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Amelanotic Melanoma: A Great Masquerader

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Abstract

Malignant melanoma is an aggressive, notorious tumor showing great variability in morphological and immunohistochemical expression, thus commonly leading to an erroneous diagnosis. Within the melanoma group, amelanotic melanoma, with its wide clinical presentations, lack of pigmentation, and varied histological appearances, has taken on a new persona as a master masquerader. Use of immunohistochemistry in the diagnosis of malignant tumors, including melanoma, is primordial and indispensable. However, the problem gets compounded in scenario of aberrant antigenic expression. The present case posed multiple diagnostic challenges in form of atypical clinical presentation, variant morphology, as well as aberrant antigenic expression. Here, we present the case of a 72-year-old male who, upon his initial presentation, was thought to be sarcomatoid anaplastic plasmacytoma, but 5 months later another biopsy from a different site revealed the actual diagnosis of amelanotic melanoma.

Keywords
- amelanotic
- melanoma
- plasmacytoma
- plasma cell neoplasm
- plasmacytoid
- sarcomatoid

Introduction

Melanoma is a malignant melanocytic tumor, arising from the melanocytes in the skin, mucosa, and the indigenous melanocytes of various internal organs. Amelanotic malignant melanoma is a subtype of melanoma that has little or no pigment on visual or histological examination. Diagnosis of malignant melanoma with presence of melanin pigment is not problematic, however, amelanotic melanomas, which constitute approximately 2 to 20% of all melanomas, are notorious mimickers and pose a serious diagnostic challenge.[1]

Primary mucosal melanoma is a rare neoplastic entity and accounts for 1.4% of all malignant melanomas.[2] These mucosal melanomas differ in their pathobiology and clinical presentation from cutaneous melanomas. Furthermore, mucosal melanomas show a diverse histomorphology including small cell, spindle cell, pleomorphic cell, epithelioid cell, plasmacytoid cell, rhabdoid cell, undifferentiated cell, and mixed patterns.[3] Plasmacytoid variant of melanoma is a rare finding which may mimic many other entities especially plasma cell neoplasm.

Case History

A 72-year-old male patient presented with sudden onset of back pain, which gradually progressed in 1 month. Computed tomography of spine showed hyperintense signal lesions in the L3 vertebral body and left posterior element, which were suspected to be metastatic lesions. On positron emission tomography (PET) scan, hypermetabolic lytic lesions were noted in the body and left pedicle of L3 vertebra. No

