CASE REPORT

Composite lymphoma: angiocentric T-cell lymphoma (CD8+ cytotoxic/supressor T-cell) and diffuse large B-cell lymphoma associated with EBV, and presenting clinically as a midfacial necrotizing lesion

Yuk-Kwan Chen[a], Eric Huang[b], Cheng-Chung Lin[a], Yu-Ju Lin[a], Shui-Sang Hsue[a], Wen-Chen Wang[a], Li-Min Lin[a],*

[a]*Department of Oral Pathology, School of Dentistry, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b]*Department of Oral and Maxillofacial Surgery, School of Dentistry, Kaohsiung Medical University, Kaohsiung, Taiwan*

Summary A composite lymphoma is defined as the simultaneous occurrence of two histologically different types of lymphomas situated in one anatomical location. Reports of composite B- and T-cell lymphomas, especially in the head and neck region, are rare. We describe a 76-year-old Taiwanese aboriginal female patient clinically presenting with a midfacial necrotizing lesion (MNL). Microscopic examination of the incisional biopsy specimen revealed extensive surface necrosis with infiltrates of inflammatory cells. Beneath the necrotic surface, there appeared to be two distinct populations of pleomorphic lymphoid cells exhibiting the characteristic features of the angiocentric distribution of the tumor cells and evidence of angiodestruction. Immunohistochemical staining revealed that these atypical lymphoid cells were positive for LCA, CD45, CD5, CD20, CD3ε, CD8, bcl-2 and bcl-6 and negative for CD56, CD4, CD68, keratin, S-100, kappa and lambda. Furthermore, these atypical lymphoid cells also expressed EBV-encoded nuclear RNAs (EBERs) following in situ hybridization. Therefore, this was a case of composite lymphoma: angiocentric T-cell lymphoma (ATCL) (CD8+ cytotoxic/suppressor T-cell) and diffuse large B-cell lymphoma (DLBL) associated with the Epstein—Barr virus (EBV) and presenting clinically as MNL.
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* Corresponding author. Tel.: +886-3121101/2292; fax: +886-7-3210637.
E-mail address: k0285@ms22.hinet.net (L.-M. Lin).

Introduction

An angiocentric T-cell lymphoma (ATCL), according to the revised European American lymphoma (REAL) classification, is listed as a peripheral T-cell lymphoma.[1] ATCL is a rare form of peripheral T-cell lymphoma that has been reported to affect most parts of the body.[2] When an ATCL was detected in the nasal cavity, sinus or palate, it was previously described, clinically, as a midfacial necrotizing lesion (MNL) possibly displaying histopathological features of pleomorphic atypical lymphoid cells featuring angiocentricity, angioinvasion, and necrosis, and possibly associated with the presence of variable numbers of inflammatory cells.[2]

A number of authors have concluded that the neoplastic cells detected from cases of MNL are of T-cell origin,[3,4] although, a few cases of B-cell lymphoma presenting as MNL have also been reported.[5–8] On the other hand, an entity termed T/NK-cell lymphoma has been reported by Imamura et al. in 1990, which also presented as MNL.[9] Some authors have considered all midline ATCL cases as being T/NK-cell lymphomas.[10,11] According

to a World Health Organization (WHO) classification of hematological malignancies, the immunophenotypical analysis of extranodal NK/T-cell lymphomas in the nasal region may be CD56+, CD3ε+ and EBV+, however, it may be that there exists an unusual EBV+, CD56- cytotoxic/suppressor T-cell phenotypic NK/T-cell lymphoma.[11]

A composite lymphoma is defined as the simultaneous occurrence of two different histological types of lymphomas situated in one anatomical location.[12] To the best of our knowledge, reports of composite B- and T-cell lymphomas, especially in the head and neck region, are rare.[13–18] In this report, we describe a case of composite lymphoma: ATCL (cytotoxic/suppressor T-cell origin) and diffuse large B-cell lymphoma (DLBL) associated with the Epstein—Barr virus (EBV), and presenting clinically as MNL.

