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Mycosis fungoides involving head and neck mucosal sites: Review of the literature

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Mycosis fungoides is the most common form of cutaneous T-cell lymphoma and comprises 4% of all non-Hodgkin lymphomas. It is characterized by the proliferation of mature, effector-memory T-cells in the skin. Lesions initially present as patches and may progress to plaques, tumors and erythroderma. The disease may spread to the viscera and bloodstream.

Mycosis fungoides presenting in head and neck mucosal sites is exceedingly rare. These lesions most often appear after cutaneous involvement, and progression to these areas often indicates a grave prognosis.[1] To date, 57 such cases have been reported in the literature. Here we present 2 additional cases treated in our institution, together with a comprehensive review of the literature.

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Case Report One

A 59-year-old Caucasian woman presented to the Cutaneous Lymphoma Clinic of the Department of Dermatology at our institution with a generalized pruritic erythematous rash and lesions consistent with tumors on her right upper extremity and chest. She had a 4-year history of a rash first localized to her palms that had spread to several cutaneous sites, notably the gluteal folds and inframammary areas. Although originally diagnosed as having pustular psoriasis, biopsies of the right upper extremity and right chest lesions were consistent with mycosis fungoides. Hematopathology did not reveal any disease in her blood and she was diagnosed with stage IIB (T3N0M0Bx) disease. Immunohistochemistry of the biopsy specimen revealed an infiltrate that was CD2+, CD3+, CD5+, CD4-/CD8-, CD7-, and CD56-, with TCR-beta F1+ phenotype. T-cell receptor gamma gene rearrangement was positive for a clonal T-cell population.

The patient initially underwent total skin electron-beam therapy to a total dose of 36 Gy delivered in 24 fractions of 1.5 Gy each using the 6-dual-field irradiation technique.[2] During this period, she reported symptoms of a dry and sore throat as well as odynophagia. Esophagogastroduodenoscopy by an outside gastroenterologist revealed signs of reflux, and she began taking Lansoprazole (Prevacid, Takeda Pharmaceuticals USA, Deerfield, Illinois) 30 mg twice daily, which offered short-lived mild relief. A barium swallow revealed an unremarkable esophagus. Upon further evaluation in the Department of Otolaryngology, areas of inflammation consistent with laryngeal and oropharyngeal candidiasis were identified, and she received treatment with oral fluconazole for 4 weeks. Although the candidiasis resolved at that time, the patient continued to complain

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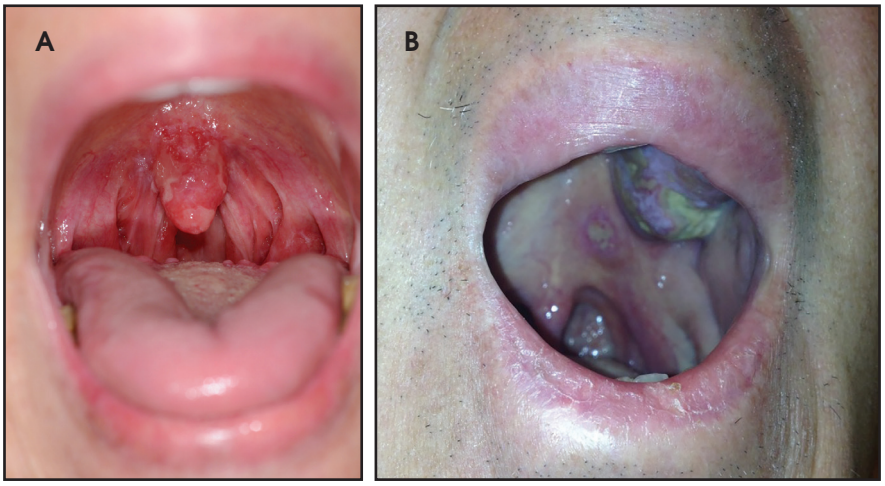

