Clinical Case Report

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Oral and maxillofacial non-Hodgkin lymphomas

Case report with review of literature

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Abstract

Rationale: Lymphomas take up about 14% of all head-neck malignancies, out of which 97% are non-Hodgkin lymphomas (NHL). The clinical courses, treatment responses, and prognoses of NHLs vary with different subtypes and anatomic sites. In the Chinese population (including the Taiwanese), head-neck NHLs are often seen with the tonsils, nasal cavity, nasal sinus, and the nasopharynx. However, oral NHLs are relatively rare. Delay of diagnosis is also often seen in clinical practice. Thus, we present 4 cases with delayed diagnosis of oral maxillofacial NHLs and discuss their clinical manifestations so as to draw a clue that can remind the doctors to take biopsies in time.

Patient concerns: Four cases, including 3 males and 1 female aged between 43 and 70 years old with oral lesions (ulcerations and/or masses) and accompanying cervical lymphadenopathies and/or skin erythemas presented to the Department of Oral and Maxillofacial Surgery, the First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China from January 2010 to January 2015.

Diagnoses: The diagnoses of non-Hodgkin lymphomas were made by pathology, including nasal type extranodal NK/T-cell lymphoma, mycosis fungoides, subcutaneous panniculitis-like T-cell lymphoma, and extranodal marginal B-cell lymphoma of mucosa-associated lymphatic tissue. Their clinical courses until confirmed diagnosis varied between 2 months and 1 year and the follow-up/survival time from diagnosis ranged between 2 and 24 months. None of the biopsies was taken at the patients' initial medical consultations.

Interventions: Cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP) and Rituximab, CHOP (R-CHOP) regimens were given to 2 (Cases 1 and 4) and 1 patient (Case 3), respectively. One patient refused further treatment.

Outcomes: Two patients, including the one who refused treatment, died at 2-2.5 months from diagnosis. The other two patients survived until their last follow-ups at 13 and 24 months from diagnosis, respectively.

Lessons: Oral lesions with aggressive growth patterns, multiple lymphadenopathies, and comorbid systemic skin lesions, elevated serum lactate dehydrogenase and poor response to medical therapies should warn the doctors of the possibility of malignancy and the necessity of biopsy. Excisional biopsy without sacrificing organs or functions should be preserved for patients whose pathological diagnoses cannot be established through aspiration or punch biopsy.

Abbreviations: CNB = core needle biopsy, DLBCL = defuse large B-cell lymphoma, ENS = extracapsular neoplastic spread, FNA = fine needle aspiration, LDH = lactate dehydrogenase, NHL = non-Hodgkin lymphoma, SCC = squamous cell carcinoma.

Keywords: biopsy, head neck, maxillofacial, non-Hodgkin lymphoma, oral

1. Introduction

Lymphomas take up about 14% of all head-neck malignancies, out of which 97% are non-Hodgkin lymphomas (NHL) with a number of extranodal onset over 2 times that of Hodgkin lymphoma, according to a recently published cross-sectional study based on large sample size.[1] Most head-neck NHLs are B-cell lineage, with defuse large B-cell lymphoma (DLBCL) being the most commonly seen subtype,[2–4] followed by small cell NHLs and Burkitt lymphoma.[4] The clinical courses, treatment responses, and prognoses of NHLs vary with different subtypes and anatomic sites. In the Chinese population (including the Taiwanese), head-neck NHLs are often seen with the tonsils, nasal cavity, nasal sinus, and the nasopharynx, with the ranking order varying in different reports.[2,5,6] However, only a very small part of head-neck NHLs presents within the oral cavity.[2,7,8]

2. Methods

From January 2010 to January 2015, 4 patients were hospitalized to the Department of Oral and Maxillofacial Surgery of the First Affiliated Hospital of Nanchang University for oral lesions and accompanying symptoms (e.g., cervical lymphadenopathies and skin lesions) which were refractory to previous treatments at other hospitals. Pathological diagnoses were established through biopsies as NHL according to the 2008 WHO Classification of Lymphoid Neoplasms. Chemotherapy was given or at least suggested as the further treatment and follow-ups were continued

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Table 1

Patient information.

