CASE REPORT

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SPONTANEOUS REGRESSION OF CUTANEOUS HEAD AND NECK MELANOMA: IMPLICATIONS FOR THE IMMUNOLOGIC CONTROL OF NEOPLASIA

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Abstract: Background. Spontaneous regression of cancer in the head and neck is a rare event. Moreover, there are rare reported cases of spontaneous regression of primary head and neck melanoma with accompanying immunohistochemical analysis of the tumor.

Methods. We used detailed preoperative and postoperative pathologic examination of a lesion in the right supraclavicular region.

Results. Pathologic examination of the initial specimen identified a melanoma of superficial spreading type with vertical growth and a thickness of 1.8 mm. The excised specimen demonstrated a complete regression of the melanoma with a florid host inflammatory response predominantly composed of a histiocytic reaction.

Conclusion. The case presented illustrates histopathologic findings occurring in a head and neck melanoma as it is undergoing spontaneous regression. These findings point to a potentially critical role for histiocytes in effecting tumor elimination. Pathologic analysis of spontaneous head and neck melanoma regression will ultimately facilitate an improved understanding of naturally-occurring tumor elimination. ©2007 Wiley Periodicals, Inc. Head Neck 30: 267–272, 2008

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In this report, we describe the case of a 39-year-old woman with a right supraclavicular primary melanoma, which was demonstrated histopathologically to undergo spontaneous regression. The disappearance of melanoma cells from the tumor site was associated with an exuberant infiltration of histiocytes.

CASE REPORT

The patient was a 39-year-old woman who presented to the Department of Otolaryngology at the Washington University School of Medicine for evaluation of a right supraclavicular melanoma, which was diagnosed after shave biopsy by a
referring dermatologist. The biopsy of this lesion revealed a diagnosis of superficial spreading melanoma with a Breslow depth of 1.8 mm. Slides from the shave biopsy were subsequently reviewed in the Department of Pathology at Washington University School of Medicine; our analysis confirmed the diagnosis of malignant melanoma. The patient had no previous history of skin cancer or other malignancy, no significant past medical history, and no family history of skin cancer. She was presented to our clinic with a dark 3 cm × 1 cm × 0.5 cm lesion with serpiginous borders that was located in the right supraclavicular region 2 to 3 cm lateral to the medial head of the clavicle (Figure 1). No other lesions were observed on physical exam, and there was no palpable lymphadenopathy. Subsequently, routine metastatic work-up showed no evidence of disseminated disease.

The patient underwent wide local excision of the melanoma with sentinel lymph node biopsy. Lymphoscintigraphy was performed prior to surgery by injecting Tc-99m sulfur colloid at 6 sites around the melanoma in the right supraclavicular region. Serial anterior images of the neck were taken, and unifocal uptake in the low anterior left neck identified the sentinel lymph node. The patient then proceeded to surgery, where isosulfan blue was injected circumferentially at the site of the lesion before the melanoma was excised with 2-cm margins. Guided by the lymphoscintigram, a 3-cm transverse incision was made in the left neck and a level 2 lymph node was identified that exhibited elevated counts by the hand-held gamma counter and had taken up blue dye. No other tissue sites with elevated counts were identified. Both incisions were closed and the patient had an uneventful postoperative recovery.

RESULTS
A 6-mm shave biopsy of the lesion performed by the referring dermatologist 12 weeks prior to wide excision showed a malignant melanoma of superficial spreading type in vertical growth phase. The melanoma was composed of large sheets of spindled and epithelioid tumor cells extending from the epidermis down into the dermis (Figure 2A). These cells displayed open chromatin with prominent nucleoli and moderate atypia. There was moderate mitotic activity and there also were occasional, markedly pleomorphic tumor cells extending from the epidermis down into the dermis. (Figure 2A). These cells displayed open chromatin with prominent nucleoli and moderate atypia. There was moderate mitotic activity and there also were occasional, markedly pleomorphic tumor cells extending from the epidermis down into the dermis.
Although scattered melanophages were observed throughout the lesion, the tumor cells constituted the majority of the cellular population. The epidermis showed melanocytes scattered throughout all levels in a “buckshot” pattern. The lesion was present extensively at the margin and had a preliminary Breslow thickness of 1.8 mm.

The wide excision specimen performed 12 weeks after initial biopsy consisted of a skin ellipse measuring 4.4 × 3.3 × 1.1 cm, which had a central, nodular and irregular, pigmented, light brown lesion measuring 1.2 × 0.4 cm. On histologic examination, the lesion consisted almost entirely of melanophages, with fewer chronic inflammatory cells including lymphocytes and plasma cells. There was no melanocytic proliferation remaining in the epidermis. Scarce, small bland nests of spindled melanocytes in the superficial dermis were without mitotic activity or atypia (Figure 3A and 3B). Immunohistochemistry for CD68 highlighted an exuberant histiocytic reaction. (D) Immunohistochemistry for Melan-A with azure blue stained rare nests of residual melanocytes (arrow) considered nondiagnostic of melanoma. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
metastasis. Thus, the pathologic findings revealed complete regression of the melanoma with a florid host inflammatory response. The rare residual melanocytes were considered non-diagnostic of melanoma as they could represent residual nevus.