FIGURE 1. *Intraoral photographs of cases 1 (A) and 2 (B) showing mucosal lesions.*

of persistent symptoms that were worse after meals and at night. Re-examination of her throat showed an irritated appearance of the posterior soft palate, uvula, and anterior tonsillar pillars (**Figure 1A**). Flexible nasopharyngolaryngoscopy revealed irritated mucosa diffusely on the epiglottis and arytenoids bilaterally with a similar appearance along the left lateral pharyngeal wall. Biopsy specimens from the uvula and epiglottis revealed lesions consistent with her previously diagnosed mycosis fungoides including an identical TCR-gamma clone. Immunohistochemistry demonstrated an infiltrate positive for CD2, CD3, CD5, CD43 and weakly positive for beta-F1. Infiltrates were negative for CD56, CD30, and CD20. Positron emission tomography and computed tomography (PET/CT) scans showed no involvement of her viscera and mild fluorodeoxyglucose (FDG) uptake of an SUV of 2.3 in her axillary and inguinal lymph nodes. The oropharyngeal and laryngeal lesions were treated with 6-MV photons using an intensity-modulated radiation therapy (IMRT) technique. The initial planned dose was 30.6 Gy to be delivered in 17 fractions. However, she developed confluent fibrinous mucositis (grade III) and severe odynophagia, which required multiple breaks in treatment, significantly prolonging treatment duration. Ultimately, we terminated her treatment at a dose of 20.8 Gy. Two years after treatment completion, the patient has had no local recurrence of her mucosal lesions. She has subsequently undergone external-beam radiation therapy on multiple occasions for localized skin lesions. She continues to follow up with dermatology and radiation oncology.

Case Report Two

A 69-year-old Caucasian man was diagnosed with cutaneous mycosis fungoides 10 years prior to his presentation to our institution. At the time he was seen in the Department of Dermatology, he noted a 2-month history of new leather-like lesions on his bilateral extensor elbow surfaces. He also had multiple exophytic nodules on his bilateral lower and upper extremities, in addition to plaques on his torso and all 4 extremities. The mycosis fungoides lesions on his scalp had been treated with radiation therapy 5 years earlier, with no recurrence at those sites. He had also received intermittent psoralen and ultraviolet A (PUVA) light therapy and methotrexate until 3 years prior to presentation. At consultation, he was taking bexarotene (Targretin, Valeant Pharmaceuticals International Inc., Laval, Quebec, Canada) 75 mg 3 times daily in addition to using triamcinolone 0.1% cream daily. A biopsy of one of the new lesions revealed marked pseudoepitheliomatous hyperplasia with dermal granulomatous inflammation. Culture of the lesions revealed staphylococcus aureus, and he began receiving daily intravenous vancomycin 1 gm for 30 days with minimal improvement. Another biopsy taken from the left forearm lesion demonstrated cutaneous T-cell lymphoma with pseudoepitheliomatous hyperplasia, a positive monoclonal T-cell rearrangement and a CD3+, CD4+, CD8+, and CD30- phenotype. PET/CT showed no metabolic disease at any site.

The patient was treated with total skin electron-beam therapy to a total dose of 36 Gy using the technique described above. Shielded areas, including the palms, soles and buttocks, received a boost of 8 Gy in 1 fraction. This was followed by 4 cycles of weekly pralatrexate 15 mg/m^2. Although this treatment initially appeared beneficial, several weeks later the patient presented with new lesions on his torso, extremities, and on the left tonsil and alveoli (**Figure 1B**). Biopsy of the left soft palate and left superior alveolar ridge again was consistent with mycosis fungoides. The oral lesions were treated with external-beam radiation therapy to a prescribed dose of 30.6 Gy in 17 fractions. However, the patient received only 10 fractions for a total dose of 18 Gy due to severe mucositis, which was not relieved by sucralfate, and eventually required hospitalization due to significant decreased oral intake and failure to thrive. His treatment was discontinued at this dose. Although the oral lesions responded well to the therapy, he eventually began a regimen of cyclophosphamide, hydroxydaunorubicin, etoposide, vincristine, and prednisone (CHEOP) chemotherapy and intrathecal methotrexate due to overall disease progression, including involvement of his bone marrow. Unfortunately, our patient succumbed to

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disseminated disease after receiving a single cycle of CHEOP.