	Gender	Age (y)	Initial symptom	Initial consultation		Site of lesions			Pathology	OTD time (mo)	Treatment	F/S time (mo)
				Diagnosis	Treatment	Oral	Skin	Lymphadenopathy				
Case 1	Male	70	Lip mass	Infection	Antibiotics	Yes	Yes	Yes	SPLTCL	12	CHOP	2.5
Case 2	Male	45	Skin erythema	Psoriasis	Steroid	Yes	Yes	Yes	MF	12	NONE	2
Case 3	Female	55	Oral ulceration	Lymphadenitis	Antibiotics	Yes	No	Yes	EMBCL-MALT	2	R-CHOP	13
Case 4	Male	43	Oral cornu ulceration	Infection	Antibiotics	Yes	Yes	No	ENKTCL-NT	2	CHOP	24

EMBCL-MALT = extranodal marginal B-cell lymphoma, EMBCL-MALT = extranodal marginal B-cell lymphoma, ENKTCL-NT = extranodal NK/T-cell lymphoma, nasal type, F/S Time = follow-up/survival time after diagnosis, MF = mycosis fungoides, OTD Time = onset-to-diagnosis time, SPLTCL = subcutaneous panniculitis-like T-cell lymphoma.

until January 2017. A summary of the patient information is seen in Table 1. These cases are reported in this article with a review of the literature on the clinical characteristics and biopsy method of this rare group of malignancies. Although a large proportion of NHL patients initially present at surgeons' offices,[3] the pathology and treatment of NHLs are often beyond the scope of surgeons' work in general practice as most lymphomas are treated with radio- and/or chemotherapy once they are pathologically confirmed, these issues are thus not discussed in this study. The use of the clinical data in this study has been approved by the Ethical Board of the First Affiliated Hospital of Nanchang University.

3. Case presentation

3.1. Case 1

A 70-year-old man was hospitalized in January 2010 with a mass at the right angulus oris for 1 year, which enlarged gradually and developed facial skin ulceration 4 months after onset. He had been diagnosed with "infection" and treated somewhere else with intravenous levofloxacin 0.2 g twice per day and intravenous ceftriaxone sodium 0.2 g twice per day combined with local application of 10% sodium chloride for 2 weeks, in spite of which the ulceration expanded with newly developed dark red soft tissue masses in his left shoulder and 4 limbs.

3.1.1. Physical examination. There was a skin ulceration sized 4×3 cm at the right angulus oris and the lower lip, where serous effusion and black crust could be seen. The lesion had an ill-defined margin and was tender to palpation. The patient had a 2nd degree trismus and extensive hyperemia of the surrounding facial skin. Multiple lymphadenopathies were palpable in the right submental, submandibular regions and the deep neck (Fig. 1). Multiple soft tissue masses were also seen in other regions of the body.

3.1.2. Laboratory examination. WBC 3.5×10^9/L, RBC 3.10×10^9/L, Hb 92 g/L; ASO 330KU/L, IgG 20.50 g/L, IgA 4.99 g/L, RF (+), CRP (+), pANCA (−), cANCA (−); no abnormality was revealed with bone marrow puncture biopsy.

3.1.3. Biopsy. Excisional biopsy of a lymph node was taken from the neck following the failure to establish a confirmed pathological diagnosis through punch biopsy.

3.1.4. Pathology. Microscopically, there were neoplastic cells angiocentrically distributed in a typical flower-ring-like pattern among subcutaneous fat lobules. Immunohistochemical (IHC): CD3 (2+), CD45Ro (2+), CD4 (−), CD8 (3+), TIA-1 (+), CD30 (+), CD56 (−), EMA (−), CD138 (−), CK (−), and CD79a (−) (Fig. 2).

3.1.5. Pathological diagnosis. Subcutaneous panniculitis-like T-cell lymphoma

3.1.6. Treatment and outcome. No relief of symptoms was achieved after 8 weeks' cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP) chemotherapy and the patient died 2 weeks after giving up further treatment.

3.2. Case 2

A 45-year-old man was hospitalized for extensive swelling of the upper lip for 3 months. He had had a round erythema of about 0.5 mm in diameter on his left shoulder 1 year earlier, followed by

