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Oral mycosis fungoides: report with immune profile

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Mycosis fungoides (MF) is a cutaneous T-cell lymphoma that uncommonly involves the oral mucosa. Oral MF is an indication of systemic progression and is often associated with an unfavorable outcome. Any oral mucosal site may be affected. This report describes a case of MF involving the hard palate of a 64-year-old woman with confirmed skin MF. The histology showed intra- and subepithelial atypical lymphocytes. Immunohistochemistry on the tissue sections showed that the CD4:CD8 ratio was high (5.8:1) and the CD8:CD3 ratio was low (0.16:1). FoxP3$^+$ (forkhead box P3−positive) regulatory T cells were conspicuous within the infiltrate, but few interleukin-17 cells were observed. This report is the first to describe a detailed immune profile in oral MF. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;■:e1-e5)

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and has been defined as a neoplastic proliferation of epidermotropic, mature CD4$^+$ helper T lymphocytes (T_H cells) that has an indolent clinical course.[1] The skin lesions are polymorphous and usually begin as scaly or erythematous patches that are followed, often many years later, by well-defined irregular infiltrative plaques, which may progress to form nodules or papules that ulcerate.[2,3] At this stage the prognosis for the patient is poor. Concomitant peripheral blood involvement defines the patients as having Sézary syndrome, which is an aggressive type of CTCL.[4]

The putative cell of origin of MF is the memory CD4$^+$CD45RO$^+$ skin-homing T lymphocyte.[5] These cells will be present in the surface epithelium, where they may form focal collections, known as Pautrier microabscesses. The subepidermal infiltrate comprises both malignant CD4$^+$ and reactive CD8$^+$ T lymphocytes with a dominant T_H1 cytokine pattern early in the disease. Higher numbers of CD8$^+$ T cells are associated with improved survival.[6] As the disease progresses, the CD4:CD8 ratio increases, with a shift to a T_H2 cytokine profile.[4]

The first report of oral involvement in MF was made in 1914,[2] and since then fewer than 40 cases have been reported in the literature.[2,7] However, on autopsy 7% to 18% of patients with MF have been found to have oral involvement.[2,8,9] Oral MF is associated with systemic progression of the malignancy and thus carries a poor prognosis.[10] This report describes MF of the palate in a 64-year-old woman with confirmed skin MF and provides a discussion of the histologic and immunohistochemical findings in the context of the published literature.

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CASE REPORT

A 64-year-old woman was referred to the Oral Surgery Clinic, Faculty of Dentistry, University of Otago by her general dental practitioner and dermatologist regarding a firm lump of 3 months' duration on the hard palate. She had a history of long-standing cutaneous MF, first diagnosed 20 years previously, which had been managed with full-body radiotherapy, PUVA (psoralen combined with ultraviolet A) photochemotherapy and topical corticosteroids. She also had been treated for multinodular goiter with radioactive iodine and was taking methotrexate and an angiotensin-converting enzyme inhibitor.

The patient claimed no history of pain, altered sensation, purulent discharge or hemorrhage from the area. On examination she had no palpable cervical or submandibular lymphadenopathy. A diffuse, raised lesion with a broad base (25 mm × 10 mm) was observed on the posterior right hard palate adjacent to a mobile first molar tooth (Figure 1). The surface of the lesion showed several focal erosions with superficial ulceration. It was firm on palpation. The rest of the oral mucosa appeared to be normal. An incisional biopsy was performed under local analgesia.

Histologically, the sections showed an ulcerated, slightly elevated lesion partially covered by an atrophic stratified squamous epithelium. Much of the submucosa was replaced by sheets of large atypical mononuclear cells (Figure 2, *A, B*). These cells had pleomorphic nuclei, some of which were vesiculated and some of which showed evidence of nuclear infolding and indentations. Scattered atypical cells were also found within the epithelium without marked Pautrier abscess formation. The neoplastic cells extended to involve all margins and at one end were abutting lobules of mixed minor salivary glands. The histologic appearance was consistent with MF.

Further sections were stained with antibodies against CD3, CD4, CD8, CD56, CD68, IL-17 (interleukin-17), and

