Malignant Melanoma of Cervical and Parotid Lymph Nodes With an Unknown Primary Site

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Forty-six patients with malignant melanoma metastatic to cervical or parotid lymph nodes with an unknown primary site were treated at UCLA Medical Center from 1964 through 1991. Treatment consisted of parotidectomy and/or neck dissection with or without adjuvant therapy. The initial presentation was a cervical mass in 74% and a parotid mass in 26% of patients. Metastasis distal to the head and neck nodal basins developed in 22% of patients. Involvement of more than four cervical or parotid nodes resulted in a significant increase in distant metastasis (P<.01). Adjuvant therapy was found to have no significant effect on survival rates. However, age at the time of diagnosis influenced the survival rates. The significance of the improved survival of these patients as compared to those with a known primary melanoma is discussed.

INTRODUCTION

Malignant melanoma comprises 1% of all malignancies of the human body and 0.9% of deaths from cancer.8 An unknown primary melanoma involves the epidermis, involvement of rare locations such as the choroid of the eye and mucous membranes of the nasopharynx has been documented.9 It has been estimated that 20% of melanomas occur in the head and neck region.4 The factor deemed most responsible for a worsened prognosis of cutaneous melanoma is the appearance of regional lymph node metastasis. The treatment of unknown primary melanomas has a different natural progression and prognosis as compared to those with a known primary site. The purpose of this study is to present 46 patients with malignant melanoma of unknown primary origin metastasized to the cervical and parotid lymph nodes. The clinical and pathological data of this rare presentation of melanoma are analyzed.

MATERIALS AND METHODS

Forty-six patients were treated at UCLA Medical Center from 1964 through 1991 with melanomas metastatic to the parotid or cervical lymph nodes with evidence of primary cutaneous, mucosal, or ocular melanoma. No distant metastasis was identified. The evaluation of each patient included a thorough history and physical examination, accompanied by an intense dermatologic investigation of cutaneous lesions and biopsy of any suspicious area. Chest roentgenograms, skin films, or, in recent years, CT scans of the head and neck region were also obtained. The diagnosis of melanoma was established by lymph node biopsy or fine-needle aspiration. The tissue was examined and verified as melanoma by a pathologist.

Treatment consisted of surgery with or without adjuvant therapy. All patients were operated on with curative intent. Surgery included superficial parotidectomy, neck dissection, superficial parotidectomy along with neck dissection, and excision biopsy for patients undergoing neck dissections, the site and number of nodes containing melanoma were recorded. Adjuvant therapy included radiation therapy, chemotherapy, and immunotherapy. The chemotherapy agents used were dacarbazine, Carmustine, procarbazine, cyclophosphamide (Cytotoxan), bleomycin, and vincristine. A group of patients received bacille Calmette-Guérin (BCG) and/or interleukin-1 (IL-1) and/or tumor cell vaccine (TCV) singly or in combination with the aforementioned chemotherapy agents. Of those treated with radiation therapy, approximately 40 to 60 Gy was delivered to the cervical or parotid nodal beds. After treatment, reappearance of disease in the original or adjacent nodal basins was regarded as a relapse. Lesions that reappeared elsewhere were all regarded as distant metastasis. The survival values were calculated based on the life-table method and were determined from the time of diagnosis of the cervical or parotid nodal metastatic disease. The chi-squared test was used when appropriate for statistical analysis.

RESULTS

Fifteen percent (7/46) of the patients were females and 85% (39/46) males. The age range was 15 to 83 years with a median age at the time of diagnosis of 43 years. All patients presented with a mass in the parotid or cervical area. Seventy-four percent (34/46) initially presented with cervical nodal metastasis and 26% (12/46) with parotid nodal metastasis. Once a biopsy was performed, the median time to definitive treatment was 3 weeks.

Of the 46 patients, all were surgically treated. Five patients had a parotidectomy; 8 had a parotidectomy and neck dissection; 27 had a neck dissection alone; and 6 had an excisional biopsy. Of the patients treated with a neck dissection, 15 underwent a modified and 20 radical neck dissection (Table II).

