

Primary malignant melanoma of the oral cavity: a case report

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A 43-year-old white man was referred to the Special Care Dentistry Center of the School of Dentistry, University of São Paulo, Brazil, for the diagnosis of an extensive nodular lesion of the maxillary gingiva.

The patient complained that his left maxilla had swollen over the last 4 months, with some exudation from the gingival crevice, sporadic bleeding, and slight tooth mobility, but no pain.

An extra-oral examination confirmed expressive swelling of the left side of the face (Fig. 1A). Palpation disclosed bilateral enlargement of the submandibular lymph nodes.

An intra-oral examination showed an extensive, reddish, nodular mass (around 11 cm in diameter) that extended from the last left maxillary molar to the right maxillary incisor, covered by a mucosa that was ulcerated in some areas (Fig. 1B,C). Palpation revealed a painless, soft, bleeding tissue that seemed to arise in the periodontal ligaments, extending to the palate and vestibular area. A small pigmented spot was found in the palatal mass.

Histopathologically, the biopsy revealed a proliferation of neoplastic cells that exhibited a wide variety of shapes, including spindle, plasmacytoid, and epithelioid forms. The atypical cells showed enlarged and pleomorphic nuclei. Mitotic activity and pigmented areas were observed (Fig. 2A,B). Immunohistochemistry was used to establish the final diagnosis. The tumor cells strongly expressed S100 protein, gp100 (HMB-45), melan A, and tyrosine antibodies (Fig. 2C,D).

With the diagnosis of malignant melanoma, the patient was referred to an oncologist for treatment. As computed tomography revealed that the lesion was deeply inserted into the skull surface (Fig. 1D), surgical intervention was not possible. The patient underwent radiotherapy, but died 14 months later.

Discussion

Primary malignant melanoma of the head and neck is a rare tumor, accounting for less than 1% of all melanomas.¹ Half of such melanomas occur in the oral cavity, followed by the nasal cavity (44%) and sinuses (8%). The age distribution varies from 40 to 70 years (average age, 55 years),² and men are more affected than women, unlike cutaneous melanoma. There is evidence that the incidence is higher in Japanese^{3–5} and black people.^{5,6} In the oral cavity, the most frequent sites of occurrence are the hard palate and the maxillary gingiva.⁴

Clinical presentation can vary widely. Oral melanoma can be dark brown, bluish black, or black. Only 5% of cases occur as a nonpigmented lesion.⁶

Oral malignant melanoma still represents a diagnostic challenge. Owing to its variable clinical and histologic characteristics, both clinicians and pathologists may misdiagnose the affliction and consequently treat patients incorrectly.^{7,8} When an intraepithelial melanocytic component is lacking in a biopsy, mucosal melanoma can be difficult to recognize.

Most lesions appear as asymmetric pigmented maculae of irregular outline, which grow in a horizontal manner for some years prior to a phase of vertical growth and submucosal invasion.^{2,4} Thus, it has been suggested that the appearance of melanin pigmentation in the mouth and an increase in lesion size or depth of color should be viewed with concern. Variations include changes in morphologic characteristics, including flat, swollen, or elevated, with or without ulceration.⁶ Most patients report a short history with rapid enlargement of an asymptomatic lesion, as in the present case. Others report a slowly developing mass in a pigmented area that has been present for months or years.^{1,2,4} In the case presented here, a small pigmented area was present on the palatal face of the tumor (Fig. 1C). Despite the occurrence of a discrete pigmented area, our first diagnosis was pyogenic granuloma; however, the expressive size and peculiar odor of the lesion led us to consider a diagnosis of malignant neoplasm. When oral melanoma is strongly pigmented, the clinical possibilities include tattoo, oral melanotic maculae, physiological pigmentation (racial and postinflammatory), and nevus melanoacanthoma.



