Case Report

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Metastatic Melanoma of Unknown Primary Presenting with Multiple Cutaneous Nodules: A Case Report with Brief Review of Literature

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ABSTRACT

Melanoma usually present as well-known primary lesions. Rarely, they present with the lymph node, subcutaneous or visceral involvement without evidence of any primary lesion. In such cases they are called Melanoma of unknown primary site (MUP). Melanoma are fast growing cancers. Many environmental and genetics factors predispose to their development.

We report a case of multiple subcutaneous swellings all over the body in a 42 year male, without any primary skin lesions. Histopathology and immunohistochemistry of these lesions confirmed them to be melanoma. Even after extensive search no primary tumour could be found in the patient.

Keywords: *Melanoma, Subcutaneous Swelling, Unknown Primary*

Introduction

Malignant melanoma arises from the melanocytes, the pigment cells of the skin. It is a primary skin malignancy, with an increasing incidence rate, although the mortality due to it has remained constant. [1] Current diagnostic criteria for melanoma of unknown primary site (MUP) include confirmation of metastatic melanoma clinically, histologically or immunohistochemically with absence of previous cutaneous tumours, pigmented or otherwise. MUP can be divided into 2 clinical groups: 1. metastatic involvement to lymph nodes or 2. non-lymph node disease. [2] Unusual primary sites like urogenital, ophthalmologic and otolaryngologic are excluded for the diagnostic criteria. [1-2] Metastatic MUP accounts for 1-8% of all melanoma cases. [1,2,4] The clinical course and prognosis of MUP are similar to patients with melanoma of known primary site (MKP) when corresponding stages are compared.[4,5]

Case Report

A 42 years old male presented with multiple swellings all over the body since 2 months. These were associated with low grade fever and significant weight loss. No other significant personal, family or past history was noted. Physical examination revealed multiple subcutaneous swellings, which were firm in consistency, and few had surface bluish hue (Fig I). Cervical, supraclavicular and inguinal lymphadenopathy were noted. Skin biopsy from these swellings on histopathology revealed sheets of malignant polygonal cells with pleomorphic hyperchromatic to vesicular nuclei, prominent nucleoli and intracytoplasmic and extracellular brown black pigment (Fig II). Immunohistochemistry (IHC) was positive for HMB-45 and S-100 in tumour cells (Fig III,IV). A diagnosis of subcutaneous metastatic melanoma was given. Even after extensive search with the help of physical examination, MRI, PET scan, no primary tumour could be found in the patient. As there were multiple swellings, wide local excision was not possible and the poor prognosis was explained to the family. Patient was started on palliative single agent chemotherapy, Temozolide 150mg,once daily for 5 days and was asked to follow up after 1 month. Patient expired after 10 days of starting chemotherapy , with an overall survival of less than 1 month since the diagnosis of MUP.

Discussion:

MUP was first described by Pack *et al.* [6] in 1952. Later on, in the year 1963 Dasgupta *et al.*[6] have laid down its diagnostic criteria. Even the exclusion criteria for MUP were stated and include patients with the following features: 1. Previous history of orbital exenteration or enucleation; 2. History of electro dissection excision or cauterization of a mole, freckle, birthmark, chronic paronychia or skin blemish; 3. Presenting in one of the node bearing areas and who have a scar of previous local treatment in the skin, drained by the anatomic lymphatic basin and 4. Without a thorough physical examination in search of the primary including ophthalmoscopy and anogenital examination. [3]

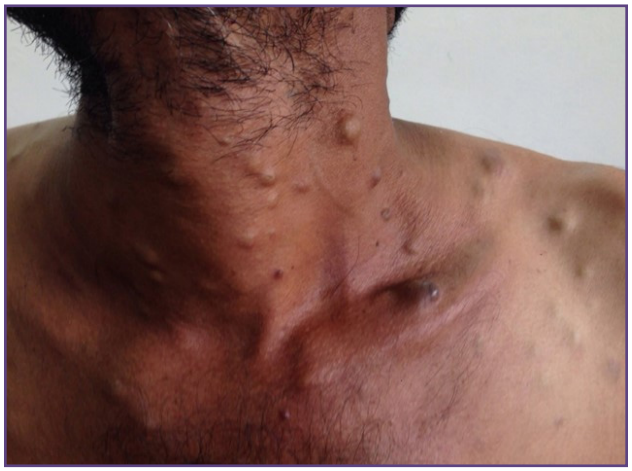

Fig. I. Multiple firm subcutaneous swellings, few with surface bluish hue.