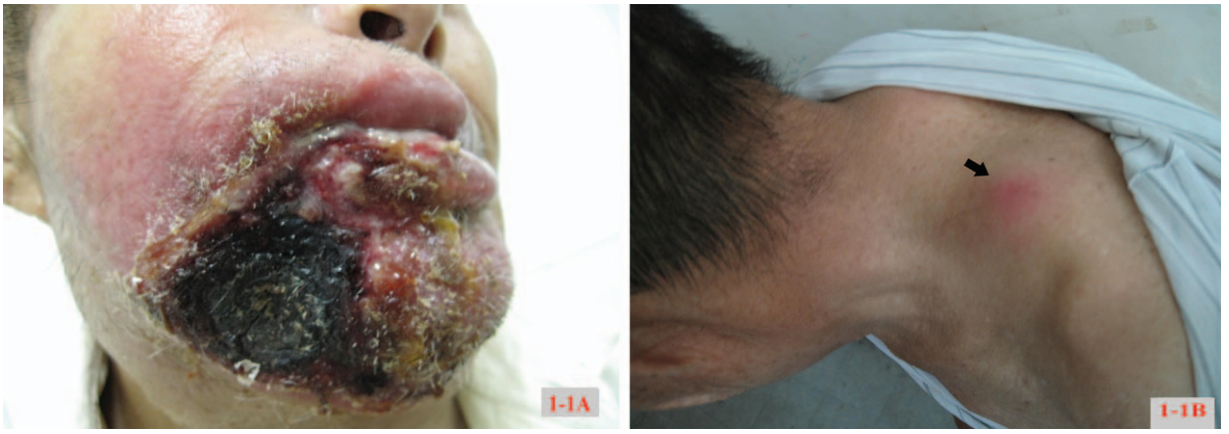

Figure 1. Clinical findings. Large-sized ulceration of the right angulus oris and the lower lip covered with black crust. The patient's right face is extensively hyperemic (A). Cervical lymphadenopathies are also shown (arrow in B).

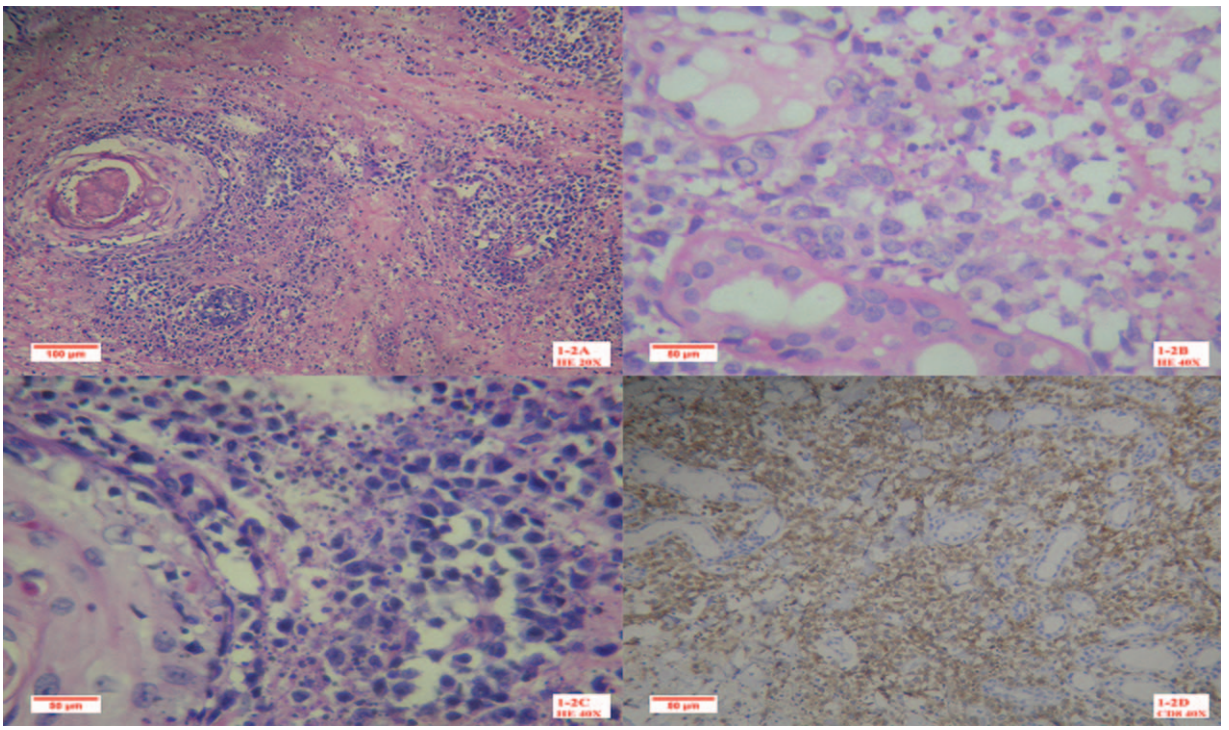

Figure 2. Pathological images. Neoplastic cells distributed angiocentrically in a flower-ring-like pattern on HE staining (A, ×20). The neoplastic cells are distributed among the subcutaneous fat lobules (B, ×40) with necrosis and nuclear fragmentation observed (C, ×40). The tumor cells are positive for CD8 with IHC (D, ×20). IHC = immunohistochemical.

development of multiple nodules and thickened erythemas with white scaling and pruritus on his abdomen and lower limbs. He had been diagnosed with psoriasis of erythroderma type in some other hospital and treated with steroid ointment (details unknown). The pruritus partially relieved following treatment but recurred after drug withdrawal.