2. Case report

A 76-year-old Taiwanese aboriginal female patient complained of an ulcerative lesion over the palate that had persisted for about 1 year. In the
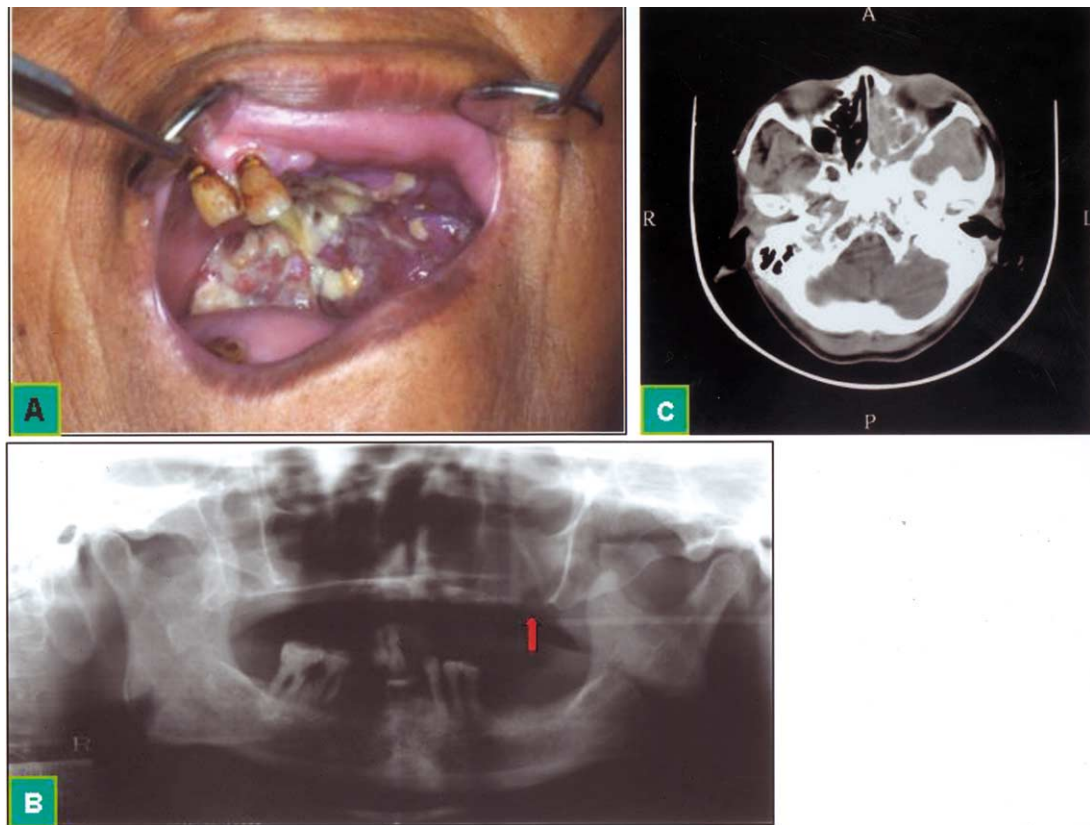

Figure 1. (A) An extensive ulcerative lesion with associated yellowish debris over the palatal area. (B) Panoramic radiograph revealing destruction of the left palate (arrow) and the cloudy appearance of the left sinus. (C) Computed tomography scan indicating massive soft-tissue lesions involving the left nasopharynx, left nasal cavities, left maxillary sinus, soft palate, and left parapharyngeal space. The adjacent bony structures appear to be destroyed.

early stages of this condition, the patient noted that water would flow from her nose whilst drinking. She visited a local hospital and an incisional biopsy was performed. The pathological report was reported to be an inflammatory lesion, although the ulceration did continue to increase in size subsequently. As a consequence, the patient was then referred to our institution for further examination. An extraoral examination revealed left facial swelling whereas an intraoral examination demonstrated an extensive painful ulcerative lesion, measuring about 7×5 cm in diameter, with associated yellowish debris (Fig. 1A). An oral-antral fistula was also noted, and headache and dysphasia were complained of. The patient denied any history of cigarette smoking or alcohol consumption but she did acknowledge that she occasionally practiced betel-quid chewing.

A panoramic radiograph revealed destruction of the left palate and the prominent and cloudy appearance of the left sinus (Fig. 1B). Computed tomography indicated massive soft-tissue lesions with heterogenous enhancement involving the left nasopharynx, left nasal cavities, left maxillary sinus, oropharynx, soft palate, left parapharyngeal space, left masticatory space, left intratemporal fossa and left buccal space. The adjacent bony structures appeared to have been destroyed, and narrowing of the nasopharynx and oropharynx was also identified (Fig. 1C). There appeared to be no evidence of palpable cervical adenopathy. The patient's lungs appeared to be clear, and no heart murmurs or gallops appeared to be evident. No abdominal masses or tenderness, ascites, or hepatosplenomegaly were noted, and a chest scan appeared to be normal. A peripheral blood smear revealed normal WBCs, and a bone-marrow aspiration demonstrated normal cellularity (45%) with an adequate level of megakaryocytes. Both myeloid and erythroid studies revealed normal maturation and differentiation with an M/E ratio of 3.4:1, and there appeared to be no evidence of obvious lymphoma-cell infiltration.