Materials and Methods

We performed a PubMed search for articles in English containing the following key words: mycosis fungoides, cutaneous T-cell lymphoma, oral cutaneous T-cell lymphoma, oral mycosis fungoides, oropharyngeal mycosis fungoides, and treatment of oral mycosis fungoides. Articles describing patients with only cutaneous manifestations of mycosis fungoides were excluded. Only reports of cases of head and neck mucosal mycosis fungoides were included for analysis. Additional cases were identified by reviewing and evaluating the references in articles retrieved from our PubMed search.

Results

Our literature search uncovered 57 previously reported patients with biopsy-proven mycosis fungoides manifestations in the head and neck mucosal areas,[1,3-44] with the first case reported in 1891. We report 2 additional cases treated in our institution. The age of these 59 patients ranged from 12 to 86 years (median 65 years, mean 60.4 years). Of these, 38 were men (64%) and 19 were women (32%) (**Table 1**). We were unable to verify the gender of 2 patients (3%).[7,13]

Since many case reports provide only the age of the original diagnosis, we estimated the exact age of a given patient at the time of head and neck mucosal manifestations using the time frame given in the reports.

Duration Before Oral Cavity or Oropharyngeal Involvement

All but 6 patients were previously diagnosed with cutaneous mycosis fungoides prior to head and neck mucosal presentation. Based on the limited information from prior publications, we were able to estimate the duration from initial cutaneous presentation of mycosis fungoides to mucosal involvement in 30 of the 53 patients (this excludes the 6 patients who presented initially with oral/oropharyngeal disease). These periods ranged from 1 month to 21 years (**Table 1**). The mean time was 5.7 years, with a median time of 4 years.

Histology and Sites of Disease

Atypical lymphocytes exhibiting cerebriform and indented nuclei were described in most biopsy specimens. Pautrier microabscesses were also noted in some reports. When examining cellular markers, 12 patients were CD4+, a common finding in mycosis fungoides.[1,33,34,36,38-42] Of these, 7 were CD4+/CD8-[1,33,38,39,41,42] and 3 were CD4+/CD8+.[34,43,44] Three were CD4-/CD8+[1,33] and only 1 patient was CD4-/CD8- (case 1 of this report), a rarity.

Although head and neck mucosal mycosis fungoides was noted in a wide array of anatomical sites, the most common sites for disease presentation were the tongue (n = 25, 42%) and hard or soft palate (n = 18, 31%). Other sites of disease were (in descending order of frequency) gingiva, epiglottis, buccal mucosa, tonsils, and lips.

Treatment Modalities

The treatment modalities of 36 patients were described. Of these, 26 patients received some form of radiation, including total skin electron-beam therapy and/or local field radiation therapy. Based on the information in the published reports, at least 18 patients received external-beam radiation therapy to their mucosal lesions. An additional 2 patients were prescribed radiation, but either declined or died before receiving radiation therapy. Prescribed doses to mucosal lesions included 65 Gy in 32 fractions, 36 Gy in 15 fractions, 30.6 Gy in 17 fractions, 27 Gy in 9 fractions, 24 Gy in 12 fractions, and 4 Gy in 1 fraction. We initially prescribed 30.6 Gy in 17 fractions to both of our patients; however, neither one could complete the entire treatment due to severe toxicities. Only 2 patients were reported to have undergone surgical tumor debulking.

Survival

Information regarding follow-up was available for 35 (59%) patients. Of these, 24 died; however, it should be noted that not all deaths were related to mycosis fungoides. The time from head and neck mucosal presentation to death in these patients ranged from 1 month to 8 years, with a mean of 1.7 years and a median of 1 year. Fourteen patients were alive at last known follow-up, which ranged from 1 month to 5 years. Of these, 7 had no evidence of oral or cutaneous disease at follow-up.

