

Case Report

Fatal Mimicry: Oral Melanoma versus Mantle Cell Lymphoma

L. Margolin¹ and A. Monselise²

¹OSU Medical Center, USA

²Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

Correspondence should be addressed to L. Margolin, leon3087@gmail.com

Received 15 October 2009; Revised 18 January 2010; Accepted 9 February 2010

Copyright © 2010 L. Margolin and A. Monselise. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We present a 71-year-old male with oral melanoma and mantle cell hyperplasia who was erroneously diagnosed and treated as mantle cell lymphoma. The differential diagnosis of MCL versus mantle cell hyperplasia is a challenging task. Thorough immunohistochemical and cytogenetic analyses are warranted before treatment administration. The more common presentation of amelanotic malignant melanoma requires a high index of suspicion for masses identified in the mouth and requires biopsy for definitive diagnosis. A meticulous physical examination is advocated.

1. Introduction

Oral cancer is an important health issue. The World Health Organization predicts a continuing worldwide increase in the number of patients with oral cancer, extending this trend well into the next several decades. In the United States, the projected number of new cases of oral and oropharyngeal cancer will exceed 31,000 per year. Significant agents involved in the etiology of oral cancer in Western countries include exposure to sunlight, smoking, and alcohol consumption [1].

Melanoma is a very aggressive tumor derived from malignant transformation of melanic cells of the basal layer of cutaneous and mucosal epithelia. Primary melanoma of the oral cavity is the most malignant head and neck tumor. In the vast majority of cases, it is asymptomatic for many years and is usually detected as a pigmented mass that is sometimes painful. Once it becomes clinically evident, its tendency is to grow toward adjacent structures and to form metastasis in cervical lymphatic nodes. Therapeutic modalities such as radiotherapy, chemotherapy, or immunotherapy have not significantly improved overall survival rates [2]. Although the incidence of malignant cutaneous melanoma has doubled each decade since the early 1960s, the mucous counterpart is still rare, representing 1.4 percent of all melanomas in Caucasian patients. In the oral cavity, this incidence is even higher, ranging from 0.2 to 8.0 percent of all melanomas. However, it is unusual for the primary location to be on the tongue and only

25 such cases have been reported in the literature. The prognosis for mucosal melanomas is clearly worse than for cutaneous melanomas, with most investigators reporting a 5-year survival rate of 10 to 25 percent. It is not clear whether mucosal melanomas are biologically more aggressive than their cutaneous counterparts or if prognosis is simply related to the fact that they are normally more advanced at the time of diagnosis. In fact, it is clear that the etiologic and pathogenetic basis for the origin of mucosal melanomas, as well as of their treatment and prognosis, is not understood nearly as well as that of cutaneous melanomas. At least 25 percent of mucosal melanomas are clinically identical to innocent lesions [3]. Gorsky and Epstein [4] reviewed 30 years of data from a tumor registry and identified 65 patients who had head and neck melanomas. Two-thirds (43) of the 65 patients were male, with the mean age in the sixth decade. Of the 65 patients, only six had melanoma that originated from the oropharyngeal mucosa. Each lesion involving the oral mucosa, manifested itself as a mass or was associated with symptoms of discomfort; only one third (2) of the lesions were pigmented.

2. Case Report

A 71-year-old male in good general health was hospitalized for an evaluation of complaints that included fatigue, low-grade fever, anorexia, and weight loss. His past history was insignificant albeit smoking one pack of cigarettes per day for

the past 60 years. The physical examination was unremarkable except for a mild left axillary lymphadenopathy. Primary evaluation included a complete blood count, which revealed a normochromic-normocytic anemia. The chest X-Ray did not reveal any pathology.

This setting of a 71-year-old patient with anemia and B symptoms can indicate a lymphoproliferative disorder. A CT scan of the chest and abdomen showed enlarged lymph nodes in the left axilla. The pulmonary parenchyma and abdominal organs did not reveal any abnormality. No lymphadenopathy was detected in the retroperitoneum, pelvis, or groin. A few cysts were present in the kidneys and the abdominal aorta under the renal arteries was enlarged up to 3.5 centimeters in diameter.

The patient underwent an axillary lymph node biopsy. The biopsy showed hyperplastic mantle zone of a lymph follicle with a preserved capsule. These findings were diagnosed as Mantle Cell Lymphoma (MCL). The patient refused chemotherapy and was referred for follow-up to the Hematology Outpatient Clinic. After a year of visits to the Hematology Outpatient Clinic, the patient complained of severe pain in the left axilla and oral discomfort. Physical examination revealed that the axial lymph nodes were enlarged. A chest CT scan revealed enlarged lymph nodes in the left axilla and normal sized nodes in the mediastinum. No pathology was found in the abdomen or retroperitoneum. The patient was prescribed a regimen of prednisone and chlorambucil, which did not induce a remission of the disease. The axillary mass continued to enlarge and 17 radiotherapy treatments proved uneventful. During the following four consecutive months, chemotherapy with the CHOP (cyclophosphamide, doxorubicine, vincristine, prednisone) protocol did not ameliorate the patient's condition.

