I would like to acknowledge Dr. Robert Osburne for providing guidance with the manuscript.

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Review

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The dearth of information regarding mucosal melanoma corresponds with the rarity of the disease. In a review of 84,836 melanoma cases from the National Cancer Data Base that were entered between 1985 and 1994, 91.2% were cutaneous, 5.2% were ocular, 1.3% were mucosal, and 2.2% were unknown primaries.[1] Mucosal melanoma was first described by Weber in 1856 and later classified as a distinct entity in 1869.[2,3] In the United States, the incidence of cutaneous melanoma continues to rise at a rate higher than that of any other form of cancer. The incidence of noncutaneous melanoma, however, remains stable. Exposure to ultraviolet radiation is a major predisposing factor to cutaneous melanoma. The occurrence of melanoma in areas of the body that have never been exposed to sunlight, such as the gastrointestinal tract, may provide important insights into the pathogenesis of melanoma in general.

Ravi reported a case of upper gastrointestinal bleeding due to a primary gastric melanoma[4] and noted that the tumor is extremely rare and has a very poor prognosis. A high index of clinical suspicion is essential to reach this diagnosis. Unusual appearance or nonhealing gastric ulcers should prompt the endoscopist to obtain multiple biopsies and consult with the pathologist to reach a diagnosis.

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The distribution of mucosal melanomas tends to center near mucocutaneous junctions, where the melanomas are thought to arise from melanocytes that have migrated from the neuroectoderm and undergone malignant transformation. Their function in these locations is believed to differ from that of cutaneous melanocytes and likely has been the reason for the lack of understanding of this malignancy. Malignant melanoma can arise in gastrointestinal mucosal sites such as the esophagus,[5] anorectum,[6] and small bowel.[7,8] Cases of primary melanoma of the stomach have rarely been reported.[9-11] The debate over the nature of such lesions early in development still persists. Thus, specific criteria have been proposed for the diagnosis of primary melanoma, including the absence of concurrent lesions and the lack of a history of melanoma or atypical melanocytic lesion removal from the skin or other organs.[6] Partial or complete regression of melanocytic nevi and melanomas is well recognized.[12] However, there are no data as to how many melanomas regress completely without metastasis. The exact mechanism of regression remains unknown and is difficult to study.[13] Such knowledge would provide an insight into cancer immunology, in general, and melanomas, in particular.

It is known that melanocytes come from neural crest cells and migrate to the skin, hair follicles, and retina; however, their function in the mucosa is not certain. Melanin may be seen in the submucosa of the

oral cavity due to phagocytosis by macrophages. Whether from injury, hormone response, or congenital factors, a variety of melanocytic lesions present clinically as both benign and malignant.[14] Diagnostic studies have been performed to further identify mucosal melanomas as a separate entity from cutaneous melanomas by using a panel of antibodies and looking for various markers seen in the cutaneous form.[15] Most of these studies have been performed retrospectively and have been analyzed immunohistochemically for melanoma-associated antigens. Stains for S100, HMB-45, and antivimentin were strongly associated with mucosal melanomas, but they were not pathognomonic for the disease due to other neural crest-derived tumors known to be associated with these substances.[16] The applicability of these studies can aid in differentiating melanomas from other poorly differentiated tumors. Unfortunately, the laborious process of performing these studies and the similar expression patterns found in cutaneous melanomas can prove to be challenging when differentiating a primary mucosal melanoma from a metastatic one.

Metastatic melanoma in the gastrointestinal tract is relatively uncommon; an antemortem diagnosis is made in 1–4% of patients with malignant melanoma. The small bowel is the most commonly involved site in metastasis occurring in the gastrointestinal tract.[17] Despite nonspecific gastrointestinal symptoms, metastatic melanoma should be suspected in patients with a history of melanoma and acute gastrointestinal symptoms. Although long-term survival remains poor, complete surgical resection of macroscopic viable tumors affords prolonged survival compared with that of palliative resection or medical treatment.

Recommendations regarding appropriate treatment strategies have been proposed in the recent literature.[18] Initially, radical surgery was advocated as the mainstay of therapy; however, local recurrence and survival rates were unchanged regardless of whether radical surgery or local excision was performed, and the most recent data have favored the conservative approach when appropriate. Unfortunately, a multitude of adjuvant therapies have been tried without any success. Adjuvant radiotherapy plays a role when combined with surgery, but this option is reserved for nodal and locoregionally advanced disease and has had no effect when used as a prophylactic method. Potential therapies based upon new biologic and immunologic findings may have promise in the future to impact this disease. Until then, this aggressive disease continues to have a poor prognosis, and surgical resection continues to be the mainstay of primary therapy.[19]

In summary, primary mucosal melanoma, particularly gastric melanoma, represents an extremely rare malignancy that does not have the same risk factors or behavior patterns as cutaneous melanoma. This malignancy occurs in areas that are not exposed to the sun, and its solid predisposing risk factors have not been identified, making the disease very difficult to diagnose or screen for. Primary mucosal melanoma is usually diagnosed at a later stage and carries a poor prognosis.[20] Differentiating a primary lesion from a metastatic melanoma is often challenging, due to the lack of definitive criteria, both pathologically and clinically. The rich vascular and lymphatic networks surrounding these lesions are likely responsible for their aggressive behavior and poor prognosis. In addition, the obscure locations where mucosal melanomas occur are an obvious reason for their late presentation at an advanced stage and hence their often incurable nature.

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