Discussion

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. Although it typically presents with cutaneous manifestations, the viscera and bloodstream may become involved. Rarely, mycosis fungoides is found in head and neck mucosal sites, generally in the context of previously diagnosed disease.[1]

The most common area for disease manifestation in the oral cavity is the tongue, with 50% of reported patients having such lesions. The palate and gingiva are the next most common areas, followed by the buccal mucosa, lips and oropharynx.[43]

Histological changes that may be seen on biopsy include Pautrier microabscesses and large, convoluted or indented nuclei. Immunostaining typically will show CD4+ and CD8- phenotypes. CD8+ cells are unusual; we report a patient with lesions found to be both CD4- and CD8- and another with CD4+ and CD8+ phenotype. In a single-center departmental review of 140 patients presenting with mycosis fungoides, 18 were found to have CD4- and CD8- staining.[45]

Treatment of oral manifestations is typically external-beam radiation therapy prescribed at doses ranging from 30-40 Gy in 15-17 fractions (ie, 1.6 to

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2.5 Gy per fractions).[43] Postorino et al, however, reported successfully treating a patient with a combination of weekly alemtuzumab 15 mg, a monoclonal CD52 antibody, once per week and 6 monthly cycles of CHOEP. Although that patient relapsed after 6 months, further treatment of alemtuzumab and gemcitabine stabilized the disease with maintenance photopheresis.[44]

Our patients both experienced severe mucositis during their treatment regimens. Reynolds et al similarly reported a patient with mucosal irritation after receiving 3000 rads to the entire oral cavity; this resolved with conservative therapy.[25] Other publications in our review did not report these or other similar treatment side effects. It is, however, important to consider these toxicities during treatment planning and to recognize them as possible impediments to treatment completion.

Conclusion

Predominantly a cancer of the skin, mycosis fungoides presenting in the oral cavity and oropharyngeal mucosa is uncommon. A review of the previously reported 57 cases and 2 new cases at our institution shows that head and neck mycosis fungoides is a rare and late manifestation of the disease and carries a poor prognosis. External-beam radiation therapy is the most common treatment modality. Toxicities can include severe mucositis and can delay or prevent full treatment regimens.

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Table 1. A Review of All Previously Reported Head and Neck Mucosal Mycosis Fungoides Cases in Chronological Order of Publication