Overall, 54% (24/46) of patients remain alive and well. The remaining 46% (21/46) died of progression of disease. Twenty-four percent of all patients had a recurrence in the parotid or cervical area. Of the patients treated with a modified radical neck dissection, 275/4 (15) experienced a recurrence compared to 26/4 (20) of patients treated with a radical neck dissection. This difference was not statistically significant. No significant difference in survival was noted when modified neck dissection was compared to radical neck dissection at 2, 5, and 10 years postoperatively. At 2 years, patients with a modified neck dissection had a 77% survival rate. At 5 years, their survival rates fell to 55% and 50%. The respective 2-, 5-, and 10-year survival for patients with a radical neck dissection were 71%, 62%, and 54%. Of those who died after treatment, the median survival of patients with a radical neck dissection was 22 months. Patients who underwent modified radical neck dissection had a median survival time of 20 months.

The location of the lymph node metastases did not significantly affect survival. The 5-year survival of patients presenting with a cervical metastasis was 58% (18/31), as compared to 50% (4/8) for those with a parotid metastasis (Table III).

Sixty-seven percent (31/46) of patients received...
postoperative adjuvant therapy. Of these, 90% received chemotherapy and/or immunotherapy. The remaining 10% received radiation therapy. There was no significant difference in the survival rate for patients treated with and without adjuvant therapy (Table IV). In fact, the survival rate of patients not receiving adjuvant therapy demonstrated a slight improvement over those receiving such treatment. The respective 5-year survival rates were 62% and 54%. This difference was not statistically significant.

Distant metastasis occurred in 22% (10/46) of the patients. In this group, the median time between completion of treatment and appearance of distant metastasis was 7 months. Of the patients who developed distant metastasis, 20% had modified neck dissection compared to 70% (3/10) who underwent a radical neck dissection. Statistical significance was not achieved. The median survival time for malignancy metastasis was 18 months. Eighty percent of these patients were dead within 2 years. Ninety percent were dead within 5 years. Patients with cervical or parotid nodes involved had a 5-year survival of 39% (3/9). Patients with fewer than 4 lymph nodes involved had a 5-year survival of 85% (16/29). However, less favorable 5-year survival rates (25%, 33%) were found in two other series.\(^\text{24,21}\)

The reasons for the possible survival advantage of stage II unknown primary melanoma as compared to melanoma with a known primary site remain obscure. Two theories on the etiology of unknown primary melanomas have been proposed. The less favored theory is that melanoma cells arise de novo within the lymph nodes or that there are ectopic melanocytes that undergo malignant degeneration.\(^\text{7,12}\) Fujimoto, et al. found a high frequency of cutaneous melanoma in non-cutaneous sites.\(^\text{12}\) Greene and Bernier have demonstrated the existence of melanoblasts in the parotid gland and reported 6 cases of primary melanoma of the parotid.\(^\text{20}\) Based on this theory, patients with unknown primary melanoma may have an improved survival because, in effect, the occult primary is removed during lymphadenectomy.\(^\text{7}\)

The more widely accepted theory is that, due to the host immune response, the primary melanoma lesion spontaneously regresses after not recognizing the regional lymph nodes.\(^\text{7,12,22}\) Melanoma accounts for 11% of all instances of spontaneous tumor regression.\(^\text{24}\) Girolamo, et al. presented 5 cases of spontaneous regression of melanoma.\(^\text{8}\) Bulkley, et al. theorized that immunology occurs in association with an immune response.\(^\text{9}\) Others have reported cases of melanoma that have demonstrated an augmented humeral and cellular immunity in patients with unknown primary melanoma.\(^\text{7,22}\) Kadl, et al. reported a patient who had spontaneous regression of malignant melanoma and who was found to have regressed in another patient.\(^\text{10}\) Specifically, a circulating factor was identified that potentiates lymphoid and cytotoxic activity in patients with a regressing melanoma.\(^\text{24}\)

Given this evidence, it is possible to suggest that a strong antitumor immune response can cause the containment of the primary tumor and the regional lymph nodes. This increased protection against subsequent spread may translate into prolonged survival times. Some investigators, however, have suggested that the level of antitumor immunity actually falls with the occurrence of metastases.\(^\text{5}\) Clearly, further studies need to be conducted to explain the possible survival advantage of patients with stage II melanoma of unknown primary origin as compared to those with a known primary site.

### CONCLUSION

Forty-six cases of metastatic melanoma of cervical or parotid lymph nodes with an unknown primary site were presented. These patients appear to have a better prognosis compared to the patients with a known primary site. Surgical intervention is the treatment of choice, including removal of all diseased neck and parotid lymph nodes without sacrificing function, and is not effective in prolonging survival in this study.