Figure 1 Clinical and radiographic characteristics of the oral malignant melanoma. (A) Swelling of the left side of the face. (B) Extensive nodular mass on the maxillary gingiva. (C) Palatal view of the tumor with a focal pigmented area. (D) Computed tomography scan showing extensive involvement of the anterior maxilla and pterygoid muscle

Often, nonpigmented forms of oral melanoma cannot be distinguished clinically from other benign or malignant oral tumors. The differential diagnosis includes giant cell granuloma, pyogenic granuloma, ill-fitting denture irritation, carcinoma, fibrosarcoma, and lymphoma.⁹⁻¹³

Recognition of the lesion is possible when the overlying epithelium breaks down, with the presence of hemorrhage or identification of a growing mass. The most common late symptoms are ulceration, swelling, loosening of the teeth, and ill-fitting dentures.^{2,6,14} This delayed detection partially accounts for the poor prognosis of oral melanoma.²

Histopathologic diagnosis rests on the demonstration of melanin, which is seen in 50–70% of cases. Immunohistochemistry has further improved the positive histologic diagnosis rate of melanoma. Markers help to distinguish lesions from other similar conditions, such as poorly differentiated carcinoma, small cell carcinoma, lymphoma, sarcoma, and, when the tumor cells are bland, fibrosarcoma.^{2,15} S-100 protein is the most sensitive melanocyte marker, followed by HMB-45, tyrosinase, and melan A.

Radical surgery is the preferred treatment for oral malignant melanoma, in association with radiotherapy or alone. Primary irradiation is also considered to be an alternative to major surgery for inoperable tumors or in elderly patients.¹⁶

Significant prognostic factors for poor disease-specific survival include advanced clinical stage at presentation, a tumor thickness of greater than 5 mm, the presence of vascular invasion, and the development of nodal and distant metastases.¹⁶ All of these factors were present in the case reported here and were associated with the poor outcome.

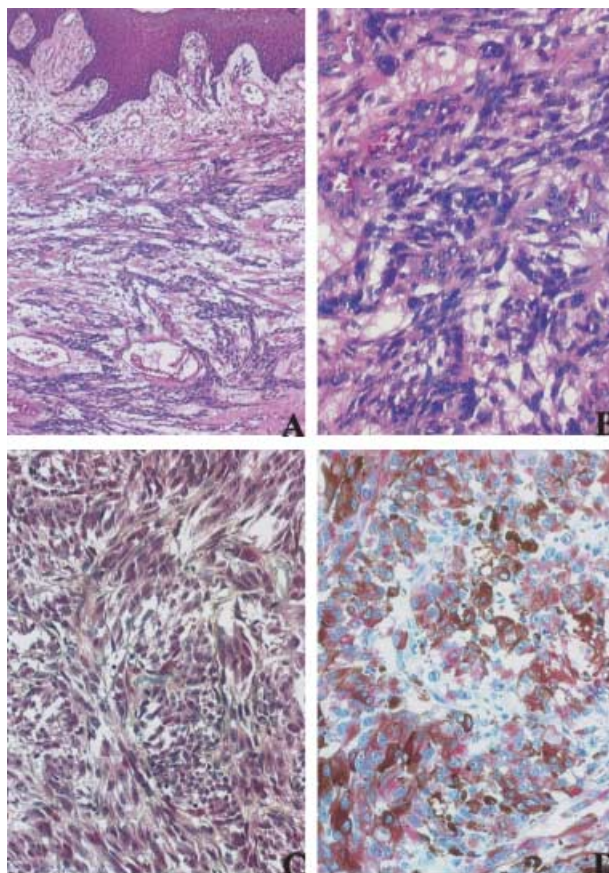


Figure 2 Microscopic biopsy findings of the oral malignant melanoma. (A) Low-power photomicrograph of the mucosa reveals the proliferation of abnormal melanocytes in the connective tissue (hematoxylin and eosin, ×20). (B) Cells of fairly uniform size and shape, arranged in an alveolar pattern (hematoxylin and eosin, ×40). (C) S-100 protein is expressed by all tumor cells (×40). (D) Melan A protein is expressed more frequently in the pigmented areas (×40)

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Cameo

Itching stretch marks and bullous lesions in a pregnant woman

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Introduction

Stretch marks are a common sign of pregnancy. They develop as asymptomatic erythematous striae. In cases with itch, this may be the first sign of pruritic urticarial papules and plaques of pregnancy (PUPP) that tend to start with erythematous, papular, urticarial or target-like cutaneous lesions along the striae gravidarum in almost 50% of patients.^{1,2} PUPP is not associated

with a higher fetal or maternal risk.³ Sometimes, however, PUPP-like presentation can be caused by another pregnancy-associated dermatosis as shown in the present case report.