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Brocq,[3] 1891	55/F	NA	NA	NA	Cutaneous lesions	Tongue	NA	Cocaine suspension	NA
Hallopeau and Jeanselme,[4] 1892	72/M	NA	NA	NA	Cutaneous lesions	Tonsils and soft palate	NA	NA	NA
Breakley,[5] 1902	33/M	NA	Biopsy	NA	Cutaneous lesions	Tonsils and tongue	NA	NA	NA
Corbett,[6] 1914	F	NA	Biopsy	NA	NA	Soft palate	NA	Surgery	NA
Sequeria,[7] 1914	NA	NA	NA	NA	NA	Tongue and buccal mucosa	NA	NA	NA
Kren,[8] 1938	86/F	NA	Biopsy	NA	Cutaneous lesions	Tongue	NA	NA	NA
Berggreen,[9] 1939	54/M	NA	Biopsy	—	Cutaneous lesions	Tongue	NA	NA	NA
Gottron,[10] 1942	57/M	NA	Biopsy	NA	none	Tongue	Initial presentation	Potassium iodine	NA
Cheridjian,[11] 1947	45/M	NA	Biopsy	NA	NA	Pharynx, larynx	NA	NA	NA
Wertheim and Smith,[12] 1948	36/M	NA	Biopsy	NA	Diffuse cutaneous tumors	Tongue, hard/soft palate	3 years	Roentgen rays to cutaneous tumors, sodium cacodylate	DFD 2 months after H&N presentation
Strauss et al,[13] 1949	56/F	NA	NA	NA	NA	Tongue	NA	NA	NA
Strauss et al,[13] 1949	NA	NA	NA	NA	NA	Tongue	NA	NA	NA
Branscheid,[14] 1950	38/F	NA	NA	NA	NA	Pharynx, larynx	NA	NA	NA
Cawley et al,[15] 1951	72/M	NA	Biopsy	Closely packed lymphoblasts and large number of plasma cells	Cutaneous lesions	Tonsils, junction of hard/soft palate	Initial presentation	NA	DFD 2 years after diagnosis
Pautrier and Ullmor,[16] 1954	64/M	NA	Biopsy	NA	Cutaneous lesions	Tongue	NA	RT	NA
Tillman,[17] 1965	60/M	NA	NA	NA	Face, extremities	Lips	NA	NA	NA
Calhoun and Johnson,[18] 1966	43/M	NA	Biopsy	NA	Cutaneous lesions	Tongue, lips, mucosa	NA	NA	NA
Kressin and Schoeder,[19] 1968	68/M	NA	NA	NA	NA	Pharynx, larynx	NA	NA	NA
Cohn et al,[20] 1971	50/M	NA	Biopsy	NA	Cutaneous lesions	Lips, tongue, mucosa, hard palate	NA	NA	NA
Strahan and Calcaterra,[21] 1971	44/F	NA	Biopsy	"Appeared to represent mycosis fungoides"	Eyelid, bridge of nose, upper lip	Upper lip, posterior tongue, oropharynx, hypopharynx	6 months	RT to face, pharynx	Diffuse disease
Laskaris et al,[22] 1978	65/F	NA	NA	NA	Cutaneous lesions	Lips, mucosa	NA	NA	NA
Crane/Heydt,[23] 1979	73/F	NA	Biopsy	NA	Cutaneous lesions	Gingiva	NA	Radiation	NA
Hood et al,[24] 1979	80/F	NA	Biopsy	Atypical lymphocytes with hyper-chromatic cerebriform nuclei	NA	True and false vocal cords bilaterally, arytenoid cartilage, epiglottis, aryepiglottic fold	Initial presentation	6500 rads in 32 Fx to oral lesions, chemotherapy for cutaneous lesions	DFD 4 years after diagnosis

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Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Reynolds et al,[25] 1981	75/F	NA	Biopsy	Large and small cells, irregular nuclei	Diffuse erythroderma	Tongue; hard palate	15 years	Local RT to symptomatic lesions (hands, inframammary): 2000 rads in 3 Fx, plus 6 meV electron beam; 6 meV electron beam in single dose of 400 rads to tongue lesion	Lesions healed within 1 week; hard palate lesion presented 4 months after treatment of tongue lesion with similar treatment and results; recurrence of tongue lesion at 3 months, received 3000 rads to entire oral cavity in 10 Fx; NED at 14 months F/U
Agarwal et al,[26] 1982	55/M	NA	NA	NA	NA	Aryepiglottic fold, arytenoids, epiglottis, false vocal cords	Initial presentation	NA	DFD within 2 years of diagnosis
Damm et al,[27] 1984	68/M	NA	Biopsy, BMB, CT scan	Diffuse dense lympho-reticular cell infiltrate, scant cytoplasm, Pautrier micro-abscesses, cerebriform lymphoid cells; insufficient amount of cells for B and T-cell typing	Upper arm and back	Hard and soft palate, left nasopharynx and sinus	Initial presentation	Chemotherapy and scheduled RT	Died from complications of chemo-therapy; no evidence of disease on autopsy
Ferlito and Recher,[28] 1986	78/M	NA	BMB, biopsy	NA	Diffuse lesions	Aryepiglottic fold, arytenoids, epiglottis	4 years	TSET 40-46 Gy	DFD
Gordon et al,[29] 1992	85/M	NA	Biopsy	CD3+, CD45-, negative for UCHL-1 (T-cell lineage marker)	Diffuse involvement	Epiglottis	4 years	27 Gy in 9 Fx to larynx, PUVA, nitrogen mustard to cutaneous lesions	Died from disease complications within 1 month of H&N presentation
Kuhn et al,[30] 1992	78/M	IV-B	Biopsy, BMB, CT	Atypical lymphoid cells, Pautrier microabscesses, cerebriform nuclei; UCHL+ (T-cell lineage marker) and L-26 negative (B-cell lineage marker)	Skin, liver, bone marrow	Left tonsil, base of tongue, left epiglottis, left aryepiglottic fold, left true and false vocal cords	6 years	PUVA, TSET, chemotherapy with VP-16, vincristine, doxorubicin cyclo-phosphamide, alpha-interferon, 2-deoxycoformycin	DFD within 1 month of H&N presentation
Kuhn et al,[30] 1992	82/M	IVb	Biopsy, CT	From autopsy: atypical lympho-cytes with cerebriform nuclei, no Pautrier microabscesses, UCHL+ (T-cell lineage marker) and L-26 negative (B-cell lineage marker), mycosis fungoides found in Para-aortic and mediastinal lymph nodes, bone marrow, liver, spleen, kidneys, GI tract, lung, heart	Diffuse cutaneous involvement	Aryepiglottic fold, true vocal cords, false vocal cords	3 years	PUVA, TSET, chemotherapy with VP-16, vincristine, doxorubicin, cyclophos-phamide, alpha-interferon, 2-deoxyco-formycin, methotrexate	DFD within 1 month of H&N presentation

