Case Report 3
Melanoma

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Introduction:

Melanoma is a relatively common neoplasm which is increasing in incidence. Melanoma appears as a variegated irregular maculopapular lesion usually on the skin, but possibly on mucosae, conjunctiva, orbit, nails and oesophagus. They may be black, brown, red-blue, grey or unpigmented. Histologically they are larger than nevi cells with irregular nucleoli and eosinophilic nucleoli. [1] Melanoma incidence in Malta is lower than that in northern Europe and is similar to that in southern Europe. However, incidence appears to be increasing. . In a study done between the years 2000-2004 the rates for invasive melanoma were of 8.81 per 100,000 (males) and 7.29 per 100,000 (females). A relatively high proportion of patients present with thick lesions emphasising the importance of continued efforts to diagnose cases earlier. [2]

Aim:

The aim of this article is to make the reader aware of the importance of early detection and prevention of melanoma, to highlight the risk factors for developing melanoma and to outline the way in which melanoma is diagnosed, treated and followed up.

Case Presentation:

A 20 year old male student initially presented at dermatologist with a pigmented macular skin lesion on the right upper posterior thigh. The lesion was painless, asymmetric with colour variation from pink to brown. The lesion was relatively small in size, with a diameter of approximately 10mm x 7mm. A total skin investigation was performed and the patient did not have many nevi. On palpation the regional lymph nodes did not appear enlarged. There was no history of recent weight loss. The patient is a known asthmatic, and is on salbutamol (SABA) for asthma control. There are no other known chronic diseases.

Family History:

There was no previous history of melanoma and no family history for melanoma.

Social history:

The patient is a full time student. There is no history of smoking or alcoholism. When the patient was asked about sun exposure, he couldn't recall any severe sunburn in childhood, and there isn't a particularly high tendency to tan. The patient also does not spend a lot of time in the sun, and has a skin type III18.

Diagnostic considerations: [3]

- Malignant Melanoma
- Benign melanocytic lesion
- Dysplastic nevus
- Blue nevus
- Epithelioid (Spitz) tumor
- Pigmented spindle cell nevus of Reed

Investigations:

The patient first underwent a surgical excision of the lesion (excision biopsy). Excision was performed after the lesion was anesthetized via local anaesthesia. A small amount of surrounding tissue was removed as well to ensure that any possible malignant cells were excised. The sample was sent for histological investigations at the pathology lab.

A skin ellipse, measuring 20mmx9mmx2mm, bearing a slightly raised, lightly pigmented lesion measuring 10mmx7mm, was excised. On microscopy the section showed nested and single atypical melanocytes at the dermal-epidermal junction, above the junction as well as infiltrating the dermis where they reached the mid reticular dermis. The tumour had the overall configuration of a naevus and the tumour cells had a nevoid appearance. However, marked nuclear atypia was present throughout the tumour including at it deepest aspect. There was no ulceration. There was no host inflammatory response to the tumour. The excision of the tumour was complete.

The lesion was confirmed to be an invasive nevoid melanoma Clarke stage IV (Tumour extends between bundles of collagen of reticular dermis (extends into reticular dermis)), T classification pT3aN0 (AJCC staging), and a Breslow thickness of 2.19mm, the mitotic count was of 0/mm [2] [4] [5]

Following diagnosis of melanoma a sentinel lymph node biopsy (SLNB) was performed for staging purposes. This is a minimally invasive technique to assess regional lymph node status in patients with malignancy. Any region of skin drains to a particular group of lymph nodes, but first the lymphatics drain through the sentinel node. Therefore it follows that if melanoma has metastasised it will first affect the sentinel node.
Identifying the Sentinel node involves two techniques. A gamma radiation emitting sulphur colloid is injected around the tumour before the operation and then the gamma emitting node is identified, and a vital blue dye (isosulphan blue) is injected intradermally at the time of surgery and the blue node is then identified. The two techniques are usually used together to ensure that the correct node is in fact identified6.
The specific and limited removal of the sentinel node allows one to predict metastasis and reduces surgical insult and morbidity compared with conventional lymphatic clearance 6. Sentinel lymph node status is the most important independent prognostic factor in terms of disease progression and melanoma-specific survival.
The Sentinel node was removed from the right groin, and results were as follows: 'A portion of fatty tissue measuring 10mm x 12mm x 9mm. On sectioning, 2 nodules are present, each measuring 7mm in maximum dimension. The diagnosis was of benign reactive lymph node changes, mostly sinus histiocytosis. No metastases were present.

