of the skin called the melanocyte.

The four main types include acral lentiginous, superficial spreading, lentigo maligna and nodular melanoma. Subungual melanoma affects the tissue beneath the nail base, known as the nail matrix, the region from which the nail forms and grows. Irregular and intense exposure to sunlight significantly increases the risk; however, ultraviolet radiation is unlikely to penetrate the nail plate to cause subungual melanoma.⁷ The nail is in fact a unique structure with sun-exposed and non-exposed melanocytes. Other recognised risk factors include a family history of melanoma, dysplastic naevi and immunosuppression including organ transplant recipients.⁸

Physical characteristics including blue or green eye colour, red hair colour, freckles and an inability to tan have also been mentioned.⁸ As subungual melanoma presents in a more disguised manner than cutaneous lesions, increased vigilance is required.⁷

It is important not to exclude a diagnosis of malignancy solely on a history of trauma, as many patients will recall an injury to the digit. It typically presents as darkened longitudinal stripes under the nail plate or may first be evident as a split nail, nail-bed swelling or crusty ulceration. Black pigmentation of the adjacent nail fold is an ominous feature, termed 'Hutchinson's sign', and describes the periungual spread of pigment into the proximal or lateral nail folds. Further signs of invasive disease include nail dystrophy and ulceration. Other diagnostic pitfalls occur as one-third of subungual melanomas appear amelanotic further challenging prompt recognition.⁷ Subungual bleeding may be caused by direct trauma or a haemorrhagic tendency in those individuals taking warfarin or with a diagnosis of a haematological malignancy or thrombocytopaenia. Cases occurring after trauma may present as persistent non-healing ulcers initially mistaken for chronic infection.⁹ Traumatic causes of subungual bleeding are associated with a proximal white transverse band.¹⁰ Amelanotic melanoma presenting as a granulating mass of the nail fold can be interpreted as an ingrowing nail resulting in a potential cause of delayed diagnosis.

¹¹In situ amelanotic melanoma of the nail unit, characterised by longitudinal striation, can mimic lichen planus.¹² In 2016, Kazi performed a qualitative histological analysis of nail units from cadaveric human tissue to detect the location of melanocytes within the nail unit.¹³

Using an array of melanocytic-specific stains, they demonstrated that the nail matrix is the primary location of melanocytes in the nail unit.¹³ Melanonychia, characterised by brown or black pigmentation within the nail plate, includes conditions such as pigmented naevus, subungual melanoma and lentigo. The differential diagnosis of a subungual tumour includes squamous cell carcinoma, including squamous cell carcinoma in situ (Bowen's disease), the most common malignant tumour of the nail, pyogenic granuloma, pigmented basal cell carcinoma or a melanoma. Bristow also advocates considering Kaposi's sarcoma, angiosarcoma, subungual fibroma, dermatofibroma or a keratoacanthoma in the differential diagnosis.¹³ Furthermore, an ingrowing toenail, foreign body, poroma, necrosis, paronychia or onychomycosis nigricans can present like a subungual melanoma.¹³ Ethnic pigmentation changes and endocrinological conditions including Addison's disease, Cushing's syndrome and hypothyroidism should also be considered. Syndromes, such as Peutz-Jeghers and Laugier-Hunziker, an acquired benign condition associated with hyperpigmented macules and longitudinal melanonychia should also be considered. A reversible blue-black hyperpigmentation of the nails due to vitamin B12 and folate deficiency has also been described. Fungal infections clinically suggesting subungual melanoma include those caused by *Scytalidium dimidiatum*, a pigmented dematiaceous coelomycete, and *Trichophyton rubrum*, a dermatophyte fungus. Both entities are known to produce black pigmentation, hence contributing to the diagnostic dilemma. Subungual haematoma and fungal infections tend to present with a homogeneous pigmentary distribution, whereas melanocytic conditions appear granular with cellular inclusions of melanin. Caution is advised as melanoma can also present with homogeneous pigmentation, especially the advanced stages. Pharmacological agents such as minocycline, tetracycline and chemotherapeutics such as 5-fluorouracil can cause melanonychia. The diagnosis of nail pigmentation remains a challenge. It certainly is not appropriate to biopsy all nail pigmentation especially melanonychia in adulthood. A thorough history with attention to the onset, progression and possible triggers should be obtained. Clinical evaluation may include dermoscopy, helping clinicians accurately decide if a biopsy of

the nail apparatus is warranted. Greyish homogeneous bands or thin grey lines are suggestive of benign melanocytic hyperplasia or ethnic pigmentation. This phenomenon of epithelial hyperpigmentation without accompanying melanocytic hyperplasia is seen in lentigo, drug-induced pigmentation and ethnic pigmentation. Upregulation of melanocytes can be seen in subungual lentigo. The classic dermatoscopic appearance of subungual melanoma includes irregular broad bands of dark brown or black pigment >3 mm that are not parallel, blurred lateral borders, Hutchinson's sign and nail dystrophy or ulceration.