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Redleaf et al,[31] 1993	55/M	NA	Biopsy	Leu-4, T4, and LCA+; irregular nuclei consistent with mycosis fungoides	Plaques and nodules, esophageal involvement	Arytenoids, pharynx, larynx	9 months	26 Gy to neck	Developed Sézary syndrome
Redleaf et al,[31] 1993	37/M	NA	Biopsy	NA	NA	Posterior and lateral pharyngeal wall	NA	NA	NA
Redleaf et al,[31] 1993	74/M	NA	Biopsy	NA	Also had esophageal involvement	Base of tongue, epiglottis, arytenoids	NA	NA	NA
Redleaf et al,[31] 1993	38/M	NA	Biopsy	NA	NA	Palate, oropharynx, hypopharynx	NA	NA	NA
Sirois et al,[1] 1993	75/M	IVa	Biopsy	NA	Cutaneous tumors	Gingiva, palate, tongue, lip, buccal mucosa, tonsil	4 years	RT-responded, then had recurrence	Died from other causes 2 years after H&N presentation
Sirios et al,[1] 1993	57/M	III	Biopsy (Sézary syndrome)	CD2-, CD3+, CD4+, CD8-, CD7-, CD30-	Skin lesions	Tongue	13 years	RT-responded fully	Died from other causes, 1 year after H&N presentation
Sirios et al,[1] 1993	49/M	IVa	Biopsy	CD2-, CD3+, CD4-, CD8+, CD7+, CD30-	Skin lesions	Gingiva, tongue	3 years	alpha- interferon had no effect	Died from other causes 1 year after H&N presentation
Sirios et al,[1] 1993	74/M	NA	Biopsy	NA	Skin lesions	Gingiva, palate	3 years	RT-partially responded	Partial remission at 1 year F/U
Sirios et al,[1] 1993	66/F	IIb	Biopsy	NA	Skin lesions	Gingiva, palate	2 years	RT-complete response	Died from other causes 3 years after H&N presentation
Sirios et al,[1] 1993	53/F	IVa	Biopsy	CD2-, CD3+, CD4-, CD8+, CD7+, CD30-	Skin lesions	Gingiva	2 years	RT-complete response	DFD 3 years after H&N presentation
Sirios et al,[1] 1993	73/F	Ib	Biopsy	NA	Skin lesions	Tongue	6 years	RT-complete response	Died from other causes 8 years after H&N presentation
Sirios et al,[1] 1993	51/M	III	Biopsy	NA	Skin lesions	Tongue	8 years	RT-complete response	DFD 2 years after H&N presentation
Harman,[32] 1998	57/M	NA	Biopsy, normal chest x-ray and abdominal ultrasound	NA	Scaling, plaques, and tumors	Gingiva, palate	4 years	NA	Died from other causes 7 months after H&N presentation
de la Fuente et al,[33] 2000	45/F	NA	Polymerase chain reaction of blood and lesions showed clonality; eosinophilia =1 x 109; ESR = 40 mm/h; normal CT and x-ray thorax; normal BMB	atypical lymphocytes, focal exocytosis, numerous mitosis and eosinophils; CD3+, CD4+, CD8-, CD30-	Many cutaneous plaques and tumors	Tongue, uvula, oropharynx	10 years	PUVA, interferon, methotrexate, carmustine, electron beam therapy, photo-phoresis; poly-chemotherapy and BMT after developing Hodgkin's; corticosteroids, methotrexate, etoposide after recurrence	DFD 6 months after develop-ment of H&N lesions