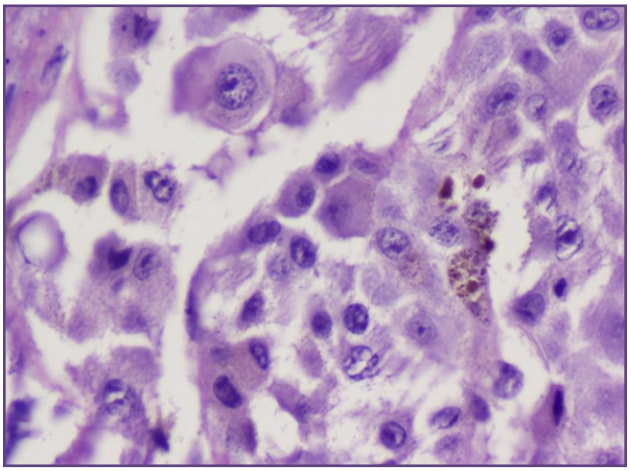

Fig. II. Malignant cells with intracytoplasmic and extracellular brown black pigment. H&E X400.

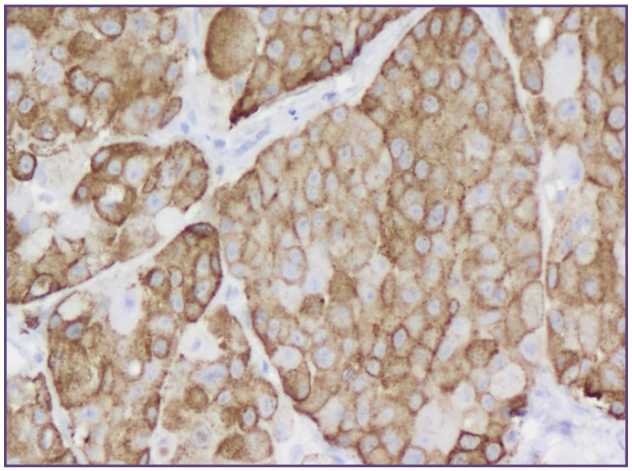

Fig. III. Tumour cells positive for HMB-45 HMB-45 X400

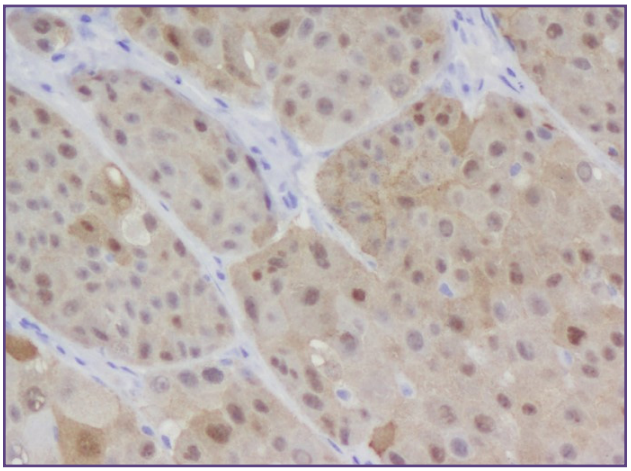

Fig. IV. Tumour cells positive for S-100 S-100 X400.

Many theories have been put forward to explain the pathogenesis of MUP. The most accepted one is the presence of antecedent unrecognized primary melanoma which has regressed spontaneously, but has metastasized prior to its regression. [1,2,5] Other theories include concurrent and undetected melanoma, melanoma arising de novo from ectopic melanocytes present within lymph nodes, the intranodal nevus cells and a previously excised clinically and histologically misdiagnosed melanoma. [1,2,5] Anbari *et al*. [5] analysed 40 MUP patients and reported that 22.5% had dysplastic nevus prior to developing MUP and 20% of the patients had a history of a skin lesion that had regressed and was never diagnosed.