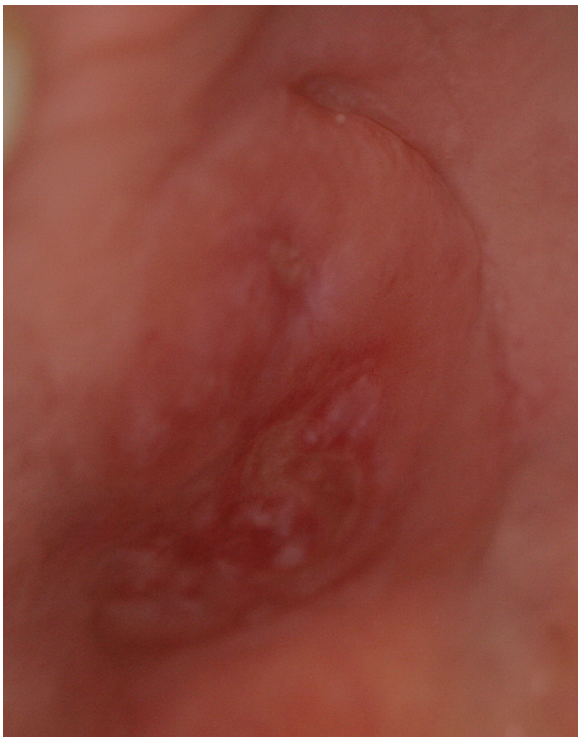

Fig. 1. Clinical photograph showing the raised firm lesion on the posterior right hard palate at the time of presentation. The surface showed several focal erosions with ulceration.

Table I. Number of positively staining cells expressed as a percentage of total cells counted

Antibody	*Primary target*	*% Positive*
CD3	Pan−T cells	49.9%
CD4	T_H cells	45.5%
CD8	T_C cells	7.8%
CD56	NK cells	3.4%
CD68	Macrophages	9.4%
FoxP3	Tregs	7.9%
IL-17	IL-17-producing cells	0.8%

IL, interleukin; *NK*, natural killer; T_C, cytotoxic T cells; T_H, helper T cells.

FoxP3 (forkhead box P3) (Table I) using routine immunohistochemical techniques. Assessment was made of lesional cells in the region of the epithelial−connective tissue interface both qualitatively and quantitatively. For the quantitation, a grid was superimposed onto photomicrographs, and all cells (negative and positive) in each grid square were counted to give a cumulative score of total cells and total positive cells. Three representative regions across the slide were counted. The results were expressed as the percentage of positive cells within the total cell population in the areas defined by the grid. Lesional cells showed a positive immunoreaction with anti-CD3, anti-CD4, and anti-CD8 antibodies with a CD4:CD8 ratio in the connective tissue immediately adjacent to the epithelial−connective tissue interface of 5.8:1 (Figure 3, *A, B*). The CD8:CD3 ratio was 0.16:1 (Figure 3, *B, C*). $CD56^+$ (see Figure 3, *D*) and $CD68^+$ cells (see Figure 3, *E*) were scattered throughout the lesion and accounted for 3.4% and 9.4%, respectively, of cells at the epithelial−connective tissue interface. There was very little expression of IL-17 associated with the lesional cells (see Figure 3, *F*), whereas FoxP3, which regulates the development and function of regulatory T cells (Tregs), was expressed in cells diffusely scattered throughout the bulk of the lesion (see Figure 3, *G*).

The patient was referred to the Oncology Department of Dunedin Hospital. The management plan involved a 36-Gy dose of radiotherapy delivered to the palate in 15 fractions. Two and a half years later, she remains well.

DISCUSSION

MF occurs most commonly in the fourth or fifth decade of life[3] and disproportionately affects black men.[11,12] However, persons of any age, gender or race can be affected.[12] Oral involvement in MF occurs over a large age range, with an average age of 61 years at diagnosis and without any gender predilection.[2] The most commonly involved intraoral sites are the tongue, palate, gingiva, buccal mucosa, lips, and oropharynx, in descending order, and more than one site may be affected.[2,10,13-15] Oral lesions generally appear some years (average, 8 years) after cutaneous involvement.[2] Oral cavity involvement is associated with poor prognosis, with a 50% mortality rate within 1 year of oral presentation. Almost all patients with such involvement die within 3 years.[2] Despite its association with advanced disease, most patients with oral MF do not have lymphadenopathy or visceral involvement.[2,10,16] Other extracutaneous sites affected include the lymph nodes, spleen, lungs, liver, kidneys, bones and heart.

Diagnosis of MF is based on a thorough history and clinical examination supported by lesional biopsy with histologic and immunohistochemical analysis. The histopathologic features of MF depend on the stage of the disease at the time of biopsy, and in the early phases the microscopic findings may be nonspecific and simulate numerous inflammatory conditions. Histologically the oral lesions appear similar to their cutaneous counterparts, although they tend to present with a deeper infiltrate and more atypical lymphocytes, signifying an advanced stage of the disease, as was seen in the current case.[2] With well-established lesions, small well-differentiated lymphocytes with round or cerebriform nuclei are observed within the epidermis, which often shows evidence of basal cell damage and acanthosis. The intraepithelial $CD4^+$ cells are often in close association with Langerhans cells,[17] and a dense band-like infiltrate of atypical lymphocytes is seen in the underlying connective tissue. The CD4:CD8 ratio in the subepithelial connective infiltrate and within the