Treatment:
The only procedure carried out for melanoma is a wider skin excision if there is no metastasis, this is done to decrease chances of local recurrence. This procedure was performed at the same time as the SNLB for logistical convenience and to because a wider excision before an SNLB would alter the lymphatics of the area rendering an SNLB impossible.
The wider skin excision was done with a skin ellipse including subcutaneous tissue measuring 57mm x 35mm x 15mm being excised (margins 3cm). The diagnosis was of no evidence of residual melanoma.

Follow up:
The patient is being followed up through outpatient appointments every 3 months for the next 2 years, every 6 months for the 2 years following those and then at least once every year for life. This follow up involves history and physical examination with special emphasis on skin and lymph nodes.

Discussion:
What is melanoma?
Melanoma is a malignant tumour of melanocytes, which are of neural crest origin. The most common forms of skin cancer are basal cell skin cancer, squamous skin cancer and melanoma. Melanoma is the least common of these. However, it causes the highest rate of mortality of the three. It is the second most common cancer in teenagers and young adults.
Melanomas have two growth phases, a radial phase during which malignant cells grow in a radial fashion in the epidermis and a vertical phase in which the malignant cells invade the dermis and develop the ability to metastasise.
There are four main subtypes of melanoma, namely the superficial spreading melanoma (about 80%), nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. Superficial spreading melanoma can occur anywhere and is characterised by slow, radial growth. Nodular melanoma can also occur anywhere, but is more common in men and exhibits rapid growth with an early vertical growth phase. This makes it more aggressive than superficial spreading melanoma. Amelanotic nodular melanoma is possible (5% of nodular melanomas). Lentigo maligna melanoma occurs in elderly with a history of sun exposure. It presents as large lesions on the face or neck, often arising from a precancerous lentigo maligna (Hutchinson's freckle). Acral lentiginous melanoma is the most common type of melanoma in coloured people and typically occurs on the palms, soles or under the nails. Rarely, melanoma may also develop on the eyes (ocular melanoma) or any mucosa (mucosal melanoma). Mucosal melanomas tend to be very aggressive. Ocular melanoma is the commonest type of ocular malignancy.

Risk Factors
The risk factors for melanoma include fair, sun-sensitive skin that burns rather than tans, many moles—more than 50, moles which are large or unusual in colour or shape, a personal history of melanoma, excessive exposure to UV from the sun or sun beds and a history of severe sunburns. In fact, about 80% of melanomas occur in white skinned people. The disease is also exceedingly common in albinos.

Close family history of melanoma, freckling (especially of the upper back), red or blond hair, blue, green or grey eyes and the presence of solar keratosis are also risk factors for developing melanoma. Each of these risk factors increases the risk of melanoma by about 3.5 times. [9]

In melanoma, as with all other skin disorders, it is important to ask about occupation and hobbies as part of the history in order to reveal any possible exposures that may have contributed to the disease process. People who work in the sun all day are at a higher risk of developing Lentigo malignant melanoma and some studies have shown that exposure to insecticides such as carbaryl may also increase the risk of developing melanoma. [10]
The Gene CDKN2A has also been implicated in the development of malignant melanoma. This gene generates a variety of transcripts varying in their first exon. Two proteins produced by these transcripts have been found to function as CDK4 Kinase inhibitors. Another transcript is known to contain an alternate open reading frame (ARF) that specifies a protein which functions as a stabilizer of the tumour suppressor p53. All these proteins share a common functionality in cell cycle G1 control and mutations in this tumour suppressor gene have been correlated with various cancers including malignant melanoma. [19] However, people with apparently no risk factors and those with darker skin can also be affected by melanoma, as was the case with this patient. A possible explanation is the general immunosuppressive effect of sunlight, leading to an increased risk of developing melanoma due to lack of immunological tumour surveillance. This risk seems to be especially highlighted in individuals who are unaccustomed to sunlight exposure, and only receive intermittent doses of strong sunlight. This explanation would also account for melanoma that occurs in areas not normally exposed to sunlight, as in this cas. [11] [12]

