Melanoma : A Frequently Missed Diagnosis

Col R Lakhtakia (Retd)*, Col A Mehta (Retd)⁺, Maj Gen SK Nema[#]

MJAFI 2009; 65 : 292-294

Key Words : Melanoma

Introduction

In 'An unforgivable delay' in the Lancet 2005 Jan 29 Issue, a psychiatrist acknowledges, how as a young internist he dismissed an inguinal soft tissue swelling in a middle-aged lady, as a 'lipoma' and to his chagrin, realized later, that it was a melanoma! [1]. The confessional prompted this review in view of recent similar experiences with diagnosis of this tumor.

Malignant melanoma is an aggressive tumor of melanocytes commonly encountered as cutaneous malignant melanoma (CMM) in fair-skinned individuals predisposed to it by ultraviolet exposure. Fewer cases present as ocular melanomas or malignant mucosal melanoma (MMM) [2,3].

India enjoys a low incidence of melanoma [4-6], which could be due to under-reporting of melanoma on account of a low index of suspicion by clinicians and pathologists alike. This is particularly true when a cutaneous lesion lacks pigmentation or an ocular or mucosal melanoma is occult and presents as metastasis. This may lead to a missed or delayed diagnosis and delayed therapy.

We draw the attention of the reader to the possible underreporting of melanoma because of our reluctance to 'think' about its existence; compounded by a variant morphology that evades diagnosis. Four recent cases highlighting the clinical and diagnostic aspects of melanoma are discussed.

Case Reports

Case 1

A 30 years old male presented with a rapidly increasing mass in the left axilla accompanied by loss of weight and weakness of three months duration. The mass was 5x4cm with a shiny, stretched skin with prominent veins. He had pallor and mild hepatomegaly. A fine needle aspiration cytology (FNAC) from the mass was reported as a poorly differentiated tumor. His general condition rapidly deteriorated within the next fortnight with development of left-sided pleural

effusion and another nodule in the right thigh. He underwent a pleural tap, pleural biopsy and biopsy of the thigh mass with no change in diagnosis. Review of slides at our centre showed that the malignant cells were dyscohesive with pleomorphic nuclei and macronucleoli (Fig.1). Careful search revealed focal presence of melanin pigment. The cells were positive for S-100 protein (an immunophenotypic marker cross-reacting with melanocytes) (Fig.2). With a diagnosis of malignant melanoma (metastatic) a search for primary in the eye and mucosal sites was suggested. Fundoscopy revealed a uveal melanoma. The patient died within two months of presentation due to disseminated disease and on autopsy the presence of a uveal melanoma with disseminated metastasis was confirmed.

Case 2

A 35 years old male presented with paraparesis. FNAC of the compressive lesion at D12 was reported as a poorly differentiated tumor: suggested primary - poorly differentiated carcinoma and melanoma. Review of the patient elicited history of amputation of a little finger for a subungual melanoma two years back.

Case 3

A 60 years old female underwent a mid-foot amputation for a squamous cell carcinoma left foot elsewhere. She reported to our centre six months later with recurrence at the amputation stump and inguinal lymphadenopathy. An FNAC of the recurrence was reported as melanoma because of the cytologic appearance of the cells though pigment was lacking. A biopsy of the lesion and review of slides of previous surgery confirmed the diagnosis, supported by immunophenotyping by S-100 and Melan A.

Case 4

A 55 years old male had a non-healing ulcer on the right leg of six months duration. A biopsy was reported as a poorly differentiated carcinoma. On further investigation during workup for surgery an ultrasonography (USG) abdomen revealed a large necrotizing retroperitoneal mass. The FNAC (USG-guided) of the mass repeatedly yielded black tarry fluid, but cells entrapped were smudged and difficult to assess. The possibility of metastatic melanoma was suggested.

*Ex-Senior Advisor (Pathology), Army Hospital (R&R), Delhi Cantt. ⁺Ex-Professor & Head (Department of Pathology), AFMC, Pune-40.

[#]MG (Med), HQ SouthWest Command, C/o 56 APO.

Fig. 1 : FNAC (Case 1) showing dyscohesive cells with large nuclei, macronucleoli and a tumor giant cell. There is sparse coarse pigment in the cytoplasm (MGG x40).

Fig. 2 : Trucut biopsy (Case 1) revealed melanin pigment in pleomorphic tumor cells (Haematoxylin & Eosin x 40). Inset: tumor cells positive for S-100 protein (IHC with DAB x20).

Fig. 3 : Variable size, shape and density of late stage melanosomes in the cytoplasm of melanoma cells (Case 4) (Uranyl acetate-lead citrate x 27,000).

Review of the original biopsy, positivity of tumor cells for S-100 protein and melanosomes on electron microscopic examination (Fig.3) of a repeat biopsy confirmed the diagnosis of malignant melanoma.