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Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
de la Fuente et al,[33] 2000	66/F	NA	Biopsy of lesions; CT revealed enlarged soft palate and tonsils with no extra cutaneous involvement	Atypical lymphocytes, irregular nuclei, many mitotic figures, exocytosis, microabscesses; CD3+, CD4-, CD8+, CD30-	Head, neck, trunk, leg-plaques, papules and nodules	Uvula	4 years	Interferon then carmustine for original disease; CHOP for recurrent disease	Alive with NED at 5 years
Chua and Veness,[34] 2002	81/M	NA	NA	CD3+, CD8+, CD4+, CD5-, CD15-, CD30-, no Pautrier microabscesses	Erythematous plaques	Hard palate, upper gingivae	1-2 years	PUVA + psoralen, external beam radiation	NED at 12 month F/U
Lippert et al,[35] 2002	75/F	NA	Biopsy	CD3+; Pautrier microabscesses	Multiple lesions on arms/legs	Left larynx, paranasal sinuses	1 year	Initial treatment of cutaneous lesions with TSET 6 x 5 Gy, cylophosphamide, vincristine, steroids; 6 Gy boost to larynx with total dose to larynx and maxillary sinuses of 40/46 Gy planned doses	DFD 4 months after H&N presentation
Wain,[36] 2003	12/M	Ib	Biopsy; PCR	Enlarged lymphocytes, Pautrier micro-abscesses; CD2+, CD3+, CD4+, CD8-, CD30-	Papules on upper/lower extremities, trunk	Right soft palate, tongue	8 years	UVB (6 weeks), emollients, topical steroids, patient declined oral PUVA and RT	H&N disease but no systemic or cutaneous disease at 3 years
Viswanathan et al,[37] 2004	69/M	NA	Biopsy; BMB	CD3+, CD20-, cytokeratin negative	Multiple skin lesions	Base of tongue, left lateral pharyngeal wall, soft palate	NA	Steroids, Levamisole	NA
Le et al,[38] 2006	36/M	IIb	Biopsy	CD4+, CD8-; residual lesions after therapy found to be CD4- and CD8+	Diffuse patches and plaques including on eyelids	Tonsils	4 years	Bexarotene interferon, PUVA, 6 cycles of doxyrubicin	NA
Wahie et al,[39] 2006	69/M	NA	Biopsy, CT scan identified inguinal and left iliac nodes; CBC, LFT, LDH all WNL	CD2+, CD3+, CD4+, CD5+, CD8-, CD20-	Diffuse involvement	Epiglottis	7 years	PUVA, gamma interferon, RT to oropharynx 24 Gy in 12 Fx	NED at 6 months F/U
Gruson,[40] 2007	60/M	Ib-IIb	NA	large atypical lymphocytes, Pautrier micro-abscesses; CD4+, CD30-, CD56-	Patches/plaques over 40% surface area, knee	Left nostril	4 years	Original: PUVA then UVB; acitretin and alpha interferon, narrow UVB; radiation for nasal lesion	Nasal lesion healed with radiation, continued treatment for other lesions at 12 months
May et al,[41] 2007	40/F	NA	CT, PET, BMB, BM aspiration all normal	CD2+, CD3+, CD4+, CD5+, CD43+, CD8-, CD10-, CD20-, CD23-, CD30-, CD56-, CD57-, cyclin D-	Left fingers, after H&N involvement	Tongue	Initial presentation	Cyclophos-phamide, vincristine, dexamethasone, then cytarabine and methotrexate	NED at 13 months F/U to stem cell transplant
May et al,[41] 2007	44/M	NA	CT, PET, BMB, BM aspiration all normal	CD3+, CD4+, CD8-, CD20-, CD30-, CD56-	Finger	Tongue	4 years	Chemotherapy and stem cell transplant, radiation after cutaneous relapse	NED 21 months after cutaneous relapse