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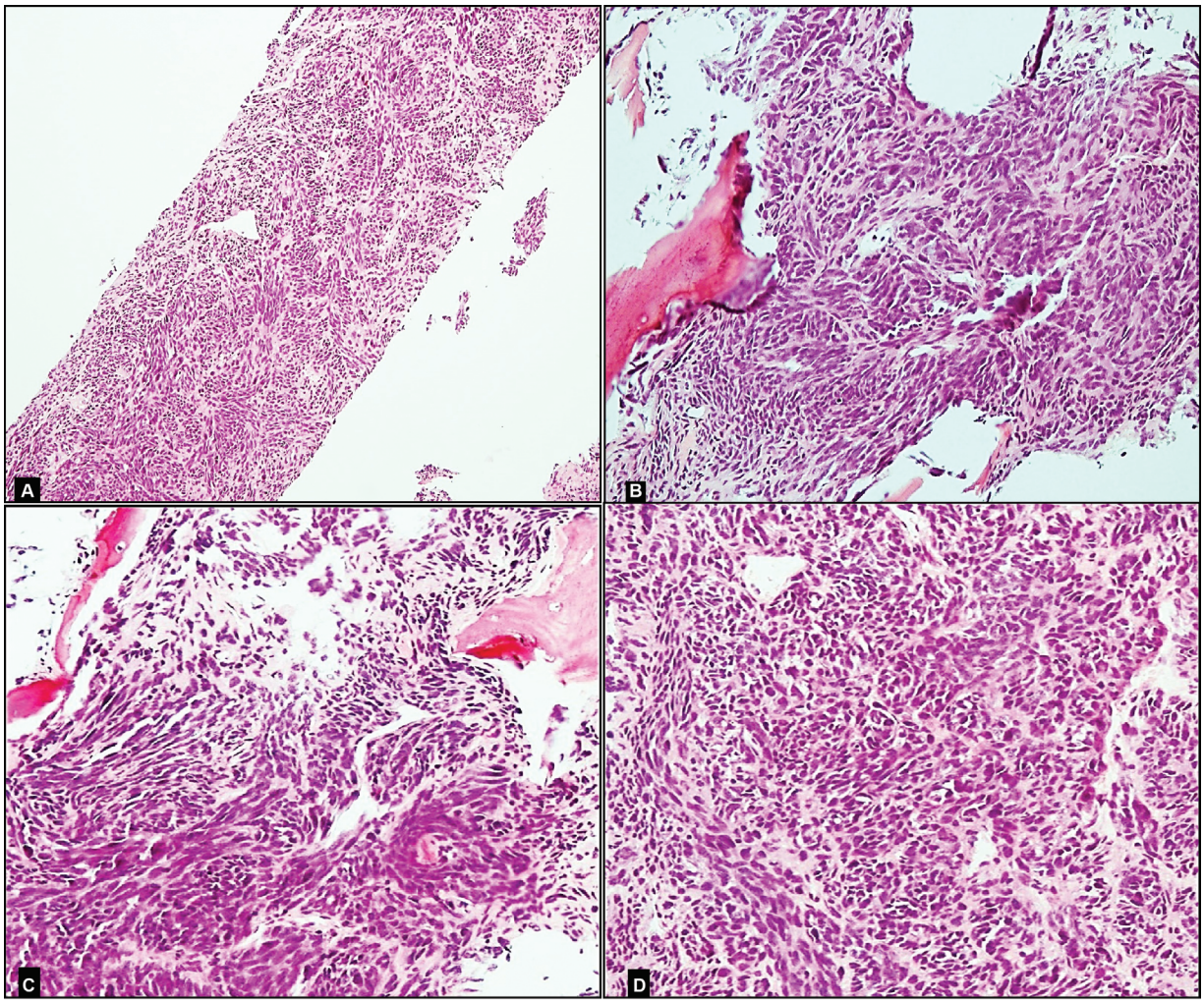

Fig. 1 (**A**) Tru-cut biopsy showing a cellular tumor composed of plump spindled cells and arranged in short fascicles and focal tight clusters/nests in a fibrous stroma (hematoxylin and eosin [H&E] 100 ×). (**B**, **C**) Tumor diffusely infiltrating in the bony tissue (H&E 200 ×). (**D**) Individual tumor cells with poorly defined cell borders, pale eosinophilic cytoplasm, large rounded to elongated nuclei, smudgy chromatin, and inconspicuous nucleoli (H&E 200 ×).