An incisional biopsy extending to the deeper areas of the ulceration was performed, and a microscopic examination of the specimen revealed
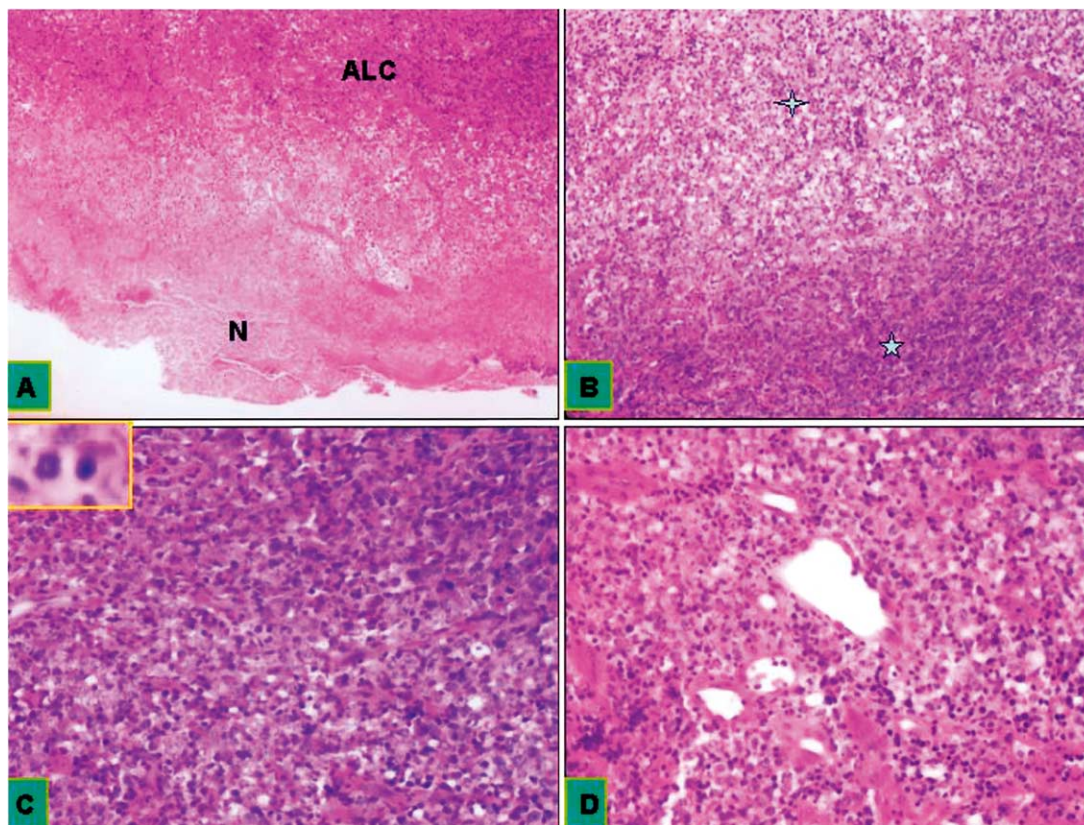
Figure 2 (A) Microscopic examination showing a diffuse collection of atypical lymphoid cells (ALC) beneath an extensively necrotic surface layer (N). (B) These pleomorphic lymphoid cells consist of two distinct populations with one population comprising mainly large immunoblast-like cells (upper asterisk) with the other population comprised chiefly by small lymphocyte-like cells (lower asterisk). (C) Multiple abnormal mitoses occurred for both populations of lymphoid cells with typical examples being shown within the left upper inset. (D) The angiocentric distribution of the tumor cells and evidence of angiodestruction can readily be seen (hematoxylin-eosin stain×100).