The deterioration on this aggressive therapy was interpreted as unusual for MCL. The question that arose was whether our diagnosis was correct. The histologic difference between MCL and Mantle Cell Hyperplasia is difficult to discern. The presence of wide follicular mantles in MCL is different from the thin mantles characteristic of reactive follicular hyperplasia. In mantle zone hyperplasia the follicles are usually localized predominantly in the cortex of the node, and the architectural effacement and diffuse areas of involvement characteristic of MCL are lacking.

In view of the failure of the treatment and the patient's complaint of oral discomfort, severe pain in the left axilla, and in the inferior aspect of the tongue, he was hospitalized. He recalled a low fever and hemophthysis that had manifested three days before his admission. On physical examination the patient was tachypneic (20 per minute), body temperature was 100.8 °F (38.2 °C), blood pressure was 140/80 mm Hg, and the pulse rate was 100 per minute. Oral inspection revealed candidal thrush and a tender mass about 4 centimeters in diameter was present on the left side of the tongue. Lymph nodes were slightly enlarged on both sides of the neck. In the left axilla, a tender mass, about 10 centimeters in diameter, adjoining the surrounding tissue was palpated. Near the left nipple was evidence of a nodular lesion, 0.5 centimeters in diameter, with a slight erythema on its border. In auscultation, there were bilateral rales over the

basilar lung fields. Abdominal inspection was normal, and organs were of normal size. Blood chemistry analysis including SMA was normal excluding a slightly elevated GGT. Immunohistochemical and translocation analysis revealed t(14:18) translocation.

The translocation analysis was inconsistent with the diagnosis of MCL. The candidal thrush was treated with nystatin gel. A sputum Ziel Nielsen stain was negative. A chest radiograph and chest CT scan revealed numerous round space-occupying lesions over both lung fields. An abdominal ultrasound traced hepatic lesions of diverse echogenicity and a biopsy of one of the hepatic lesions revealed a malignant process with poor differentiation. Biopsies from both tongue and axilla showed a poorly differentiated malignant process similar to that of the liver biopsy. The liver, oral, and skin biopsies were stained positively for vimentin, S-100 and HMB 45. The patient underwent a bronchoscopy with bronchoalveolar lavage and a transbronchial biopsy that was nondiagnostic.

The massive lung involvement as well as the liver biopsy result were inconsistent with the diagnosis of MCL that has a tendency to involve the gastrointestinal tract but not the lungs. The immunohistochemical and histologic picture was consistent with malignant melanoma. The lack of pigmentation of the oral lesion on physical examination, and the absence of melanin on histology are characteristics of amelanocytic malignant melanoma of the oral cavity, which was confirmed by biopsy of the lesion. The findings from the biopsy of the first lymph node which were interpreted as MCL were essentially Mantle Cell Hyperplasia, most probably secondary to micrometastasis of malignant melanoma.

During his last hospitalization, the patient's condition deteriorated rapidly and he died.

3. Discussion

Diagnosis of MCL may be difficult to make if there is an incomplete obliteration of the normal lymph node architecture, benign-appearing germinal centers are present, and the capsule is intact. In our patient, micrometastasis that originated from the lingual melanoma could induce a follicular hyperplastic reaction in the lymph-node, masquerading as MCL. Immunohistochemical stains may be helpful in distinguishing reactive follicular hyperplasia from MCL that is typical for its monoclonality and CD5, CD43, and cyclin D1 positivity. Translocation analysis may contribute to the diagnosis: the translocation 14:18 that was found in our patient is inconsistent with MCL; the translocation t(11:14)(q13;q32) [5, 6] is a characteristic of the majority of MCL cases.

Other translocations involving the 11q13 breakpoint also have been reported [7]. Secondary abnormalities that have been described in MCL include the loss of chromosome 13 and Y, deletions of chromosomes 6q, 11q22, 13q14, and various abnormalities of chromosome 6q15 [8, 9]. The t(14:18) translocation was shown to occur in nonmalignant tissue and on its own, it will not lead to malignancy [10].

Mantle cell lymphoma is an increasing challenge for oncologists. It is an aggressive type B cell lymphoma that accounts for up to 6 percent of non-Hodgkin's lymphomas. Complete or partial remission has been reported in the vast majority of cases using a combination of cyclophosphamide, doxorubicine, vincristine, and prednisone [11–13]. The deterioration under aggressive therapy that was observed in our case is inconsistent with the diagnosis of MCL. Cyclophosphamide, doxorubicine, vincristine, and prednisone were not shown to induce melanoma; furthermore this malignancy has a tendency to partial response to chemotherapy.

Adjuvant interferon- α (IFN- α) may improve disease-free and overall survival, particularly in patients with metastases of melanoma [14]. Schiller et al. [15] conducted a trial of IFN- α -2a plus CHOP chemotherapy in order to determine the maximum dose of IFN- α -2a that could be administered without compromising the dose intensity of CHOP. Of the 21 patients included in the trial, all five patients with non-Hodgkin's lymphomas, and one out of five patients with melanoma responded to the treatment. The latter patient, with metastatic melanoma, responded positively to a maintenance dose of IFN- α -2a for three years.

