Large Cell Transformation of Oral Mycosis Fungoides

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Received: 11 July 2017 / Accepted: 20 July 2017 / Published online: 24 July 2017
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Abstract Mycosis fungoides (MF) accounts for approximately 50% of all primary cutaneous lymphomas. MF occurrence in the oral cavity is extremely rare with approximately 45 cases reported to date. We present a case of a 68 year-old man with a raised nodular lesion of the ventral tongue with clinical impression of irritational fibroma. Histopathologic and immunohistochemical (IHC) examination revealed a phenotype consistent with MF with large cell transformation in the context of Sezary syndrome. The histological diagnosis of oral MF requires a high index of suspicion and IHC panel to rule out large cell transformation. To our knowledge, only four cases of large cell transformation of oral MF have been reported in the English literature. The clinical and histopathologic features of a rare case of intra-oral MF with large cell transformation are exemplified in this article.

Keywords Mycosis fungoides · Sezary syndrome · T-cell lymphoma · Large cell transformation · Oral cavity

History and Clinical Findings

A 68 year-old man presented with a 6-month history of burning sensation of the tongue, significantly aggravated by hot food/drinks and carbonated beverages. Initial therapies with topical anti-fungal agents failed to completely ameliorate his tongue symptoms. Clinical examination revealed multiple well-demarcated erythematous macules measuring 0.2×0.3 cm on the bilateral upper and lower distal extremities (Fig. 1). Intra-oral examination revealed several partially-demarcated white hyperkeratotic plaques ranging in size from 0.2 to 0.5 cm on a background of diffuse erythema of the tongue dorsum, bilateral ventrolateral tongue, left buccal mucosa and midline posterior hard palate (Fig. 2a–c). On palpation, the hyperkeratotic plaques demonstrated a firm rubbery texture with an overlying glossy/shiny surface. The patient also had a 0.4×0.3×0.2 cm raised red well-circumscribed nodule with an overlying erosive surface on the left anterior ventral tongue. The referring clinician's clinical impression was of a traumatic fibroma. The patient reported irritation from traumatizing this fibroma with his lower anterior teeth and the lesion was subsequently excised (Fig. 2b: black arrow) and submitted for histopathological examination.

Diagnosis and Treatment

Histopathologic examination revealed fibrous tissue with overlying surface epithelium (Fig. 3a). Infiltration of the overlying surface epithelium with atypical lymphoid cells was evident. Further examination showed presence of Pautrier microabscesses in the upper spinous layer of the epithelium characteristic of mycosis fungoides (MF) (Fig. 3b). The lymphoid cells showed a polymorphous mixture of

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Fig. 1 Cutaneous lesions of MF on the lower extremities. Multiple well-demarcated erythematous macules measuring 0.2×0.3 cm on the patient's right shin consistent with MF

small cerebriform lymphocytes (Fig. 3c) and large atypical lymphocytes (Fig. 3d). Some of the large cells demonstrated large eccentric nuclei and amphophilic cytoplasm. There were atypical mitoses and some cells showed multinucleation (Fig. 3c, d). An organoid pattern of infiltration was seen. An initial immunohistochemical (IHC) panel showed atypical lymphocytes positive for CD3 (Fig. 4a) and negative for CD20 (Fig. 4b), S-100, and HMB45. More than 25% of the atypical CD3 positive cells exhibited large nuclei (Fig. 4a). Further analysis showed tumor cells to be diffusely positive for CD4 and CD5. The tumor cells were 50% positive for Ki-67 and 60% dimly positive for CD30 (Fig. 4c–f). Tumor cells were negative for CD7 and CD8. Increased expression of CD30 in combination with a high

proliferative index rendered a final diagnosis of large cell transformation of MF (LCT-MF) [1].

After consultation with the patient's physician, the patient's medical history was significant for Sezary syndrome. Sezary syndrome was diagnosed in January 2011 and the patient initially received ultraviolet light-B (UVB) phototherapy. A PET-CT scan obtained in August 2014 was negative for lymphoma recurrence and showed no foci of abnormal FDG uptake. The patient continued to receive ultraviolet light-B (UVB) phototherapy until December 2015 and was then switched to psoralen ultraviolet light-A (PUVA) photochemotherapy, which he is currently receiving, in addition to topical corticosteroids for his cutaneous lesions.

Discussion

Lymphoma accounts for ~5% of all malignancies in the head and neck, representing the second most common malignancy at this site [2, 3]. Lymphomas are generally classified into Hodgkin's and non-Hodgkin's subtypes and both subtypes can occur at nodal or extranodal sites in the head and neck region. Moreover, the head and neck is the second most common site of extranodal involvement of non-Hodgkin's lymphoma [3]. The majority of extranodal non-Hodgkin's lymphomas represent B-cell lymphomas and T-cell lymphomas at this site are rare.

MF is a non-Hodgkin's T-cell lymphoma that accounts for approximately half of all primary cutaneous lymphomas [4]. Although it is the most common cutaneous T-cell lymphoma, MF is relatively rare (~1200 new cases annually in the United States) [5]. Furthermore, oral MF is extremely rare and represents ~1% of all MF cases [5–8]. MF usually occurs between the fifth and sixth decades of life and is twice as common in males than in females [4, 5, 9]. MF

Fig. 2 Multi-focal intra-oral heterogeneous lesions of MF. **a** Multiple partially-demarcated white hyperkeratotic plaques ranging in size from 0.2 to 0.5 cm on a background of diffuse erythema of the tongue dorsum, **b** bilateral ventrolateral tongue, and **c** left buccal mucosa and

midline posterior hard palate. **(b)** Black solid arrow indicates the site of excisional biopsy of the raised red well-circumscribed nodule on the left anterior ventral tongue

Fig. 3 Histological features consistent with LCT-MF. **a** Section shows fibrous tissue mass with overlying surface epithelium. **b** Malignant lymphoid infiltrates forming Pautrier microabscesses in the upper spinous layer of the epithelium. **c** Pautrier microabscesses

showed polymorphous mixture of small cerebriform cells (*dotted arrow*) and intermediate types, as well as **d** large cells exhibiting multiple nuclei ($\times 100$). LCT-MF: large cell transformation in mycosis fungoides

is more common in certain demographic groups, namely African-Americans [5].