other osteolytic lesions were noted on skeletal magnetic resonance imaging. Laboratory studies revealed serum calcium 12 mg/dL, creatinine 0.8 mg/dL, total protein 7.27 g/dL, albumin 4.24 g/dL, globulin 3.03 g/dL, and alkaline phosphatase 96 IU/L. Serum protein electrophoresis showed a polyclonal rise in gamma globulins (1.77 g/dL). Bone marrow and imprint smears were cellular and showed all hemopoietic elements with normal maturation. Plasma cells comprised 2% of the nucleated cells. Subsequently, bone biopsy from lumbar vertebra was done which revealed a cellular tumor composed of plump spindled cells. The tumor cells were present in short fascicles and focal tight clusters/nests in a fibrous stroma (►**Fig. 1A**). The tumor was diffusely infiltrating in the bony tissue (►**Fig. 1B**). At places hemangiopericytomatous pattern was observed. Individual tumor cells had poorly defined cell borders, pale eosinophilic cytoplasm, and large rounded to elongated nuclei with smudgy chromatin, irregular nuclear membrane, and inconspicuous nucleoli (►**Fig. 1C, D**). Only occasional admixed mature plasma cells were noted. Few mitotic figures including occasional atypical forms were identified. No melanin pigment was identified. On immunohistochemistry (IHC), the cells showed positivity for CD138, vimentin, and CD56 (►**Fig. 2A–C**). Kappa and lambda light chain IHC revealed kappa restriction (►**Fig. 2D, E**). Tumor cells were negative for CK, EMA, LCA, CD79a, MUM-1, CD34, STAT-6, and CD30. Ki67 proliferative index was 15% (►**Fig. 2F**). The morphological and IHC features suggested this as to be anaplastic plasmacytoma with sarcomatoid morphology. The patient was given radiotherapy and was on regular follow-up. No new osteolytic lesions were found on repeat scans in the initial months of treatment. However, 2 months after the last cycle of radiotherapy, the patient revealed new hypermetabolic lesions in the skeleton, liver, and lungs on PET scan. Ultrasound-guided liver biopsy from the suspected lesion was sent for histopathological examination.

Microscopic examination revealed a cellular tumor arranged as cohesive sheets (►**Fig. 3A**). However, the morphology was contrasting as compared with the initial biopsy. The tumor cells were relatively plump, and predominantly plasmacytoid in morphology with ovoid nuclei (►**Fig. 3B, C**). The cells showed eccentrically placed nuclei

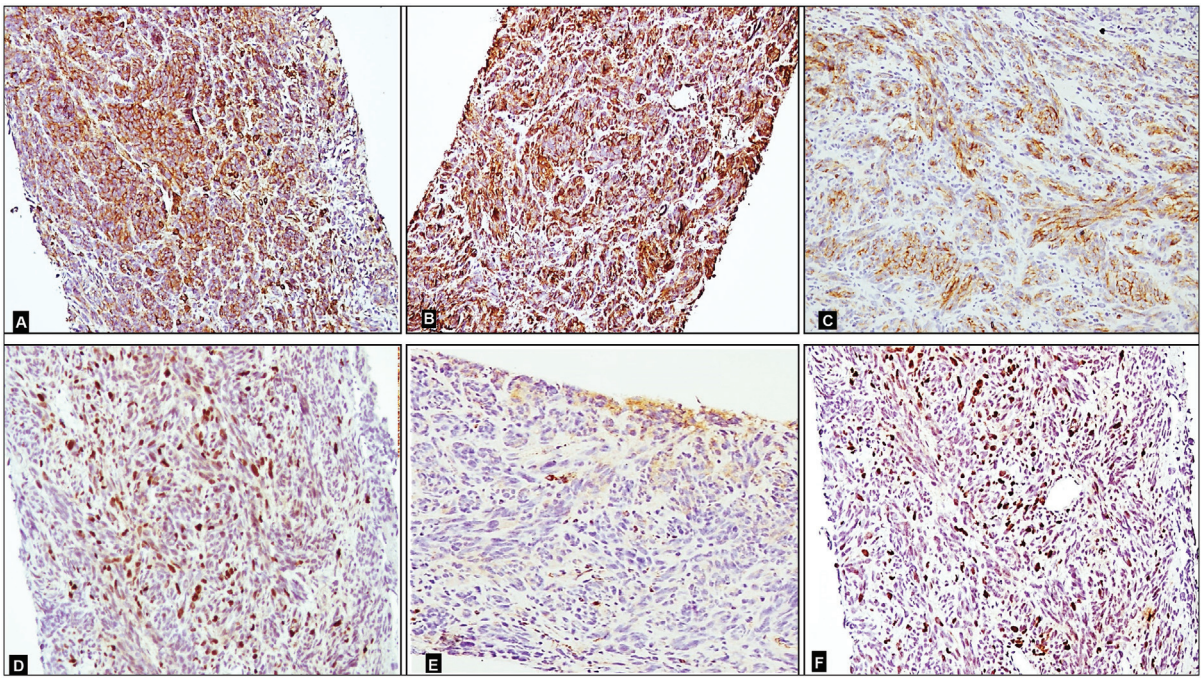

Fig. 2 Immunohistochemistry (IHC) staining (**A**) CD138 positive (200 ×); (**B**) vimentin positive (200 ×); (**C**) CD56 positive (200 ×); (**D**) kappa positive (100 ×); (**E**) lambda negative (200 ×); (**F**) Ki67 proliferative index approximately 15% (200 ×).