The differential diagnosis of MCL versus mantle cell hyperplasia is a challenging task. Thorough immunohistochemical and cytogenetic analyses are warranted before treatment administration.

In the initial axillary lymph-node biopsy, the diagnosis of MCL was concluded. Although no images are provided, it seems that the diagnosis was only made on the histopathological inspection of the biopsy. However, according to the 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (Edited by Swerdlow et al., IARC, Lyon, 2008), the presence of a t(11;14)(q13;q32) chromosomal translocation detected with conventional cytogenetics or by FISH and/or the detection of the overexpression of the protein cyclin D1 by immunohistochemistry is necessary for the correct diagnosis of this lymphoma subtype. Nevertheless, a small minority of cases (probably less than 1% of MCL cases) are considered cyclin D1 negative.

We advocate the use of FISH, RT-PCR and genetic tests to verify the diagnosis.

The more common presentation of amelanotic malignant melanoma requires a high index of suspicion for masses identified in the mouth and requires biopsy for definitive diagnosis. A meticulous physical examination is advocated.

References

- [1] J. J. Sciubba, "Oral cancer: the importance of early diagnosis and treatment," *American Journal of Clinical Dermatology*, vol. 2, no. 4, pp. 239–251, 2001.
- [2] J. L. Cebrián Carretero, M. Chamorro Pons, and N. Montesdeoco, "Melanoma of the oral cavity. Review of the literature," *Medicina Oral*, vol. 6, no. 5, pp. 371–375, 2001.
- [3] R. Bovo, A. Farruggio, M. Agnoletto, M. Galceran, and F. Polidoro, "Primitive malignant melanoma of the base of the tongue," *Acta Otorhinolaryngologica Italica*, vol. 16, no. 4, pp. 371–374, 1996.
- [4] M. Gorsky and J. B. Epstein, "Melanoma arising from the mucosal surfaces of the head and neck," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, vol. 86, no. 6, pp. 715–719, 1998.
- [5] D. D. Weisenburger, W. G. Sanger, J. O. Armitage, and D. T. Purtle, "Intermediate lymphocytic lymphoma: immunophenotypic and cytogenetic findings," *Blood*, vol. 69, no. 6, pp. 1617–1621, 1987.
- [6] D. Leroux, F. Le Marc'Hadour, R. Gressin, et al., "Non-Hodgkin's lymphomas with t(11;14)(q13;q32): a subset of mantle zone/intermediate lymphocytic lymphoma?" *British Journal of Haematology*, vol. 77, no. 3, pp. 346–353, 1991.
- [7] R. Rimokh, F. Berger, C. Bastard, et al., "Rearrangement of CCND1 (BCL1/PRAD1) 3' untranslated region in mantle-cell lymphomas and t(11q13)-associated leukemias," *Blood*, vol. 83, no. 12, pp. 3689–3696, 1994.
- [8] B. Johansson, F. Mertens, and F. Mitelman, "Cytogenetic evolution patterns in non-Hodgkin's lymphoma," *Blood*, vol. 86, no. 10, pp. 3905–3914, 1995.
- [9] O. Monni, R. Oinonen, E. Elonen, et al., "Gain of 3q and deletion of 11q22 are frequent aberrations in mantle cell lymphoma," *Genes Chromosomes and Cancer*, vol. 21, no. 4, pp. 298–307, 1998.
- [10] J. Limpens, D. de Jong, J. H. J. M. van Krieken, et al., "Bcl-2/JH rearrangements in benign lymphoid tissues with follicular hyperplasia," *Oncogene*, vol. 6, no. 12, pp. 2271–2276, 1991.
- [11] P. Meusers, M. Engelhard, H. Bartels, et al., "Multicentre randomized therapeutic trial for advanced centrocytic lymphoma: anthracycline does not improve the prognosis," *Hematological Oncology*, vol. 7, no. 5, pp. 365–380, 1989.
- [12] E. Zucca, E. Roggero, G. Pinotti, et al., "Patterns of survival in mantle cell lymphoma," *Annals of Oncology*, vol. 6, no. 3, pp. 257–262, 1995.
- [13] I. Teodorovic, S. Pittaluga, J. C. Kluin-Nelemans, et al., "Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes," *Journal of Clinical Oncology*, vol. 13, no. 11, pp. 2819–2826, 1995.
- [14] E. Braunwald, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, and J. L. Jameson, *Harrison's Principles of Internal Medicine*, McGraw-Hill, New York, NY, USA, 15th edition, 2001.
- [15] J. H. Schiller, M. J. Hawkins, M. J. O'Connell, K. Sielaff, and E. C. Borden, "A phase I trial of interferon- α -2a plus cyclophosphamide, vincristine, prednisone, and doxorubicin," *Journal of Biological Response Modifiers*, vol. 8, no. 3, pp. 252–261, 1989.