Detection, Clinical Features and Prevention
Self detection or detection by a family member of the melanoma has very high success rates with research showing that 53% of melanomas are discovered by the patients themselves and a further 17% by their family members. A skin self-exam is simple and takes only 10-15 minutes once per month8. A mirror can be used to visualise hard to see places.
Melanomas are usually dark brown or black, and they may be flat or raised. Many melanomas arise from a pre-existing melanocytic naevus (at least 50%13), so it is essential to report any recent changes in a mole to a doctor.
The main signs for melanoma may be summarized in the mnemonic ABCDE:

- Asymmetry
- Borders (irregular)
- Colour (variegated)
- Diameter (greater than 6 mm)
- Evolving over time

Other features of a pigmented lesion that are suggestive of advanced melanoma include bleeding, ulceration, satellite or in-transit lesions, sensations of local discomfort and the presence of a red halo around the lesion. Melanomas (especially the superficial spreading type) may also show patches of regression.
Satellite lesions are lesions occurring around the main lesion due to lateral spread of cells via the dermal lymphatics, while in-transit lesions occur along the route of lymphatic drainage of the naevus.
Although spread to regional lymph nodes occurs quite quickly, haematogenous spread tends to occur late. However, when it does occur it is unpredictable and tends to be aggressive.

Protection of the skin by staying out of the sun during midday hours (11am – 4pm), wearing protective clothing and wearing sunscreen with an SPF of 50, and which protects against UVA and UVB, are all important in preventing melanoma. Sunscreen should not be used to prolong exposure, and it is important to reapply sunscreen at 2 hour intervals. Protective clothing should include hat, sunglasses and preferably a long sleeved shirt and trousers. Tanning beds and sunlamps should also be avoided as they expose the user to harmful UVA and UVB rays14.
Educating the public on melanoma and how to prevent it is probably the best way to reduce the incidence of melanoma and other skin cancers [15]

Prognostic Features
The importance of self examination of the skin cannot be emphasised enough as the prognosis for melanoma changes drastically for early lesions and more advanced lesions. The most accurate indicator of prognosis is the Breslow's depth of the lesion. A Breslow's depth of less than 1mm has a 5 year survival rate of over 95%, and one of more than 4mm has only a 50% 5 year survival rate assuming there is no nodal or distant metastasis7. Amelanocytic melanomas have a worse prognosis than their melanocytic counterparts simply because they are often diagnosed late. This further emphasises the importance of early detection.
The presence of satellite or in-transit lesions and ulceration of the lesion both make the prognosis worse. Also, males tend to do worse than females. As in this case, the absence/few mitotic bodies improve prognosis.

Finally, the presence of metastases has a huge impact on prognosis. A single positive node is associated with a 40% 10-year survival rate, while 2 positive nodes give a 13% survival rate. If distant metastases are found, there is only a 25% 2 year survival rate. [9]

Treatment Options

Treatment of melanoma is primarily surgical. In this case, an excision biopsy is performed (or an incision biopsy for an exceptionally larger lesions) to confirm the diagnosis and determine the Breslow thickness and Clark stage. Next, depending on the Breslow thickness, a clear margin (including subcutaneous tissue) needs to be excised: [9]

Breslow Thickness (mm)	Recommended Margin (cm)
In Situ	0.5
<1	1
1-2	1-2
2-4	2-3
>4	3

It is important to have clear margins to lower the risk of local recurrence and eliminate undetected satellite lesions.
Regarding lymph nodes, SLNB is the mode. This was in fact what was used in this case. In patients with melanoma of less than 1mm depth SNLB is not recommended unless there are other poor prognostic factors like ulceration and high mitotic rate. If the SNLB is positive a radical lymph node dissection is recommended as this prolongs the disease few survival, although it does not affect the overall survival rate. [20]

Medical management is reserved for adjuvant therapy of patients with very advanced melanoma (Breslow >4mm). This was, hence, not required in this case. However, modified radiotherapy may reduce recurrence and improve survival rates. [9] Immunotherapy (interferon or interleukin) may be used in conjunction with chemotherapy or surgery to increase the immune system's ability to recognise and destroy cancer cells. [16] Chemotherapy is of limited usefulness, but is sometimes used in disease that has spread or to slow the progression of the disease, as in locally advanced melanoma with regional or in-transit metastasis, where surgery is not an option.