Case Report

A 32-year-old woman was pregnant for the second time. She had given birth to a healthy child before. She now presented



Figure 1 Erythematous stretch marks with urticarial papules. (a) Overview; (b) detail

during the last week of pregnancy with itching skin lesions. She suffered from a gestational diabetes during the last trimester but was otherwise healthy.

Clinical examination revealed periumbilical erythematous stretch marks with an urticarial and papular appearance (Fig. 1). The clinical diagnosis of PUPP was made and indifferent topical treatment was suggested. However, 3 days after delivering a healthy mature child she noted bullous lesions on the lower legs and itching lesions on the trunk and arms. On examination, we found tense bullae, up to 1.3 cm in diameter, in the pretibial area of both lower legs (Fig. 2) and erythematous-squamous eczematous lesions on the upper arms and on her flanks. We took a biopsy from a bullous lesion and neighboring skin. In hematoxylin-eosin stained routine sections, sub- and intraepidermal blisters were observed along with a predominant lymphocytic dermal infiltrate mixed with eosinophils. Direct immunofluorescence demonstrated linear basement membrane deposits of IgG and C3.

In laboratory examinations, the blood sedimentation rate was measured as 200 mm/h. Direct immunofluorescence for pemphigus and pemphigoid antibodies was negative.

The diagnosis of herpes gestationis with PUPP-like initial presentation was confirmed. Systemic treatment



Figure 2 Tense bullae and eczematous reactions on the lower leg

with prednisolone 100 mg/day intravenously for 2 days was initiated and blister formation stopped. The steroid dosage was tapered rapidly.

Discussion

Stretch marks are a common sign of pregnancy. They develop as asymptomatic erythematous striae. PUPP dermatosis was originally described by Lawley *et al.* in 1979.² It is quite common to find that the lesions start within abdominal stretch marks but later may also appear on other parts of the body.²⁻⁴ Since stretch marks are usually flat and nonpruritic, the development of erythematous, itchy lesions seems to be an early sign for PUPP. The disease is self-limited and does not require intensified specific treatment. A mild topical therapy is sufficient. There is no risk to mother or child from PUPP.^{3,4}

In the present case, a bullous eruption developed within 3 days after delivery after initial PUPP-like clinical appearance. Tense bullae suggested the diagnosis of herpes (pemphigoid) gestationis, which was confirmed by histology and direct immunofluorescence. Herpes gestationis may occur from very early pregnancy until a week after delivery.⁵ There are autoimmune features of herpes gestationis characterized by basement membrane deposits and circulating autoantibodies, which can be detected in about 30% of patients by indirect immunofluorescence but in up to 100% by immunoblotting.⁶ In our patient, indirect immunofluorescence was negative. Molecular mapping of herpes gestationis autoantibodies demonstrated selective immunoreactivity with sec180e, a 120-kDa recombinant protein encompassing the entire BP180 extracellular domain. The herpes gestationis-associated epitopes on BP180 are restricted to the NC16A domain.⁷

Herpes gestationis carries a risk of small-for-date babies.⁸ There is diaplacental transmission in some pregnancies lead-

ing to neonatal herpes gestationis in the child.⁹ Treatment is a matter of debate. Some authors have seen good clinical responses with class IV topical corticosteroids;¹⁰ others have found that systemic corticosteroids or even more aggressive systemic treatment is necessary.^{11,12}

We observed rapid relief of pruritus and bulla formation with intravenous prednisolone for 2 days followed by oral steroid, rapidly tapered. We would like to highlight the observation of itching erythematous stretch marks as a possible early sign of the development of herpes gestationis, and recommend close collaboration between gynecologists and dermatologists and early skin biopsy to prevent cutaneous signs for fetal risk being overlooked.