an extensive surface necrosis superimposed with infiltrates of inflammatory cells (Fig. 2A). Beneath the necrotic area, there appeared to be two distinct populations of pleomorphic lymphoid cells (Fig. 2B). One consisted mainly of large or immunoblast-like cells whilst the other appeared to be comprised, chiefly, of small lymphocyte-like cells (Fig. 2B). Prominent abnormal mitoses could be seen frequently for both populations of lymphoid cells (Fig. 2C). Another striking feature was the angiocentric distribution of the tumor cells and evidence of angiodestruction, which mimicked vasculitis (Fig. 2D). Immunohistochemical staining with various antibodies was performed (Table 1), whilst In situ hybridization for the detection of EBV-encoded nuclear RNAs (EBERs) was also performed on paraffin sections of biopsied tissue using standard procedures and commercially available reagents (Dako In Situ Hybridization Detection Systems). Both positive and negative controls were included for each batch of staining. Double immunohistochemical staining for B-cell markers (CD20) and T-cell markers (CD3ε) further identified the existence of two populations of atypical lymphoid cells (Fig. 3A). In summary, these atypical lymphoid cells were positive for LCA, CD45, CD5, CD8 (Fig. 3B), CD3ε (Fig. 3C), CD79a (Fig. 3D), and were negative for CD56 (Fig. 3E), CD4 (Fig. 3F), CD68, keratin, S-100, kappa and lambda. Further, bcl-2 (Fig. 3G) and bcl-6 (Fig. 3H) positivity were also noted for the atypical lymphoid cells present, and these atypical lymphoid cells expressed EBER on in situ hybridization (Fig. 3I). Therefore, a histological diagnosis of composite lymphoma: ACTL (CD8+ cytotoxic/suppressor T-cell origin) and DLBCL associated with EBV was made. Subsequent to the completion of one course of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) chemotherapy, the patient's condition became stable and revealed a partial response, however, she refused to undergo any further treatment and has, unfortunately, been lost to follow-up subsequently.

3. Discussion

The term composite lymphoma, as originally coined in 1954 by Custer[12] and then subsequently modified by Rappaport et al.[19] in 1956 and again by
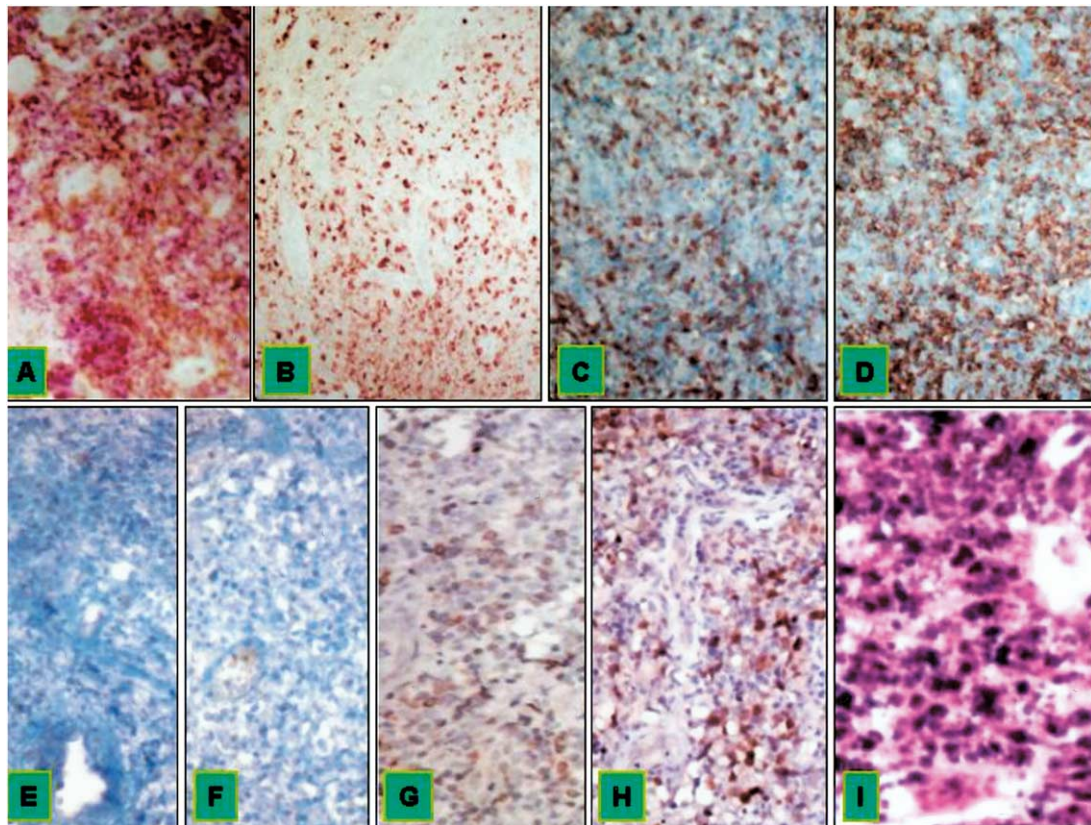
Figure 3 (A) Double immunohistochemical staining for a B-cell marker (CD20; brown color) and a T-cell marker (CD3ε; red color) identified the two populations of atypical lymphoid cells. Atypical lymphoid cells stained positively for CD8 (B); CD3ε (C); CD79a (D) and negative for CD56 (E); and CD4 (F). Atypical lymphoid cells also stained positively for bcl-2 (G) and bcl-6 (H) and also EBER following in situ hybridization (I) (×100).

