A Rare Case of Epidermotropic Metastatic Malignant Melanoma

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Introduction

The incidence of malignant melanoma has continued to increase over the past 30 years. Although it accounts for less than 5% of all skin cancers, malignant melanoma due to its aggressive nature is responsible for the majority of skin cancer related deaths. In the early stages malignant melanoma is potentially curable with surgical excision, however due to its highly metastatic potential and resistance to current treatments, in the later stages the 5-year survival is only 15% (1). Metastases in melanoma commonly occur to lymph nodes, lung, brain, liver and skin. When melanoma metastasizes to the skin, it typically occurs to the dermis. Epidermotropic metastatic malignant melanoma (EMMM) is a rare and distinct form of metastatic malignant melanoma that shows epidermotropism and displays specific histopathological features. Its pathological appearance can be similar to that of primary melanoma, and thus recognizing this entity is important in order to administer the appropriate treatment (2). In this report we present a case of a 27 year-old man who presented three years after his primary melanoma with over 100 epidermotropic melanoma metastases.

Case Report

A 27-year-old man presented with a three month history of skin colored pruritic papules that started on his arms and spread to involve his trunk, face and lower limbs. His past medical history was notable for a stage III (T3bN1M0) amelanotic nodular melanoma of his left cheek three years prior. He was treated with a wide local excision, parotidectomy and neck dissection. His adjuvant radiation therapy was curtailed to ten out of twenty sessions, as the patient was unable to tolerate the procedure. Physical exam revealed over 100 pink to skin-colored dome-shaped, well-circumscribed monomorphic firm papules of various sizes, measuring 1-8mm. These were scattered throughout the face, neck, chest, abdomen, back, upper and lower extremities, with most significant involvement of the upper chest.

A skin biopsy revealed severely atypical predominantly dermal melanocytic proliferation and numerous dermal mitoses, and an overlying atypical intraepidermal melanocytic proliferation with pagetoid spread, delineated to the epidermis overlying the dermal nodule. Together with the clinical picture this was consistent with epidermotropic metastatic malignant melanoma (EMMM). This was confirmed by immunoperoxidase staining with Mart-1/Melan-A and S-100 protein. The greatest thickness was at least 4mm, with no ulceration. The patient's prior biopsy of his original melanoma was reviewed and had a similar histologic appearance. Immunoperoxidase staining for BAP1 was performed, showing retention of BAP1 in lesional cells. The melanoma was positive for the BRAF V600E mutation. Whole body PET-CT showed several hypermetabolic lymph nodes in the neck, and a hypermetabolic nodule in the left lower lobe of the lung, suspicious for metastatic disease.

With a diagnosis of stage IV melanoma, the patient was treated initially with five doses of the checkpoint antibody ipilimumab, 3mg/kg. Despite crusting of the tops of the epidermotropic metastases, there was relentless progression of disease, confirmed after 5 months. As the metastases carried the BRAF V600E mutation, the patient then received dabrafenib plus trametinib, achieving a rapid partial response that is ongoing now for over 5 months. The patient is currently awaiting a PET/CT to further evaluate disease response to treatment.

Discussion

EMMM is a rare entity with only a handful of cases reported in the literature. The diagnosis can be challenging as it can mimic primary melanoma histologically and thus requires both clinical and pathological correlation. Histopathologically EMMM is characterized by: 1. thinning of the epidermis by aggregates of atypical melanocytes within the dermis, 2. atypical melanocytes within intradermal endothelial-lined spaces, and 3. a zone of atypical melanocytes within the dermis, equal to or wider than that within the epidermis (3).

The clinical presentation of EMMM could be confused with the BAP-1 cancer syndrome. The latter results from a mutation in the BAP-1 gene, a tumor suppressor gene that is inherited in an autosomal dominant manner. The clinical presentation is characterized by multiple skin-colored papular melanocytic nevi which vary in histology from epitheloid nevi to atypical melanocytic proliferations that can show histological features similar to melanoma. Patients may also develop mesotheliomas, uveal and cutaneous melanomas (4). The BAP-1 cancer syndrome was ruled out in our patient by the retention of BAP-1 in the lesional cells, and also a lack of a family history of the BAP-1 cancer syndrome.

The unusual clinical presentation of this patient raises the question, why the vast majority of his melanoma metastases occur to his skin in preference to more common sites of melanoma metastases. Although he did have metastases to the lung and lymph nodes, involvement at these sites was significantly less in comparison to the numerous lesions in his skin. It is becoming widely accepted that cancer metastasis is not random, as depicted by certain tumors preferentially metastasizing to specific organs. Emerging literature suggests that malignant melanoma initiating cells (MMICs) may drive melanoma progression in a multi-stage fashion, utilizing a combination of selectin, integrin and chemokine receptors to home metastases to target organs. This concept, termed ‘leukocyte mimicry’ is akin to the mechanism utilized by leukocytes to migrate (1,5).

Thus far, we are unable to predict to which organ a melanoma cell may preferentially metastasize. It is conceivable that the expression of certain cell surface markers may in part, determine a preferential site of metastasis. In the case reported, this raises the question as to what molecular keys enable the melanoma metastases in the patient to home preferentially to his skin.

It is well established that a subgroup of memory T-cells circulate specifically to the skin. These are T-cells that have clonally expanded in response to antigens encountered in the cutaneous environment and are required for cutaneous immune surveillance. The adhesion molecule cutaneous lymphocyte antigen (CLA) and the chemokine receptors CCR4, CCR10 and CXCR3, have been proposed as critical mediators that enable these memory T-cells to home to the skin (6,7). Using this analogy we hypothesize that metastatic lesions of melanoma to the skin may be facilitated by a combination of cell surface molecules, perhaps similar to those found on skin homing T-lymphocytes. A better understanding of the molecular keys that influence the sites of melanoma metastases could aid in prognosis and targeted therapies in melanoma in the future.

References