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Cameo

Insect bite-like reaction associated with mantle cell lymphoma: a report of two cases and review of the literature

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Abstract

Background An insect bite-like reaction and exaggerated reactions to insect bites are nonspecific phenomena described primarily in association with chronic lymphocytic leukemia (CLL), but also with other hematological malignancies. Two cases of mantle cell lymphoma (MCL), one associated with an insect bite-like reaction and the other with a true hypersensitivity to mosquito bites, have previously been reported in the English language literature. The pathogenesis of the skin eruption may be related to the release of different cytokines that also trigger an IgE elevation and dermal eosinophils.

Case report We describe two additional cases of MCL associated with an insect bite-like reaction. One patient had been diagnosed with MCL 4.5 years prior to the appearance of the skin eruption, and in the other patient the skin symptoms preceded the diagnosis of the MCL by 2 years and led to its diagnosis.

Conclusions Insect bite-like reaction may appear in patients with MCL. It is important to recognize this entity because it may be the presenting sign of MCL.

Introduction

An exaggerated reaction to an insect bite is a nonspecific phenomenon described primarily in association with chronic lymphocytic leukemia (CLL).¹⁻⁵ However, this phenomenon is also included amongst various rashes associated with hematoproliferative disorders⁶ and diseases that result in altered immune reactivity, such as human immunodeficiency virus (HIV)-1 infection,⁷⁻⁹ congenital agammaglobinemia,¹⁰ and natural killer lymphocytosis.¹¹ The term "insect bite-like reaction" was coined by Barzilai *et al.* in 1999.⁶ After reviewing the English language literature, they realized that most patients with this phenomenon had no recollection of an arthropod bite preceding the lesions. Moreover, in their study, though they did observe the clinical presentation and histologic characteristics of the lesions suggestive of insect bites, neither the clinical histories nor the responses to preventive treatments were suggestive of an arthropod assault.

Mantle cell lymphoma (MCL) is a poorly differentiated B-cell lymphoma comprising 3–10% of non-Hodgkin lymphomas (NHL). It is typically associated with t(11; 14)(q13;q32), a median age of onset of 60 years and marked male predominance. The most common sites of involvement are the lymph nodes and often include the spleen and bone marrow. The most commonly involved extranodal sites are the gastrointestinal tract and Waldeyer's ring. The majority of patients present with stage III or IV disease and in at least 25% of cases peripheral blood is involved.^{12,13} Two cases of MCL have been described in association with an insect bite-like reaction or hypersensitivity to mosquito bites.^{6,14} We report two additional cases of MCL associated with an insect bite-like reaction. In one case the skin eruption was the presenting sign of the hematological malignancy and led to its diagnosis. This case emphasizes the importance of recognizing this entity and performing an oriented evaluation.

Case 1

A 61-year-old man was referred to our department for the evaluation of a generalized pruritic skin eruption of 6 months' duration. He had been diagnosed with stage IV MCL 5 years previously and received various chemotherapy treatments, including CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), DVIP (dexamethasone, VP-16, ifosfamide and cisplatin) and FC (fludurabine and cyclophosphamide). Consequently, partial remission was achieved. Numerous erythematous papules and nodules were present predominantly on the upper and lower limbs (Fig. 1). Some of them were covered by small vesicles and superficial erosions. In addition, a few erythematous plaques were also observed. Neither lymphadenopathy nor hepatosplenomegaly was detected on physical examination. Blood tests demonstrated elevated lactate dehydrogenase (LDH) at 288 U/L (normal < 225 U/L) and elevated serum Ig at 410 IU/mL (normal



Figure 1 An erythematous nodule on the thumb (case 1)

< 100 IU/mL). Other serum immunoglobulins (IgG, IgA, and IgM) were in normal range as were complete blood count (CBC), with an absolute eosinophil count of 310 cells/ μ L, erythrocyte sedimentation rate (ESR), liver enzymes and kidney function tests. A skin biopsy of a lesion demonstrated, in the epidermis, spongiosis and spongiotic microvesicles containing numerous eosinophils. The upper dermis was edematous and a diffuse dense infiltrate consisting predominantly of eosinophils, but also containing neutrophils and nuclear dust, was present throughout the dermis. There were also mononuclear cells without atypical features which could suggest cutaneous involvement with MCL. Direct immunofluorescence was negative for IgG, IgA, IgM and C3. In situ staining of skin lesions to Epstein-Barr encoded RNA (EBV-EB) was negative.