Table 1 Antibodies used, their specificity and results

Antibodies	Sources (dilution)	Specificity	Results
CD20/CD3 (double staining)	Dako (1:100)	B-/T-cells	+/+
CD45RO	Dako (1:200)	Leukocytes	+
CD79a	Dako (1:100)	B-cells	+
CD45	Dako (1:200)	T-cells	+
CD5	Novocastra (1:200)	T-cells and B-cell subset	+
CD8	Dako (1:200)	T-killer cells	+
CD4	Dako (1:200)	T-helper cells	−
CD56	Dako (1:200)	Natural killer cells	−
CD68	Dako (1:200)	Macrophages	+
Anti-kappa	Dako (1:200)	Kappa light chain	−
Anti-lambda	Dako (1:200)	Lambda light chain	−
Keratin (AE1/3+Cam 5.2)	Chemican International (1:50)	keratinocytes	−
S-100	Dako (1:200)	S-100 protein	−
Bcl-2	Novocastra (1:80)	Anti-apoptptic death protein	+
Bcl-6	Novocastra (1:30)	Bcl-6 putative transcription factor	+

Kim in 1977,[20] was used to describe two morphologically distinct lymphomas located in the same anatomical location. More recently, the definition has been refined in order to include cases with morphologically complex intermingling of two immunologically distinct lymphomas/cellular populations in the same location.[21] Composite lymphoma may be two distinctly demarcated types of non-Hodgkin's lymphoma (NHL) or the rare association of Hodgkin's lymphoma with a form of NHL within a single organ or tissue.[22] Most examples of such lesions are thought to arise from two different clones; occasional cases may be related clonally and represent progressive evolutionary stages of the same neoplastic clone.[23] Reported cases of composite lymphoma have, mostly, pertained to single clonal B-cell disorders, particularly follicular lymphoma and lymphocytic lymphoma, lymphomas which can reflect a different morphology and a different immunophenotype to each other and featuring a notable progression of the disease and/or further differentiation of the neoplastic clone.[13,19,20] From a thorough review of the English-language medical literature, to the best of our knowledge, only a few cases of composite lymphomas involving both T and B lineages would appear to have been reported,[13–18] and of these reports, only one referred to a lesion that occurred in the head and neck region, it describing a composite lymphoma of myocosis fungoides and chronic lymphocytic leukemia affecting the skin of an earlobe.[17]

In our study, two morphologically distinct populations of atypical lymphoid cells were identified to have been present in the sample of biopsied tissue. Furthermore, these two morphologically distinct populations of lymphoid cells were confirmed, immunologically (by way of double immunohistochemical staining), to be either B- or T-cell in origin. Further, these atypical lymphoid cells of a B-cell origin were suggested to derive from a DLBL based upon morphological and immunohistochemical findings. On the other hand, the atypical lymphoid cells noted in this current report are characterized by frequent angioinvasion as well as extensive necrosis, and have been identified as ACTL in the REAL classification. Therefore, a composite lymphoma of ACTL and DLBL would appear to have been identified for the present case. To the best of our knowledge, this may be the first reported case of an intra-oral composite lymphoma. Furthermore, our case also appears to be unique in that, again, to the best of our knowledge, it would appear to be the first composite lymphoma featuring a combination of ATCL and DLBL, although whether the two cellular populations belong to the same neoplastic clones or to two different clones remains to be identified using more advanced molecular genetic techniques.

Several mechanisms contributed for the pathogenesis of composite lymphoma are under consideration. Four possible mechanisms were proposed by Medeiros and Stetler-Stevenson (1992),[24] namely: (1) mutations at the stem cell level; (2) shared genetic predisposition; (3) exposure to a common carcinogen; and (4) unknown humoral agent(s) secreted from the first neoplasm may foster emergence of a second neoplasm. Other explanations have been suggested that the second lymphoma may be therapy-related,[25] and that the two lymphomas occur in a patient only by chance.[19,26] In any event, the pathogenesis under-

lying composite lymphoma remains unclear at present.