having immature to mature chromatin, small to conspicuous nucleoli, and moderate amount of cytoplasm. Perinuclear hoff was noted in few of the tumor cells. Occasional scattered binucleated plasmacytoid cells and few tiny clusters of mature plasma cells were also observed. The tumor interface with liver parenchyma showed many plasma cells (►**Fig. 3D**). Brisk mitotic activity and foci of tumor necrosis were noted. Few cells also showed presence of Russell bodies, which was not obvious in the previous biopsy. No demonstrable melanin pigment was seen on morphology as well as on Masson–Fontana stain. Due to the unusual clinical course of the disease and contrasting morphology observed in both biopsies, an extensive panel of IHC was applied on the current and the previous biopsy in an attempt to include a broad spectrum of tumors and reach the correct diagnosis. Both biopsies showed the same IHC profile for plasma cell markers (as described earlier) (►**Fig. 4A–C**). In addition, various markers for melanocytic differentiation were also applied in both biopsies. Surprisingly, both biopsies showed positivity for S-100, SOX-10, HMB-45, and Melan-A, thus confirming melanocytic lineage (►**Fig. 4D–F**). Other markers like CK, HepPar-1, LCA, MPO, Myogenin, SMA, CD34, and synaptophysin were negative (thus ruling out epithelial, hematolymphoid, sarcomatous, and neuroendocrine differentiation). In view of morphology and IHC findings, a revised final diagnosis of metastatic amelanotic melanoma was given.

The patient was thoroughly inspected again for any skin lesion, but no cutaneous primary tumor was identified. In addition, no history of any biopsied or excised skin lesions in the past was present; thus, suggesting it to be a primary mucosal melanoma. However, endoscopy was not performed to confirm the exact primary site as the tumor had already metastasized at the time of presentation. The primary site of tumor could not be determined. The patient received two doses of immunotherapy and is presently doing well with no signs of recurrence or any new metastatic lesion.

Discussion

Melanoma is an aggressive malignancy with a growing prevalence. The principal morphological features include variable size and configuration of tumor cells, large nuclei with prominent macronucleoli, intranuclear cytoplasmic inclusions, and presence of melanin pigment in the cytoplasm of tumor cells. However, not all melanomas contain melanin pigment (amelanotic melanoma) and may not display characteristic morphological appearance, thus posing diagnostic dilemma. Metastatic melanoma often presents with one or more amelanotic secondary lesions even when the primary tumor was pigmented.[4] Further, melanomas are known to show a gamut of histomorphological findings, hence mimicking many malignant neoplasms. They have a varied differential diagnosis consisting of a variety of carcinomas, sarcomas, and hematolymphoid malignancies like non-Hodgkin's lymphoma and plasmacytoma/myeloma. There are few case reports where abnormal morphology of melanoma cells has been displayed. For example, prominent vacuolization of the cytoplasm (balloon cell melanoma) has been mistaken for metastatic adenocarcinomas.[5] They may also show rhabdoid morphology and nuclear grooving in melanoma cells.[5] Primary mucosal melanoma is a rare entity and the amelanotic form tends to be even more exceptional. Around 50% of all mucosal melanomas are in the head and neck region.[6] Like in other sites of malignant melanoma, the histopathology is variable and when lacking melanin