The patient denied having an arthropod bite preceding any of the lesions and preventive measures were also ineffective in preventing new lesions from appearing. There was no personal or family history of atopy.

These results support the diagnosis of insect bite-like reaction. Treatment with topical corticosteroids and antipruritics

did not lead to improvement. However, treatment with prednisone 40 mg/day proved beneficial. In a follow-up evaluation of the patient, the skin condition improved. Although new lesions had continued to appear, they were smaller and no vesicles emerged. The disease later relapsed and the patient was treated with Rituximab (F. Hoffman-La Roche, Basel, Switzerland) anti-CD-20 monoclonal antibodies and a partial response was achieved. Subsequently, the patient died due to an acute coronary event a few months later.

Case 2

A 64-year-old man was referred to the Department of Dermatology for the evaluation of a pruritic skin eruption of 2 years' duration. The eruption appeared in interchanging sequences with no connection to the seasons of the year and was accompanied by lymphadenopathy of the axilla and groin. A previously performed biopsy of a skin lesion demonstrated a dense dermal infiltrate of predominantly eosinophils which was interpreted as compatible with a reaction to an insect bite. A computed tomography (CT) scan of the thorax, abdomen and pelvis demonstrated marked lymphadenopathy in both axillas and in the left pelvis. The patient denied having night sweats, high fever or weight loss and could not recall having been bitten by an arthropod. There was no personal or family history of atopy.

Physical examination revealed a generalized bilateral skin eruption located predominantly on the extremities but also on the trunk and consisting of red papules, nodules and plaques with well-defined borders. Lymphadenopathy was palpated bilaterally in the axilla (2×2 cm) and in the left groin (3×3 cm) with no hepatosplenomegaly. Blood tests demonstrated elevated ESR at 72 mm/h (normal < 20 mm/h), elevated serum protein at 9.1 g/dL (normal < 8 g/dL) and elevated serum immunoglobulins: 88,100 IU/L IgE (normal < 100 IU/mL), 476 mg/dL IgA (normal < 350 mg/dL) and 2660 mg/dL IgG (normal < 1560 mg/dL). LDH and CBC were in the normal range. The absolute eosinophil count was 265 cells/ μ L.

A repeated skin lesion biopsy demonstrated within the dermis a dense, diffuse infiltrate composed predominantly of eosinophils but also with numerous neutrophils. The epidermis was uninvolved (Fig. 2).

Lymph node and bone marrow biopsies revealed MCL. The patient was referred to the Hematology Department for further evaluation and chemotherapy. He began a regimen of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and Rituximab (anti-CD-20 monoclonal antibodies), during which the skin lesions improved.

Discussion

An exaggerated reaction to an insect bite is a phenomenon described most often in association with CLL¹⁻⁵ but also with