Clinically, MF is a slowly evolving polymorphous cutaneous disease that demonstrates three clinical stages (1: erythematous, 2: plaque, 3: tumor), with each stage progressing slowly over several years [5, 6, 10]. MF presenting in the oral cavity as the initial presentation of the disease is extremely rare [11, 12]. In most cases, oral MF is preceded by cutaneous involvement by an average of 8 years [5, 9, 10]. Approximately 45 cases of MF have been reported in the oral cavity to date [5–8]. Intra-orally, MF can present at any clinical stage similar to cutaneous MF with erythema, indurated plaques or ulcerated nodules [5, 13]. As featured in our case, multi-site oral disease has been reported in approximately 48% of cases [9]. The most frequently

involved intra-oral sites in decreasing order are the tongue, palate, gingiva and buccal mucosa [5–7, 9, 10, 13–15]. The main clinical differential diagnosis for multi-focal partially demarcated white hyperkeratotic lesions on a background of erythema, with a clinical picture similar to the above case, includes oral lichenoid lesions, proliferative leukoplakia, and chronic hyperplastic candidiasis. On histologic evaluation, oral lichenoid lesions demonstrate civatte bodies, basal cell degeneration, and a band-like lymphocytic infiltrate whereas proliferative leukoplakia is characterized by verrucous epithelial architectural changes [16]. The presence of candidal hyphae are evident in chronic hyperplastic candidiasis and this condition may resolve following antifungal therapy [5]. None of these histologic features were evident in our case. Therefore, histopathologic

Fig. 4 Immunohistochemical panel consistent with LCT-MF. **a** CD3 demonstrating strong diffuse positivity for tumor cells. **b** CD20 was negative. **c** Ki-67 was positive in 50% for tumor cells. **d–e** CD4 and

CD5 showed strong diffuse positivity for tumor cells. **f** CD30 was dimly positive for 60% of the tumor cells

examination is required to differentiate these entities and a heightened index of suspicion is required to rule out MF especially in cases with a previous history of cutaneous MF or Sezary syndrome.

Histopathologically, MF is characterized by epidermotropism, a phenomenon that involves migration and invasion of atypical pleomorphic small to medium-sized malignant T lymphocytes into the epidermis or epithelium [4, 5, 17]. The malignant lymphoid cell infiltrates form classic Pautrier microabscesses in the epithelium that are the sine qua non of MF [5, 6, 14]. The atypical malignant lymphoid cells demonstrate a cerebriform morphology [5, 14]. The typical immunophenotype is strong positivity for CD3, CD4 and CD5 with loss of CD7 [4, 6, 15]. LCT-MF is defined as the presence of “large T cells exceeding 25% of the total lymphoid infiltrate or forming microscopic nodules” [18, 19]. Lymphomatoid papulosis (LP) is a CD30 positive lymphoproliferative disorder that can coexist with MF [18] and considering that our case was positive for CD30 in 60% of tumor cells, this raises the possibility of LP coexisting with MF. However, the high proliferative index of the large cells in a patient with a history of Sezary syndrome is more in keeping with a diagnosis of LCT-MF

rather than LP [1]. The histologic differential for CD30 positive lesions on the tongue also includes traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), however our case did not feature stromal eosinophilia and clinically, our case was devoid of oral ulcerations [20].

Management of early stage MF mostly consists of topical corticosteroids, topical nitrogen mustard, topical retinoids, local radiotherapy or photochemotherapy [5, 14, 21]. Recalcitrant cases of MF to topical therapies or cases of advanced MF with visceral involvement usually mandate chemotherapy with or without adjunctive systemic retinoids (e.g. bexarotene) or biologic therapies (e.g. anti-CD52 monoclonal antibody) [5, 21, 22]. Cutaneous MF has a relatively indolent course and is slowly progressive with a median survival of 8–10 years [4, 5], however, MF presenting in the oral cavity is typically a sign of advanced disease with a more aggressive course (mortality rate is ~50% at 1 year with the majority of patients dying by the 3rd year) [6, 9, 12, 15].

Sezary syndrome is an aggressive disseminated form of MF that represents a dermatopathic T-cell leukemia [5]. Progression of MF to Sezary syndrome necessitates extracorporeal photopheresis and chemotherapy

[5]. Extra-cutaneous spread frequently involves the lymph nodes, liver, spleen, lungs and blood [4, 10, 13]. Sezary syndrome incurs a relatively guarded prognosis with a median survival of 2–3 years from the time of diagnosis [5]. Furthermore, LCT-MF (defined as the presence of >25% infiltrating large lymphoid cells) is an adverse prognostic sign [1, 4] and to our knowledge, there have only been four cases of oral LCT-MF reported in the English literature [8, 23, 24].

In conclusion, the aforementioned case illustrates the clinicopathologic features of oral MF and highlights the importance of a comprehensive panel of IHC to rule out large cell transformation.

Funding No funding sources to disclose.

Compliance with Ethical Standards

Conflict of interest No conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective case report, formal consent is not required. The tumor tissue included in the manuscript was obtained as part of the standard of care for the patient and retrospectively collected for the case report.

Informed Consent No identifier information is included in the case report, and the study meets the waiver criteria for the institutional review board of University of Maryland Baltimore.

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