Benign melanocytic pigmented subungual lesions appear as parallel bands of homogeneous pigment with a narrow width <3 mm, with no involvement of the skin of the nail fold. Clinical photography is a useful adjunct to document the dimensions of pigmented lesions. Additional assessment includes palpation of axillary and inguinal lymph node. Further investigation with an ultrasound scan or CT may be required. Diagnosis of subungual melanoma is very difficult to establish merely on the basis of clinical examination with misdiagnosis as subungual haematoma, chronic trauma or onychomycosis is still a frequent occurrence. Indeed, Gosselink states that approximately 85% of cases are misdiagnosed initially.¹⁴ The use of the simple acronym ABCDE is a useful tool in remembering the main clinical signs of a potential melanoma by aptly referencing the asymmetry of the lesion, its border, colour, diameter and its evolution.² Levit has used a modification of the ABCD rule and applied it to the nail unit, with an age range of 20–90 years and a peak in the five to seven decades.¹⁵ Levit also describes the pigment, breadth and border of the nail band, including any rapid growth or failure of nail dystrophy to improve despite adequate treatment.¹⁵ The digit involved and the extension of pigment to involve the proximal or lateral nail fold or the free edge of the nail plate are referenced. A history of previous melanoma or a dysplastic naevus is also included.²

Histopathology is the gold standard for diagnosis, with subungual melanoma having a unique histopathological profile and may be consistent with superficial spreading (50%), acral lentiginous (67%) or sometimes both forms.¹⁶ The Fontana-Masson stain, which identifies melanin, may be helpful in the diagnosis of subungual melanoma, with an increased number of pleomorphic melanocytes, florid pagetoid cells, atypia and multinucleation observed in the basal layer of the specimen. The immunostains Melan-A, S-100, HMB-45 and NKI/C3 protein markers may aid diagnosis. The mean Breslow thickness at diagnosis is 4.8 mm, with 79% staged as Clark level IV, signifying advanced disease at diagnosis when comparing with cutaneous melanoma.¹⁷

The gold standard of treatment for subungual melanoma is a biopsy including part of the nail-bed, nail plate and nail matrix followed by wide local excision in the form of amputation of the distal phalanx of the digit in order to achieve at least 10 mm margin of clearance.¹⁸ This has remained unchanged since Hutchinson advocated amputation in the early 1800s. In 1992, Park introduced digit-sparing surgery, for example, Moh's surgery preserves a significant amount of nail matrix so that an almost normal appearing nail regrows. Recent studies have suggested a good cosmetic and functional outcome along with compatible prognosis, in patients with in situ or minimally invasive subungual melanoma.¹⁹ Radial margins should be assessed by the Breslow depth. The National Institute for Health and Care Excellence (NICE) guidelines advocate a clinical margin of at least 0.5 cm when excising stage 0 melanoma, 1 cm for stage I disease and at least 2 cm for stage II melanoma.¹ The National Cancer Institute does not have guidelines for the treatment of subungual melanoma, and there is a paucity of prospective,

randomised or comparative studies that would help elucidate whether amputation is superior to a more conservative, digit-sparing approach.²⁰

There has been little evidence demonstrating survival with non-amputative surgery involving wide excision of the nail unit followed by a skin graft for invasive subungual melanoma.²¹

Smock reported the case of a man with a 1.2 mm Breslow thickness subungual melanoma of his thumb who refused amputation.²² A 1 cm wide local excision down to bone was performed, and the defect was later grafted. He remains disease-free with a fully functional thumb and a good cosmetic result. Furthermore, Rayatt described a digit-sparing approach in four patients, involving local excision with 1 cm margins down to and including the periosteum and a local flap reconstruction.²³ A 6-year follow-up revealed one recurrence and no deaths.

However, when the thumb is involved, as in our case, functional and aesthetic loss can be substantial. Miranda advocates that in cases where the skin surrounding the nail is involved, this skin should also be biopsied, even if it is less pigmented than the primary lesion.²⁴

Immediate lymphadenectomy in cases of positive sentinel lymph node biopsy improves disease-free survival.²⁵ If targeted systemic therapy is a treatment option, NICE guidelines state to offer individuals genetic testing.¹ Immunotherapy including high-dose interleukin-2 in metastatic disease, alpha-interferon for resected high-risk nodal disease and ipilimumab is useful.²⁵ Dacarbazine should be considered for those individuals with stage IV disease.^{1 26} Generally, radiation therapy is not used to treat the original melanoma but often to relieve symptoms, when the melanoma has spread, or following lymph node dissection where many nodes are involved. This Case Report demonstrates a missed opportunity to diagnose subungual melanoma of the thumb and aptly illustrates the diagnostic challenges to prompt diagnosis of nail-bed lesions. As subungual melanoma presents in a more disguised manner than cutaneous lesions, increased vigilance and awareness is required to achieve an early diagnosis and prompt treatment, thus yielding enhanced outcomes in this patient cohort.

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Learning points

- Subungual melanoma typically presents as longitudinal melanonychia or may first be evident as a split nail, nail-bed swelling or crusty ulceration. 'Hutchinson's sign', describing black pigmentation of the adjacent nail fold, is an ominous sign.
- The differential diagnosis of a subungual tumour includes Bowen's disease, squamous cell carcinoma or melanoma. It is prudent to include endocrinological conditions and syndromes such as Peutz-Jeghers or Laugier-Hunziker in the differential diagnosis. Fungal infections such as those caused by *Scytalidium dimidiatum* and *Trichophyton rubrum* may clinically suggest subungual melanoma.
- The diagnosis is rendered by clinical evaluation with dermoscopy, clinical photography, examination of lymph nodes, ultrasound scan or further evaluation with a CT.
- Histopathology is the gold standard for diagnosis, with the Fontana-Masson stain helpful in the diagnosis. The immunostains Melan-A, S-100, HMB-45 and NKI/C3 protein markers may aid the diagnosis.
- The gold standard of treatment is a biopsy including part of the nail-bed, nail plate and nail matrix followed by wide local excision.

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