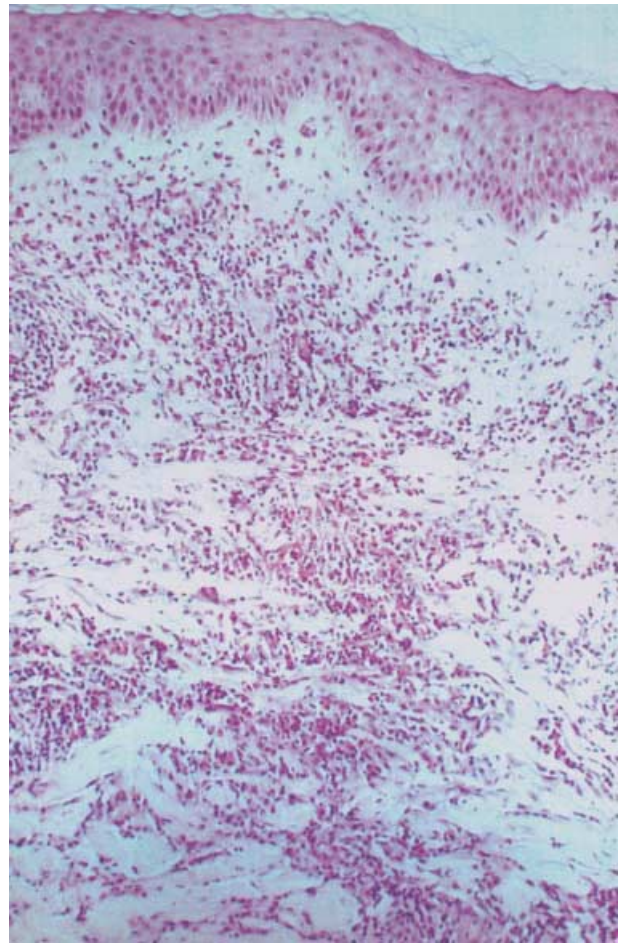


Figure 2 A photomicrograph of a lesion (case 2). In the upper dermis there is a dense diffuse infiltrate composed of predominantly eosinophils but also many neutrophils (hematoxylin-eosin)

other hematological malignancies⁶ and diseases with altered immune reactivity.⁷⁻¹¹ A debate has ensued as to whether this phenomenon represents a hypersensitivity reaction to an actual arthropod bite or an insect bite-like reaction in the absence of an arthropod bite.

Barzilai *et al.*⁶ argued that this reaction occurred with no connection to an arthropod assault. They studied eight patients with various hematological malignancies. Each had clinical appearances of itchy papular or vesiculobullous eruptions that were suggestive of insect bites. Although the clinical picture and the histologic findings were compatible with a reaction to an insect bite, neither the history nor the distribution, course, or efficacy of preventive measures and treatments supported an exaggerated reaction to a true insect bite. Therefore, they proposed new terms to describe this phenomenon: "insect bite-like reaction" or "eosinophilic eruption of hematoproliferative disease". Davis *et al.*⁵ reported eight cases

Table 1 Summary of reported cases of mantle cell lymphoma (MCL) associated with insect bite-like reaction and hypersensitivity to mosquito bites

Report	Case no.	Sex/age (years)	Clinical features	Known bites	Temporal relationship of onset of skin lesions to MCL diagnosis	Serum IgE (IU/mL) (normal < 100 U/mL)
Barzilai <i>et al.</i> ⁶ (1999)	1	M/42	Red, itchy papules and plaques	No	Preceded by 2 years	No data
Mori <i>et al.</i> ¹⁴ (2000)	2	M/61	Bullae followed by ulcers and scars	Yes	Preceded by 3 years	139,400
Present report Case 1	3	M/61	Red, itchy papules, plaques and nodules, some with vesicles	No	Followed by 4.5 years	410
Case 2	4	M/64	Red, itchy papules, plaques and nodules	No	Preceded by 2 years	88,100

of exaggerated arthropod bite lesions in patients with CLL for which the clinical and histologic features suggested arthropod bites. However, most of these patients could not recall having been bitten. Rosen *et al.*² described 10 patients with CLL and vesiculobullous eruptions. The histopathology of the lesions was consistent with the criteria for an insect bite. However, none of the patients had a history of insect bites and no insect parts were found histologically in any of the lesions. Despite the findings described, one cannot ignore the reports in the literature of patients with hematological malignancies developing hypersensitivity to insect bites.^{1,3,4,14} Regarding the two new cases introduced in this report, the term “insect bite-like reaction” is appropriate as there was no history of arthropod bites and preventive actions were not helpful in preventing recurring lesions.