3.2.1. Physical examination. There was a mass in the upper lip at the $\underline{2-1|1-3}$ extension, which was solid to palpation with a clear border. The skin and the mucosa of the upper lip were both dark red in color. There were also multiple erythemas and nodules with well-defined margins and diverse sizes and shapes covered with white scaling on his back, abdomen, lower limbs, etc. (Fig. 3). There were multiple lymphadenopathies which were solid to palpation in the bilateral submandibular areas and the deep neck.

3.2.2. Biopsy. Excisional biopsies of the lip mass and a skin lesion of the abdomen were taken.

3.2.3. Pathology. The pathological examination demonstrated diffuse medium-sized neoplastic cells with abundant cytoplasm. Invasion of epithelium by neoplastic cells is seen in some area. IHC staining: CD3 (2+), CD45Ro (3+), CD4 (2+), CD8 (−), CD20 (−), CD56 (3+), HMB45 (−), S100 (−), Melan-A (−), CD79a (−), CK (−), Bcl-6 (−), CD34 (+), KI-67 of about 5% and TIA-1 (+) (Fig. 4).

3.2.4. Pathological diagnosis. Mycosis fugoides.

3.2.5. Treatment and outcome. The patient refused treatment and died 2 months after diagnosis.

3.3. Case 3

A 55-year-old woman presented with an ulceration of the left floor of the mouth for 2 months. The lesion had an onset as a small nodule with pain that influenced eating. It was initially diagnosed as acute lymphadenitis and treated with antibiotics (details unknown) for 1 month, after which the pain severed and the nodule ulcerated with a foul smell.

3.3.1. Physical examination. The patient had a 2nd degree trismus. There was an ill-bordered ulceration of the left mouth floor mucosa at the $\overline{|3-7}$ dimension sized about 4×2.5 cm, which was tender to palpation and covered with whitish to yellowish pseudomembrane. Multiple lymphadenopathies were palpable in the left submental and submandibular areas (Fig. 5).

3.3.2. Laboratory examination. WBC 2.42×10^9/L, procalcitonin 0.14 ng/mL, CPR (+), AST 71U/L.

3.3.3. Biopsy. Multiple punch biopsies were taken at the margin of the lesion.

3.3.4. Pathology. Small-sized atypical lymphoid cells with irregular nucleic types were disseminatedly distributed in the neoplastic tissue. Lymphoepithelial changes were seen resulting from the invasion of neoplastic cells into the salivary ducts. IHC staining revealed CD3 (−), CD4 (−), CD8 (−), CD56 (−), CD20 (2+), CD79a (+), CK (−), Ki-67 of about 2%, Granzyme B (−), and Epstein-Barr virus-encoded RNA (−) (Fig. 6).