Patients with distant metastases may consider radiotherapy or chemotherapy (dacarbazine), though these would have only a palliative role. Surgery may be considered in oligometastatic disease, or to prevent pain or ulceration. Very advanced patients may consider enrolling in a clinical trial. [17] Melanoma vaccines are the best near term hope for improving mortality in patients with advanced disease. Currently trials are aimed at treatment of patients with advanced disease, but their relatively low toxicity makes them attractive for adjuvant therapy in stage I patients at high risk for recurrence. [21] In short, melanoma with distant metastases is not normally curable, so efforts should be aimed at prevention and early detection of the disease.

References

1. Mitchell, Kumar, Abbas, Fausto (2006) Robbins and Cotran Pathological basis of disease 7th ed. London: Churchill Livingstone Elsevier

2. Dalmas M, England K, Boffa MJ, Degaetano J, Gatt P.Cutaneous melanoma in the Maltese Islands: 2000-2004 Eur J Cancer. 2007 Jul;43(10):1604-10. Epub 2007

3. http://emedicine.medscape.com/article/280245-differential. Retrieved on 9th January 2012

4. Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol. Aug 15 2001;19(16):3635-48.

5. American Joint Committee on Cancer. AJCC Staging Manual. 6th edition. 2002.

6. Malcolm R Kell, senior specialist registrar, Michael J Kerin, consultant surgeon Sentinel lymph node biopsy - Is now an established and widely available technique for breast cancer and melanoma. BMJ. 2004 June 5; 328(7452): 1330–1331

7. British Association of Dermatologist Guidelines 2002

8. http://www.dermatology.ca/programs/melanomainfo/index.html. Retrieved on 10th January 2012

9. Burkitt, Quick, Reed (2007). Essential Surgery. 4th ed. London: Churchill Livingstone Elsevier. p672-674.

10. Dennis LK, Lynch CF, Sandler DP, Alavanja MC. Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environ Health Perspect. 2010 Jun;118(6):812-7. Epub 2010 Feb 17

11. P J Nelemans, H Groenendal, L A Kiemeney, F H Rampen, D J Ruiter, and A L Verbeek Effect of intermittent exposure to sunlight on melanoma risk among indoor workers and sun-sensitive individuals. Environ Health Perspect. Aug 1993; 101(3): 252-255

12. Poon TS, Barnetson RS, Halliday GM Sunlight-induced immunosuppression in humans is initially because of UVB, then UVA, followed by interactive effects J Invest Dermatol. 2005 Oct;125(4):840-6

13.Levison, Reid, Burt, Harrison, Fleming (2008). Muir's Textbook of Pathology. 14th ed. London: Hodder Arnold. p501-503.

14. http://www.cancer.org/Cancer/SkinCancer-Melanoma/DetailedGuide/melanoma-skin-cancer-prevention. Retrieved on 15th January 2012.

15. http://www.cancer.org/Cancer/SkinCancer-Melanoma/DetailedGuide/melanoma-skin-cancer-new-research. Retrieved on 15th January 2012.

16. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001853/. Retrieved on 15th January 2012.

17. British Journal of Dermatology Revised U.K. BAD guidelines for the management of cutaneous melanoma 2010 J.R. Marsden, J.A. Newton-Bishop, L. Burrows, M. Cook, P.G. Corrie, N.H. Cox, M.E. Gore, P. Lorigan, R. MacKie, P. Nathan,H. Peach, B. Powell and C. Walker. http://www.ashfordstpeters.nhs.uk/attachments/1023_Melanoma%20guidelines%202010.pdf Retrieved on 15th January 2012

18. Skin Type Charting
http://new.dhh.louisiana.gov/assets/oph/Center - EH/sanitarian/fooddrug/SkinTypingChart.pdf Retrieved on 3rd March 2012

19. CDKN2A cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) [Homo sapiens] Gene ID: 1029, updated on 26th Feb 2012
http://www.ncbi.nlm.nih.gov/gene/1029 Retrieved 3rd March 2012

20. F. Wright, K. Spithoff, A. Easson, C. Murray, J. Toye, D. McCready, T. Petrella, and the Melanoma Disease Site Group. Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-Negative Cutaneous Melanoma of the Trunk or Extremities. A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO). May 17, 2010

21. Mark F. Naylor. Melanoma vaccines. Dermatology Online Journal 6(1): 5 available at http://dermatology.cdlib.org/DOJvol6num1/transactions/melanoma/naylor.html