MCL is a distinctive disease entity within NHL and is considered to have an aggressive clinical course with a reported median survival of only 3 to 5 years.^{12,13}

Two patients with insect bite-like reaction and MCL are described in this article. To the best of our knowledge, only two other cases of MCL associated with insect bite-like reaction or hypersensitivity to mosquito bites have been reported in the English language literature.^{6,14} (Table 1) In the four cases described, all the patients were males, three in their early sixties and the fourth 42 years old. The clinical features were quite similar in three cases (cases 1, 3, and 4; Table 1), characterized mainly by red, itchy papules and plaques. The fourth case presented differently, with predominantly bullae formations followed by ulcers and scars (case 2; Table 1). No known insect bites were reported in three of the four cases, and the authors described the skin lesions as insect bite-like reactions (cases 1, 3, and 4; Table 1). In the fourth case, hypersensitivity to mosquito bites was characterized by a severe skin reaction at bite sites accompanied by general symptoms including fever and lymphadenopathy (case 2;

Table 1). In three of the four cases, the skin eruption preceded the diagnosis of MCL by at least 2 years (cases 1, 2, and 4; Table 1). In the remaining case (case 3; Table 1), the skin lesions appeared 4.5 years after the diagnosis of the MCL was made.

In three of the four cases, serum IgE levels were significantly elevated, despite no history of atopy (cases 2, 3, and 4; Table 1). In the fourth case (case 1; Table 1), serum immunoglobulins levels were not reported. An elevated serum IgE level is not part of the classical laboratory manifestations of MCL. However, in a cohort of 42 patients with MCL, irregular amounts of serum immunoglobulins, both hypogammaglobulinemia and monoclonal gammopathy, were described.¹⁵ No abnormalities of serum IgE levels were mentioned in that study. In one case of MCL associated with chronic dermatitis, exceptionally high levels of serum IgE were observed (174,780 IU/mL).¹⁶ The pathogenesis of the different skin lesions might be related to the release of different cytokines that also trigger an IgE elevation and dermal eosinophils.

The pathogenesis of an insect bite-like reaction associated with hematological malignancies is still poorly understood. One suggestion is that the cytokine imbalance, with an excess of interleukin (IL)-4 and IL-5, leads to a proliferation of malignant B cells and to a modified immune response characterized by eosinophilic infiltration.⁶ Another suggestion is that the neoplastic B cells may be responsible for the skin hypersensitivity reaction.⁶

Several treatment modalities have been attempted in the various reported cases. Barzilai *et al.*⁶ reported treatment failure with topical antipruritics and corticosteroids, systemic antihistamines, UV-B phototherapy, isolated chemotherapy, and interferon therapy. The only treatment effective in suppressing the rash was prednisone in a dosage of at least 40 mg/day. However, lesions recurred as corticosteroids were

tapered. One patient responded to Dead Sea phototherapy, and for a 47-year-old woman whose acute lymphoblastic leukemia was cured, the eruption resolved spontaneously.⁶

Davis *et al.*⁵ reported improvement in the cutaneous lesions using oral glucocorticoids. Variable improvements were observed in CLL patients who were treated with chemotherapy, and one patient's lesions began to clear after treatment with intravenous immunoglobulins. In our experience, oral corticosteroids and avlosulfon may be effective in the treatment of CLL associated with an insect bite-like reaction (unpublished data). In the report by Mori *et al.*¹⁴ hypersensitivity to mosquito bites persisted even following chemotherapy treatments that achieved partial remission of MCL. One of our two patients (case 3; Table 1) had a partial response to treatment with prednisone 40 mg/day. No response was detected when they were treated with topical corticosteroids and antipruritics alone. Also, after starting chemotherapy treatment, the skin lesions improved. In the different studies of insect bite-like reaction and exaggerated reactions to insect bites, no correlations were found amongst the occurrences of the skin lesions, the disease course and the treatment modalities.^{1-6,14} Moreover, the skin eruption preceded or followed the malignant hematological disease by several years. Therefore, clinicians should be aware of this entity, which may present another cutaneous marker of hematological malignancy, including MCL.

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