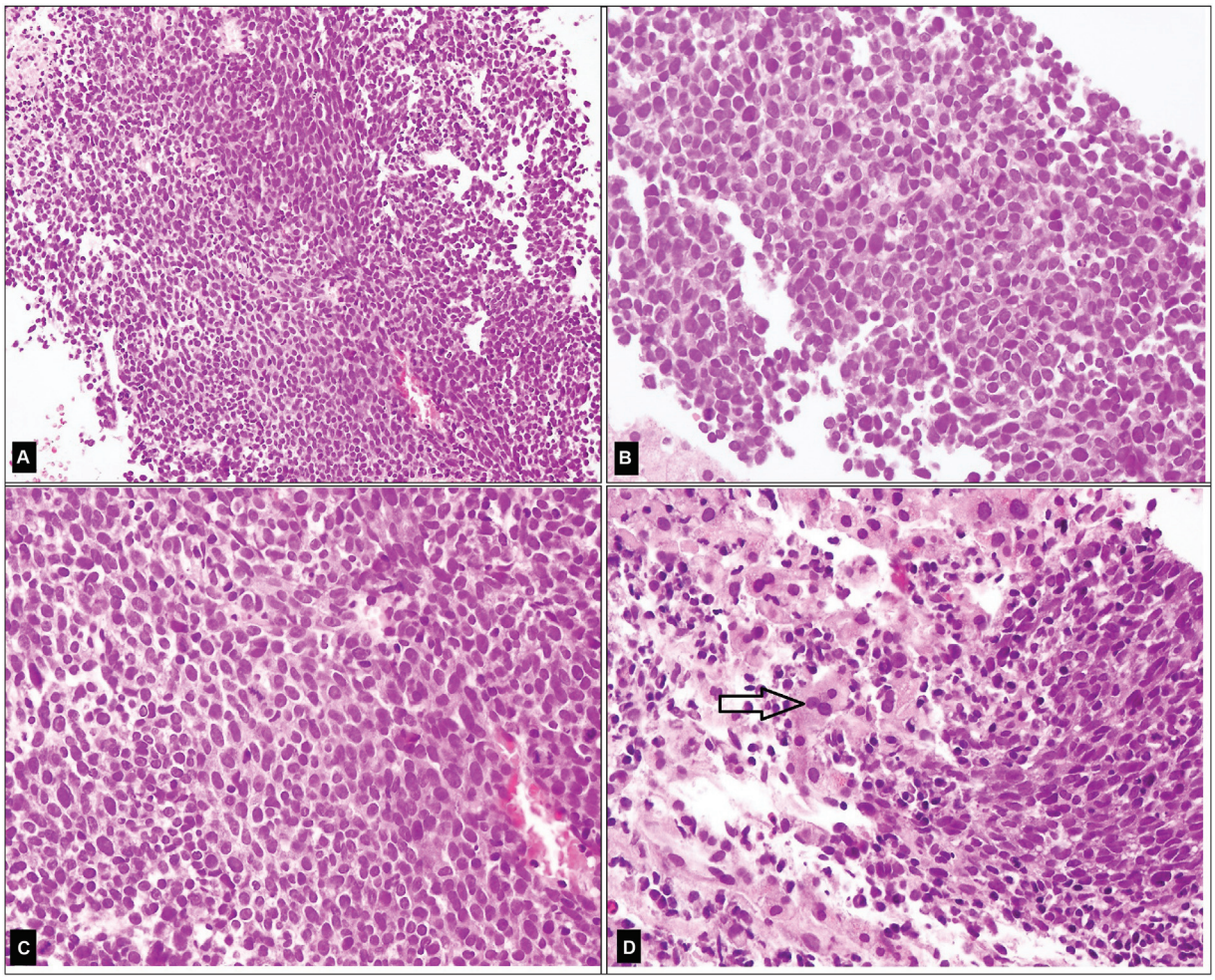

Fig. 3 (**A**, **B**) Tru-cut biopsy showing a cellular tumor present in cohesive sheets with a relatively plump, plasmacytoid morphology, and ovoid nuclei (hematoxylin and eosin [H&E] 100 ×, 200 ×). (**C**) Tumor cells showing eccentrically placed nuclei having immature to mature chromatin, small to conspicuous nucleoli, and moderate amount of cytoplasm (H&E 400 ×). (**D**) The tumor interface with liver parenchyma (*arrow*) showed many mature plasma cells (H&E 200 ×).

pigment, can mimic many neoplasms particularly in small biopsy specimens.