According to a WHO classification of hematological malignancies, an immunophenotypical analysis of extranodal NK/T-cell lymphoma, in the nasal region is most likely to reveal CD56+, CD3ε+ and EBV+,[12] although, it may also be an unusual EBV+, CD56- cytotoxic T-cell phenotypic NK/T-cell lymphoma.[11] Most investigators include lymphomas that demonstrate a CD3ε+, CD56- cytotoxic T-cell, EBV+ phenotype amongst the nasal type NK/T-cell lymphomas because these cases show a similar clinical progression to cases featuring CD56 expression.[11] Interestingly, the immunohistochemical analysis of the current case has been confirmed to be CD3ε+, CD56- cytotoxic T-cell (CD8+) and EBV+; therefore, this reported case study is suggested to be a rare example of cytotoxic T-cell (CD8+) phenotypic NK/T-cell lymphoma. In summary, this is an infrequent case of composite lymphoma: ACTC (CD8+ cytotoxic/suppressor T-cell) and DLBCL associated with the EBV.

T-cell-rich B-cell lymphoma (TCRBCL) is a large B-cell lymphoma type, morphologically characterized by the presence of a small number of neoplastic large B-lymphocytes dispersed in a reactive infiltrate consisting mainly of polyclonal T-cells, non-epitheloid histiocytes and plasma cells.[27] The present case, however, cannot be diagnosed as TCRBCL due to the presence of angioinvasion and the characteristic necrosis pattern, such features not having been observed for previous cases of TCRBCL.[27] Furthermore, the high frequency of atypia of the nuclei of the lymphoid cells of T-cell origin, as observed in our case, has not been a characteristic finding for previous TCRBCL cases. Finally, the large number of B-cells originating from lymphoid cells that were observed for our present case would also tend to not implicate TCRBCL.

EBV is highly associated with peripheral T-cell lymphoma, especially amongst patients in the Asian region, and less frequently so with B-cell non-Hodgkin's lymphoma.[28] Following in situ hybridization, EBERs were detected in tumor cells from this patient suggesting that EBV might be associated with the etiology of the lymphomagenesis, although its role as regards causality and disease progression as opposed to a role as a passenger continues to be controversial. Furthermore, tumor necrosis is a constant feature of ATCL, and such necrosis may not only be induced by lymphoid cell angioinvasion but may also result from the EBV induction, by virally infected neoplastic lymphocytes, of increased levels of cytokine production including tumor necrosis factor.[29]

Of interest in this case is the finding that both bcl-2 and bcl-6 proteins were able to be positively stained for, both bcl-2 and bcl-6 being implicated with cell-cycle regulation amongst B-cell lymphomas.[30] It has been previously reported that the bcl-2 gene has revealed rearrangement in less that 5% of cases of primary diffuse large cell lymphoma[31] whereas bcl-6 rearrangement was suggested to be strongly correlated with extranodal diffuse large cell lymphoma.[32] On the other hand, the bcl-2 protein has been reported to correlate with tumor apoptosis and proliferation in examples of peripheral T-cell lymphomas.[33] Bcl-6 protein has also been detected in peripheral T-cell lymphomas.[34]

Clinically, MNL tends to present, most frequently, as a neoplasm of T-cell origin[3,4] (such as ACTL), and occasionally similarly to neoplasms of B-cell origin.[5-8] Our case appears unique in that it is a case presenting as a MNL of both T- and B-cell origin. For cases of MNL, an adequate biopsy is essential, the biopsy should extend deeply and be repeated if necessary, in order to obtain a sufficient quantity of material that is uncontaminated by superimposed tissue that may be inflamed or undergoing necrosis. This was especially the case for our patient with her substantial palatal involvement.

Despite ATCL being a potentially lethal disease, with early diagnosis and adequate therapy there remains every possibility for a good long-term remission.[2] Several different approaches have been suggested for ATCL treatment, these including immunosuppressive drugs, radiotherapy either alone or combined with chemotherapy or chemotherapy alone.[2] For the present case, although we deemed it to be a composite lymphoma, we adopted the treatment protocol of chemotherapy alone with the patient showing a partial response, although unfortunately, the patient did not complete the whole treatment course and she was lost to follow-up.

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