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Maleki and Azmi,[42] 2010	69/M	NA	Biopsy	D3+, CD4+, CD 7-, D8-, CD20-	Diffuse involvement	Left true vocal cord	21 years	Nitrogen mustard, total body irradiation, photopheresis, methotrexate and alpha-interferon surgical debulking of tonsillar mass	NA
Goldsmith et al,[43] 2014	64/F	NA	Biopsy of lesions	Sheets of atypical large mononuclear cells with nuclear indentations; CD3+, CD4+ CD8+; CD56-, CD68-, FoxP3-, IL-17-	Diffuse involvement	Posterior right palate	20 years	Full body radiotherapy; PUVA; topical corticosteroids; received 36 Gy in 15 Fx to oral lesion	NED at 2 ½ year F/U
Postorino et al,[44] 2016	60/M	NA	Biopsy	CD3+, CD2+, CD4+, CD8+, CD7	Tumor on leg	Buccal mucosa	Initial presentation	Alemtuzumab and CHEOP	Relapsed at 6 months, treated with alemtuzumab and gemcitabine
Our case report 1	59/F	IIb	Biopsy	CD2+, CD3+, CD4-, CD8-, CD5+, CD56-; TCR-beta F1+ immunophenotype	Diffuse involvement	Epiglottis, uvula	< 1 year from beginning of treatment	Initially with UVB, bexarotene and prednisone, then TSET 36 Gy in 12 Fx + 12 Gy boost to soles, 20.8 Gy/ 30.6 Gy to oral lesions	TSET relieved all areas aside from inframammary folds, infraglutial region, palms and soles
Our case report 2	69/M	NA	Biopsy	NA	Patches, plaques keratotic nodules; upper and lower extremities, trunk, scalp	Oral cavity and tonsils	11 years	TSET 36 Gy in 24 Fx, 8 Gy in 1 Fx to soles, palms, ventral penis, and buttocks, HDR 8 Gy in 1 Fx to left knee, PUVA, bexarotene, methotrexate, triamcinolone; 18Gy/ 30.6 Gy to oral lesions and later, systemic pralatrexate and CHEOP	Initially responded well to TSET; DFD within 1 year of oral presentation

Abbreviations: BMB, bone marrow biopsy; CBC, complete blood count; CHEOP, cyclophosphamide, hydroxyduanorubicin, etoposide, vincristine (Oncovin, Genus Pharmaceuticals, Newbury, UK) and prednisone; CHOP, cyclophosphamide, hydroxyduanorubicin, vincristine (Oncovin, Genus Pharmaceuticals, Newbury, UK) and prednisone; CT, computed tomography; DFD, died from disease; ESR, estimated sedimentation rate; F, female; F/U, follow-up; Fx, fractions; GI, gastrointestinal (tract); H&N, head and neck (mucosa); LDH, lactate dehydrogenase; LFT, liver function tests; M, male; NA, not available; NED, no evidence of disease; PUVA, psoralen and ultraviolet A radiation; RT, radiation therapy; TSET, total skin electron therapy; UVB, ultraviolet B radiation; WNL, within normal limits.