Discussion

There are few reports in the literature on cutaneous malignant melanoma (CMM) in the Asian population. India is one of the low incidence regions of the world. Cancer registries in India report that the age specific incidence rates for CMM are less than 0.5 per 1,000,000 [4]. In a 15 year period study from RCC Trivandrum, a total of 163 cases of melanoma were identified, of which 21 had a lesion in mucosal sites [5]. Indian ethnic migrants to Great Britain also enjoy low mortality in relation to melanoma [6]. In a series of 79 CMM cases at RCC Trivandrum the peak age was 79 years with male: female ratio of 1.6:1 [4] while in Bombay males exceeded females in the above 45 years age group [7].

In contrast CMM incidence in most affluent countries has increased over the last three or four decades. Increased incidence of uveal melanoma is seen in France, Italy and Japan [2, 3]. It is interesting that when Jews residing in various parts of the world were studied those in Asia and Africa had the lowest incidence [8].

The Bombay Cancer group found sole of foot and internal mucous membranes as major anatomic sites in Indians. This cancer in Indians resembles that in blacks and nonwhites in affecting less pigmented epithelia and skin [7]. Plantar acral melanomas also constituted one-fourth of all melanomas in a study from Manipal [9]. In Hong Kong Chinese (who have a low incidence of cutaneous melanomas like India) cutaneous melanoma was found predominantly at an older age with the acral lentiginous histologic type located mainly on the feet [10]. Only 9/32 anal melanomas reported from Delhi were clinically diagnosed as melanomas [11].

Two of our cases were acral in location presenting as non-healing ulcers, which were interpreted as a poorly

differentiated carcinoma. It is to be remembered that squamous carcinoma is extremely rare on skin not previously damaged by radiation, burns or chronic inflammation.

Though uveal melanomas are rare in Asian Indians, they occur in younger persons (mean age 45.7 years), majority involve the choroid, have a greater mean basal diameter (12.44mm) than of Caucasians and are predominantly of the mixed cell type [12,13]. In Chinese, uveal melanoma is the leading ocular tumor after 15 years of age [14]. Thus Asian Indians present at an earlier age with larger tumors which emphasises the racial differences in presentation of uveal melanoma.

The 'typical' tumor shows epithelioid and/or spindle cells with pleomorphism, large nuclei and mitosis. Eosinophilic macronucleoli are seen in the epithelioid cells. Melanin content may be variable [15]. The tumor often assumes many other 'faces' and may have signet ring, balloon rhabdoid and round cells making diagnosis difficult in amelanotic tumors especially at unexpected sites [16]. It is, therefore, important that melanoma be listed in the differential diagnosis of a poorly differentiated malignancy and confirmed with immunophenotyping or ultrastructural findings. Antibodies used include S-100, HMB45 and Melan-A/MART 1 [17]. It is worth remembering that S-100 is more likely to be positive in the spindle cells and HMB45 in the epithelioid areas. S-100 positivity was found in 76% of anal melanomas in one report [11]. PNL2 has recently shown greater specificity and is especially useful in metastatic tumors [18]. Where available, electron microscopy can demonstrate pre-melanosomes and melanosomes complemented by immunolabelling in lattice-deficient melanomas [19].

Melanoma is one of the most notorious tumors both for metastasis at unusual locations or after a long latent period (sometimes years later when the excision of the primary is forgotten) [20-22]. Our two cases of

metastasis from subungual melanoma (where history was elicited on probing) and uveal melanoma (where clinicians were guided to search for it) are cases in point.

While five-years survival of 25.2% is reported in cutaneous melanomas, almost one-third of the patients from Trivandrum failed locally while another third developed distant metastasis during the follow-up period [4]. Mucosal melanomas of the nasal cavity are aggressive and carry a uniformly poor prognosis [23]. Mucosal melanomas in South India had a dismal outlook with a survival of 6.6% at three years [5]. In a large series of 72 anal melanomas diagnosed and treated over a 11 year period from TMH, Mumbai two-third cases had distant metastasis at presentation with a mean survival of 10.3 months [24]. Similar aggressive behaviour and poor long term outcome was seen in a pooled analysis of 60 published cases of mucosal melanomas of the head and neck across the Indian subcontinent where palate and alveolus were the commonest sites [25].

The existence of malignant melanoma, though uncommon in our country, needs to be recognized and considered in the diagnosis of poorly differentiated lesions at any site. Inclusion of melanoma markers in the panel for immunophenotyping will prevent under reporting of this highly aggressive malignancy.