**DISCUSSION**

In this case report, we provide histopathologic evidence to demonstrate the complete spontaneous regression of a melanoma in the head and neck region. Moreover, immunohistochemical analysis shows that tumor regression was correlated with the emergence of a dense infiltrate composed chiefly of histiocytic cells. This report thus demonstrates a likely connection between complete tumor regression of a primary head and neck melanoma and the types of immune cells at the tumor site, which may have mediated such a clinical response.

From initial diagnosis, there was a 12-week period until definitive treatment due to patient compliance and insurance issues. However, during this time frame, the patient’s melanoma spontaneously regressed due likely to a successful host antitumor immune response. Notably, there were no intervening changes in the patient’s medical status during this time, including no change in her medications, no interval infections, and no cancer-directed therapy. In our department, surgery for cancers in the head and neck are usually completed within 3 to 4 weeks after diagnosis. Because of the 12-week lapse after this patient’s diagnosis to surgery, we made a potentially important observation: naturally-occurring tumor regression is perhaps a more common outcome than previously recognized in the natural history of a tumor, which has developed in an immunocompetent individual. Indeed, metastatic melanoma of unknown primary accounts for approximately 2.5% of all presenting melanomas, and 1 possibility underlying this clinical entity is that an undetected primary melanoma underwent near-complete regression prior to metastatic progression. Importantly, the identification of spontaneous regression must not preclude vigilant clinical observation for the development of metastatic disease, especially considering that the Breslow depth in a tumor exhibiting immune-associated regression may have been greater prior to the initiation of an antitumor host response.

Of the many possible mechanisms that have been proposed to explain melanoma regression, the florid immune infiltrate at the site of the tumor regression strongly suggests that the patient’s antitumor immune response effected tumor elimination. In fact, substantial data exist to support the notion that the immune system protects individuals from the development of cancer. This idea, which historically has been codified in the “cancer immunosurveillance” hypothesis (reviewed in refs. 6–8) is highlighted by several lines of evidence. First, while immunosuppressed patients develop a higher incidence of virally induced cancers, they also develop a higher incidence of tumors with no known viral etiology (reviewed in refs. 6, 7). Specifically, both immunocompromised adult and pediatric populations develop a 2- to 4-fold greater incidence of melanoma than age-matched control populations. Second, cancer cells express distinct antigens that are recognized by the immune systems of cancer patients. It has been well-described that humans generate spontaneous CD4+ and CD8+ T cell responses to a wide range of tumor antigens, including those such as gp-100 and Melan-A/MART-1 expressed on melanoma cells. Finally, many studies have shown that the presence of tumor-infiltrating lymphocytes (TILs) in a cancer patient’s tumor presages an improved clinical outcome. Specifically, some of the first studies that established a strong correlation between patient survival and the presence of TILs involved collectively nearly 900 patients with primary or metastatic melanoma. In addition to melanoma, the presence of TIL and improved prognosis has also been documented in ovarian, colorectal, renal cell, and esophageal cancers. Moreover, the presence of CD68+ macrophages—the predominant cell type in the infiltrate discussed in this report—has been found to correlate with increased survival in nonsmall cell lung and gastric cancers.

Upon review of the literature, the incidence of complete regression of melanoma in case series is variable but rare; a combination of 5 series showed a regression rate of 0.24% in 2464 melanoma patients. Other series have reported the incidence of complete melanoma regression to be between 2.4% and 8.7%. However, the incidence of histopathologic regression may be much higher than previously recognized, with some studies documenting evidence of partial regression in over 50% of cancers depending on their...
Histological regression of malignant melanoma has been stratified into 3 stages: early (ie, active), intermediate, and late. The progression from the early to late stages is accompanied by a decrease in both the inflammatory infiltrate as well as the amount of tumor present. It is unclear whether this classification can be applied to our case as histopathologic analysis of the specimen showed a near-total absence of tumor in the setting of a florid immune infiltrate, suggesting that a residual “active” component of the tumor regression was superimposed onto the “late” stage of complete regression.

It will be critical to conduct careful histopathologic analysis of each case of regressing melanoma because mechanisms underpinning spontaneous tumor regression may be distinct between individuals. For instance, in the case described herein, our observation that melanoma regression was correlated with a florid histiocytic infiltrate points to a potentially important role for the histiocytic lineage in tumor destruction. It is therefore possible that, as elements of the innate immune system, resident tissue macrophages could kill tumor cells and/or participate in the phagocytosis, processing, and presentation of tumor antigens to cells of adaptive immunity. In sum, it will be important to continue to report clinical spontaneous tumor regression because, as Houghton and others have commented, these “n = 1” events represent “experiments of nature,” which are imperative to accumulate and analyze. Thus, although naturally-occurring tumor regression is a rare event, its systematic careful documentation and analysis may facilitate an enhanced understanding of how this process may be recapitulated therapeutically to eradicate neoplastic disease.

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REFERENCES