Malignant melanomas express aberrant immunophenotypic staining for several markers of other tumors including cytokeratin, desmin, glial fibrillary acidic protein, smooth muscle actin, carcinoembryonic antigen, epithelial membrane antigen, factor XIIIa, synaptophysin, and chromogranin.[7] Knowledge of this anomalous immunophenotyping is important to prevent misdiagnosis.

In the present case, no known history of any mucosal/skin lesion, clinical presentation as solitary vertebral osteolytic lesion, spindled morphology, absence of pigment in tumor cells, and positivity for plasma cell markers (CD138 and kappa restriction), prompted a diagnosis of sarcomatoid plasmacytoma in the first biopsy. On the other hand, in subsequent biopsy from liver lesion, the cells appeared plump to plasmacytoid having small to conspicuous nucleoli. Unusual clinical presentation and presence of conspicuous nucleoli in tumor cells this time around prompted use of additional IHC, where immunopositivity for melanocytic markers (S-100, SOX-10, HMB-45, and Melan-A) was demonstrated. This distinct morphological and immunoexpression of cancer cells led a final revised diagnosis of amelanotic melanoma.

CD138 is a well-known marker for plasma cells and is expressed on most of the myeloma tumor cells and certain other tumors of B lineage. However, its expression by other nonhematopoietic tumor cells could be misleading. O'Connell et al reported CD138 expression (moderate to strong membranous staining) in up to 50% of melanoma cases.[8] Similar to our case, there are occasional case reports showing unusual IHC results of melanoma leading to an incorrect diagnosis. Charfi et al, in their case report showed positivity for CD138/syndecan-1, MUM-1, and immunoglobulin lambda light chain in a bladder tumor leading to a diagnosis of plasmablastic lymphoma/plasma cell myeloma, which on later evaluation was diagnosed as metastatic plasmacytoid melanoma from a primary esophageal mucosal melanoma.[9] Lehmer et al, in their case report diagnosed plasma cell myeloma in a 63-year-old lady who had a fungating mass in right elbow. Reevaluation of the patient after an interval revealed malignant melanoma (MART-1 and S-100) of ipsilateral breast.[10] Azoulay et al, reported a case of melanoma (Melan-A,