MUP are found to be more common in men with a male: female ratio of 1.7:1. [5,8] This gender inequality in the presentation of MUP can be explained by the theory of regression and also by the fact that men are more exposed to sun. Melanoma is one of the most common tumours to undergo regression; other two being neuroblastoma and hypernephroma.[2] Spontaneous regression of cancer was first defined in 1968. Mărgăritescu *et al*. [9] stated that partial regression in primary cutaneous melanoma is more common as seen in 10-35% cases, whereas complete histological regression is rare with an estimated rate of 0.22-0.27%. On the other hand authors Walton et al.[1] stated that regression of melanoma is well documented with a postulated frequency of 3.7-8.7%. Men are more likely to ignore a pigmented lesion for the longer time, till it regresses completely and then presents metastatically. Alternatively, men may develop melanomas in places in which regression is more likely to occur. Regression is a sign of good host immune response and this might be the reason for survival advantage seen in MUP patients in some studies as compared to patients with known primaries. [7] Giuliano *et al*. [10] described histological changes in a melanoma undergoing spontaneous regression as dense

infiltrate of lymphocytes dividing the tumour into clumps of cells, with areas of degeneration and in later stages fibroblast proliferation with neovascularization.

Egberts *et al*. [11] noted that the mutational profile of MUP and MKP (cutaneous melanomas) were identical and both harboured BRAF mutations and V600E more commonly as compared to V600K.

In a study by Schlagenhauff *et al*. [4] the median age of patients with unknown primary was 53 years while those with primary cutaneous melanoma were slightly younger at 51 years. According to Mărgăritescu *et al*. [9] the mean age of presentation MUP was 49 years with an age range of 21-71years. Patients with visceral metastasis at the time of diagnosis were older at about 70 years of age.

Schlagenhauff *et al*. [4] in their study found that 50.6% of MUP presented with cutaneous or subcutaneous metastasis, 45.3% with lymph node metastasis and 1.33% with visceral metastasis at the time of presentation. The authors also documented the site preference between the genders. Female patients usually presented with metastasis to head, neck and extremities whereas male patients showed a predominant predilection for the axillae, followed by head, neck and trunk. MUP may also present as amelanotic lesions in young patients and hence, require a high index of suspicion to arrive at the correct diagnosis. [12] At times may also present as multiple asymptomatic gradually progressing skin coloured nodules all over the body in middle aged population along with multiple visceral involvements. [13] Unusual sites for metastasis of MUP are endobronchial region and colon. [14.15] Our case presented with multiple subcutaneous nodules all over the body.

Clark and Breslow staging systems are the two important staging systems for melanoma. The Breslow system is based on the microscopic depth of invasion in millimeters. The Clark level is based on five level depth of invasion.[2]

Melanoma is primarily treated by wide local excision, sentinel lymph node biopsy, wide local excision with elective lymphadenopathy, radiation therapy and/or systemic therapy. Sentinel lymph node biopsy has improved efficacy in identifying occult metastases and aids in staging and prognosis of patients.[2]

It has been seen that MUP has a similar or better prognosis as compared to MKP as seen in studies by Schlagenhauff *et al*. [4] and Anbari *et al*. [5] Immune responses which cause regression of the primary tumor sustain improved control of the disease on metastasis. [2] Studies have found better survival in patients of MUP with nodal metastasis after lymphadenectomy.[2] They noted 5 year survival in 55% patients after lymph node dissection compared to 27% without lymph node dissection. Das Gupta *et al*. [7] noted an overall survival of 30% in MUP patients in 5years. A study of 98 patients at M.D. Anderson Cancer Center in Houston reported an overall 5 year survival rate of 33% in MUP patients. [16] A study by Chang *et al.* [16] on 166 patients of MUP, noted that the clinical course of MUP was similar to Stage II and III patients with overt primary lesions.

Conclusion

Metastatic melanoma of unknown primary site continues to be unique entity, with an elusive presentation warranting a strong index of suspicion. A thorough workup is required for the diagnosis of this disease. Inspite of being a well-known entity, elucidation of the mechanisms behind this phenomenon needs to be unraveled. Also, a consensus needs to be established to describe the presentation, management and prognosis for these cases for better management.

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