Conflicts of Interest

None identified

References

1. Foglia A. An unforgivable delay. *Lancet*. 2005; 365:445.
2. Stang A, Parkin DM, Ferlay J, Jockel KH. International uveal melanoma incidence trends in view of a decreasing proportion of morphological verification. *Int J Cancer* 2005 10;114-23.
3. Ohtsuka H, Nagamatsu S. Changing trends in numbers of deaths from malignant melanoma in Japan, 1955-2000. *Dermatology* 2003;207:162-5.
4. Nair MK, Varghese C, Mahadevan S, Cherian T, Joseph F. Cutaneous malignant melanoma—clinical epidemiology and survival. *J Indian Med Assoc* 1998;96:19-20.
5. Pandey M, Mathew A, Abraham EK, Ahamed IM, Nair KM. Primary malignant melanoma of the mucous membranes. *Eur J Surg Oncol* 1998;24:303-7.
6. Swerdlow AJ, Marmot MG, Grulich AE, Head J. Cancer mortality in Indian and British ethnic immigrants from the Indian subcontinent to England and Wales. *Br J Cancer* 1995;72:1312-9.
7. Krishnamurthy S, Yeole B, Joshi S, Gujarathi M, Jussawalla DJ. The descriptive epidemiology and trends in incidence of nonocular malignant melanoma in Bombay and India. *Indian J Cancer* 1994;31:64-71.
8. Iscovich J, Andreev H, Steinitz R. Incidence of cutaneous malignant melanoma in Israel, 1960-1989 *Public Health Rev* 1995;23:1-23.
9. Vijaykumar DK, Kanan RR, Chaturvedi HK. Plantar acral melanoma—an experience from a regional cancer centre, India. *Indian J Cancer* 1996;33:122-9.
10. Luk NM, Ho LC, Choi CL, Wong KH, Yu KH, Yeung WK. Clinicopathological features and prognostic factors of cutaneous melanoma among Hong Kong Chinese. *Clin Exp Dermatol* 2004;29:600-4.
11. Vijayaraghavan M, Kharbanda K, Mathur M. S-100 staining for the diagnosis of melanoma of the anal canal. *Indian J Pathol Microbiol* 1992;35:113-7.
12. Biswas J, Kabra S, Krishnakumar S, Shanmugam MP. Clinical and histopathological characteristics of uveal melanoma in Asian Indians. A study of 103 patients. *Indian J Ophthalmol* 2004;52:41-4.
13. Eskelin S, Kivelä T. Mode of presentation and time to treatment of uveal melanoma in Finland. *Br J Ophthalmol* 2002;86:333-8.
14. Cheng CY, Hsu WM. Incidence of eye cancer in Taiwan: an 18-year review. *Eye* 2004;18:152-8.
15. Barnhill RL, Mihm MC Jr. The histopathology of cutaneous malignant melanoma. *Semin Diagn Pathol* 1993;10:47-75.
16. Elder DE, Murphy GF. Melanocytic tumors of the skin. *Atlas of Tumor Pathology. Third series Fascicle 2*. Washington DC. Armed Forces Institute of Pathology 1990.
17. Burnier MN Jr, Mclean IW, Gamel JW. Immunohistochemical evaluation of uveal and melanocytic tumors. Expression of HMB-45, S-100 protein, and neuron-specific enolase. *Cancer* 1991;68:809-14.
18. Busam KJ, Kucukgol D, Sato E, Frosina D, Teruya-Feldstein J, Jungbluth AA. Immunohistochemical analysis of novel monoclonal antibody PNL2 and comparison with other melanocyte differentiation markers. *Am J Surg Pathol* 2005;29:400-6.
19. Eyden B, Moss J, Shore I, Banerjee SS. Metastatic small cell malignant melanoma: a case requiring immunoelectron-microscopy for the demonstration of lattice-deficient melanosomes. *Ultrastruct Pathol* 2005;29:71-8.
20. Lee WT, Weber PC. Melanoma metastasis masquerading as bilateral acoustic neuromas. *Otolaryngol Head Neck Surg* 2005;132:505-6.
21. Mirallie E, Rigaud J, Mathonnet M, et al. Management and prognosis of metastases to the thyroid gland. *J Am Coll Surg* 2005;200:203-7.
22. Drlicek M, Bodenteich A, Urbanits S, Grisold W. Immunohistochemical panel of antibodies in the diagnosis of brain metastases of the unknown primary. *Pathol Res Pract* 2004;200:727-34.
23. Nakaya M, Mochiki M, Takeuchi S, Yuge T, Nakao K, Nakamura N, et al. Malignant melanoma of nasal cavity: report of 16 Japanese patients. *Auris Nasus Larynx* 2004;31:233-7.
24. Das G, Gupta S, Shukla PJ, Jagannath P. Anorectal melanoma: A large clinicopathologic study from India. *Int Surg* 2003;88:21-4.
25. Pandey M, Mathew A, Iype EM, Sebastian P, Abraham EK, Nair KM. Primary malignant mucosal melanoma of the head and neck region: pooled analysis of 60 published cases from India and review of literature. *Eur J Cancer Prev* 2002;11:3-10.