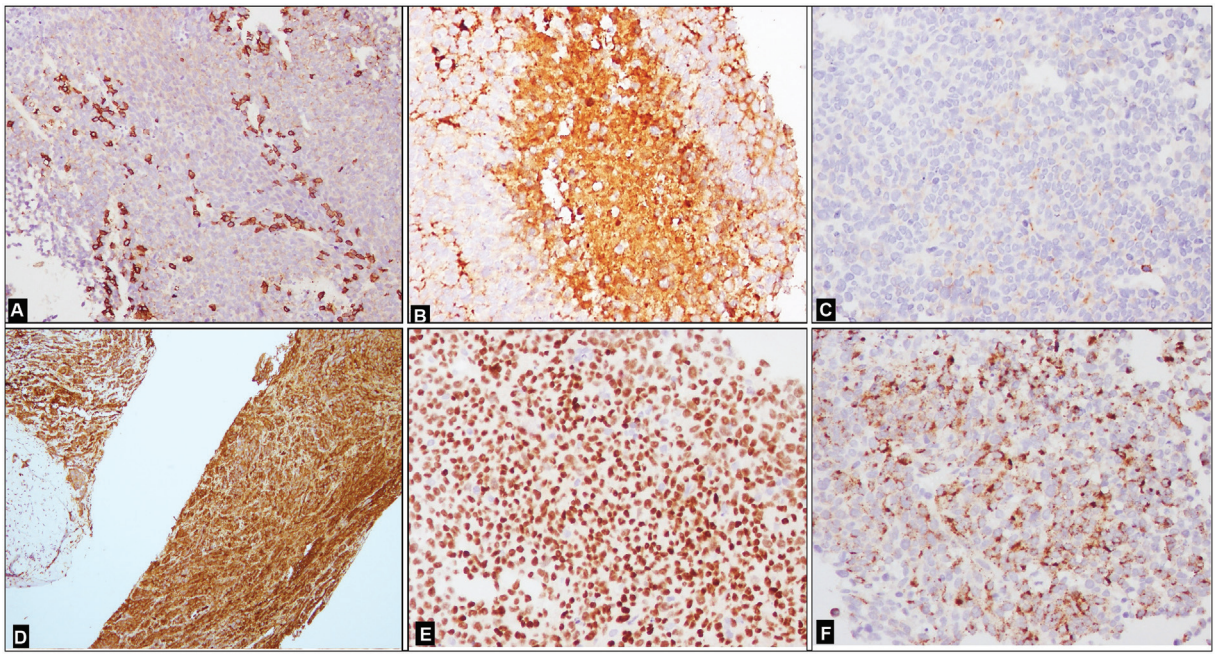

Fig. 4 Immunohistochemistry (IHC) staining (**A**) CD138 positive (200 ×); (**B**) kappa positive (200 ×); (**C**) lambda negative (200 ×); (**D**) S-100 positive (200 ×); (**E**) SOX-10 (200 ×); (**F**) HMB-45 positive (200 ×).

HMB-45, and BCL-1 positive) in a lymph node in a known case of multiple myeloma which was initially thought to be plasmacytoma.[11] Thus, a panel of immunomarkers, and not isolated markers, should be included in cases showing plasmacytoid morphology so as to increase the sensitivity of detection of melanocytic differentiation. S-100 immunomarker is the most sensitive marker and is found to be positive in approximately 95 to 100% of primary mucosal melanomas as compared with 86 and 84% with HMB-45 and Melan-A immunostaining, respectively.[12,13] However, HMB45 and Melan-A are more specific markers. Blessing et al in their study on melanoma variants found diffuse positive S-100 and patchy positive HMB-45 in majority of desmoplastic/spindle cell melanomas.[13] Atypical melanomas, with atypical morphologic features like small cell, signet ring cell, and rhabdoid cell often failed to express S-100.[14] In hematolymphoid system, MUM-1 plays a significant role in terminal B cell differentiation, thus considered as a potential specific marker for plasmacytic differentiation. MUM-1 positivity is noted in a variety of hematolymphoid malignancies and in malignant melanomas. The study of Sundram et al has shown that MUM-1 is more sensitive than both HMB-45 and Melan-A in cases of conventional primary and metastatic melanomas.[15] The significance of plasma cell marker expression and their role in the biologic behavior of melanocytic tumors still remain unclear and may need additional studies for clarification. The treatments of mucosal melanoma include surgery, radiotherapy, chemotherapy, and immunotherapy. The prognosis of melanoma varies with the site and stage of the disease. Lung, liver, and bone are the most frequent sites of metastasis.[16] Distant metastasis or recurrent disease may occur without any evidence of primary lesion.

Conclusion

Melanomas are considered notorious, in terms of their occult presentation, varied morphology, and aberrant immunohistochemical expression. This case reiterated the fact that plasma cell markers are not entirely specific and can be expressed in melanoma. Thus, a panel of immunohistochemical markers is recommended which should include at least one melanocytic marker to exclude malignant melanoma. Knowledge of the varied morphology and anomalous IHC profile is desirable for the pathologists to reduce the risk of erroneous interpretation of such aberrant outcomes.

Informed Consent

The authors certify that they have obtained the appropriate consent from the parent. The parent has given his consent for the images and other clinical information to be reported in the journal. The parent understands that the name and initials will not be published, and due efforts have been made to conceal the same.

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Conflict of Interest

None declared.

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