3.3.5. Pathological diagnosis. Extranodal marginal B-cell lymphoma of mucosa-associated lymphatic tissue.

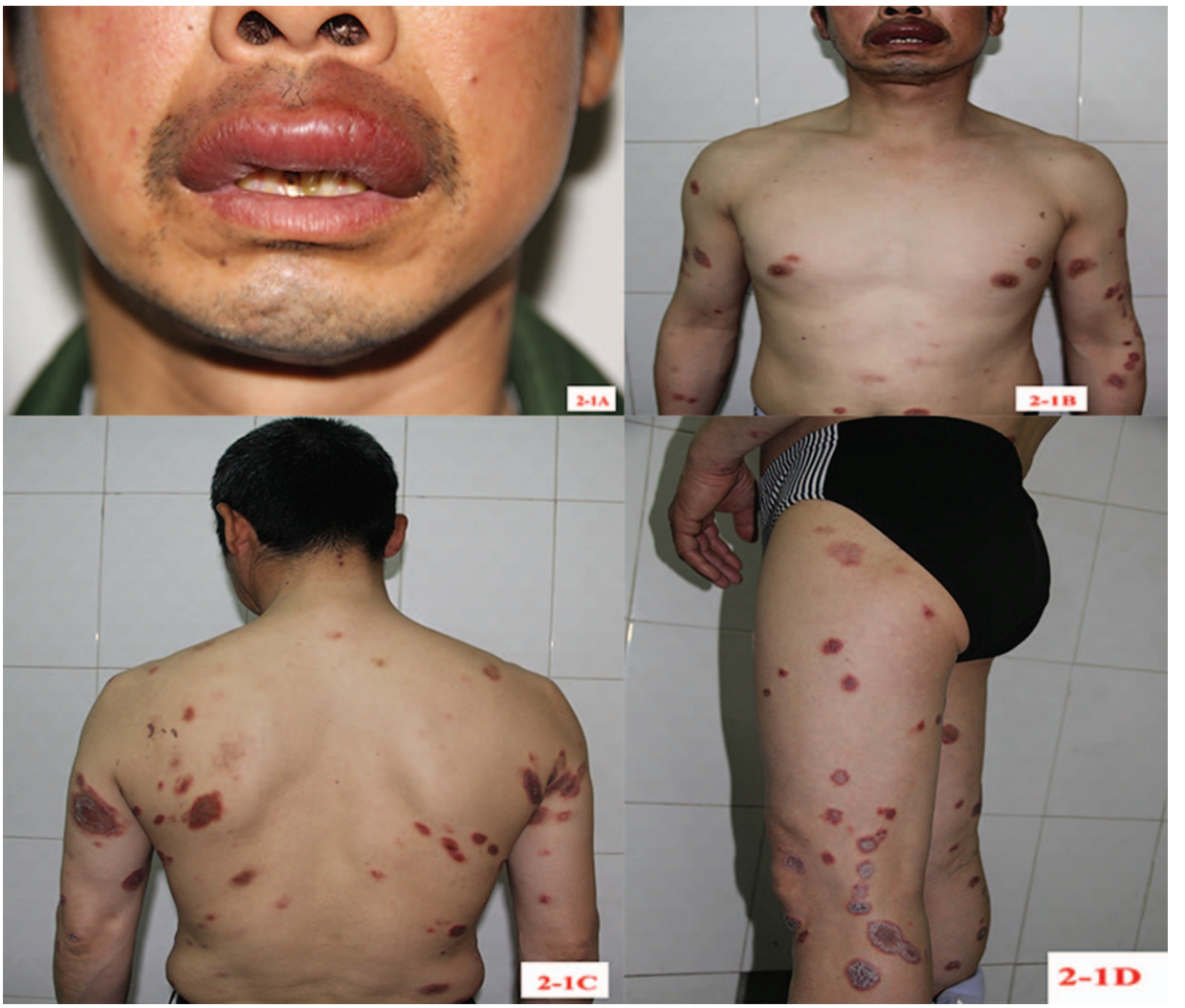

Figure 3. Clinical findings. Swelling of the upper lip (A) and systemic skin erythemas (B–D) of the patient. Note the well-bordered skin lesions covered with white scaling.

3.3.6. Treatment and outcome. The patient had R-CHOP chemotherapy and survived over 30 months (after diagnosis) at the last follow-up.

3.4. Case 4

A 43-year-old man complained extensive swelling and ulceration with his palate mucosa complicated with loosening of his anterior maxillary teeth for 2 months. His disease experienced a rapid progress, although he had been previously treated with antibiotics in some other hospital for "infection."

3.4.1. Physical examination. There was extensive swelling and ulceration of the mucosa of the whole hard palate and part of the soft palate. The lesion was dark red in color, soft and tender to palpation, and covered with whitish pseudomembrane. The margin of the ulceration was ill-defined from the peripheral normal mucosa. The patient had mobility of teeth 2–1|1–3 to the 3rd degree with a pain to percussion. The labial side of the anterior maxillary gingiva was nodulated with a slice-shaped neoplasm at the 2–1|1 vestibular groove. Systemic physical examination demonstrated a round skin erythema protuberant at the area of the right brachial biceps. The skin lesion was about 5 cm in diameter with a clear boarder, covered with yellowish crust and solid and tender to palpation (Fig. 7).

3.4.2. Radiology. As was seen on the cone-beam computed tomographic images, there was complete exposure of the dental roots of 2–1|1–3 teeth due to the corruption of the labial side of the alveolar bone (Fig. 8). PET-CT scanning discovered multiple lymphadenopathies in the left postauricular area and the left deep upper neck (Level II). Hypermetabolism of fluorodeoxyglucose was detected at the left roof of the nasopharynx and the left inferior meatus.

3.4.3. Biopsy. Both the mucosa and the skin lesions were surgically resected for pathological examination.

3.4.4. Pathology. Microscopically, the tumor grew in an angiocentric and invasive pattern with infiltration of abundant inflammation cells and diffusely spreading medium-sized atypical lymphoid cells (Fig. 9). The IHC staining showed CD3 (2+), CD4 (−), CD8 (−), CD56 (+), CD43 (3+), Granzyme B (2+), CD79a (−), KI-67 of about 50%, and TIA-1 (±). Epstein–Barr virus was positive to in situ hybridization for Epstein-Barr virus -encoded RNA (Fig. 10).

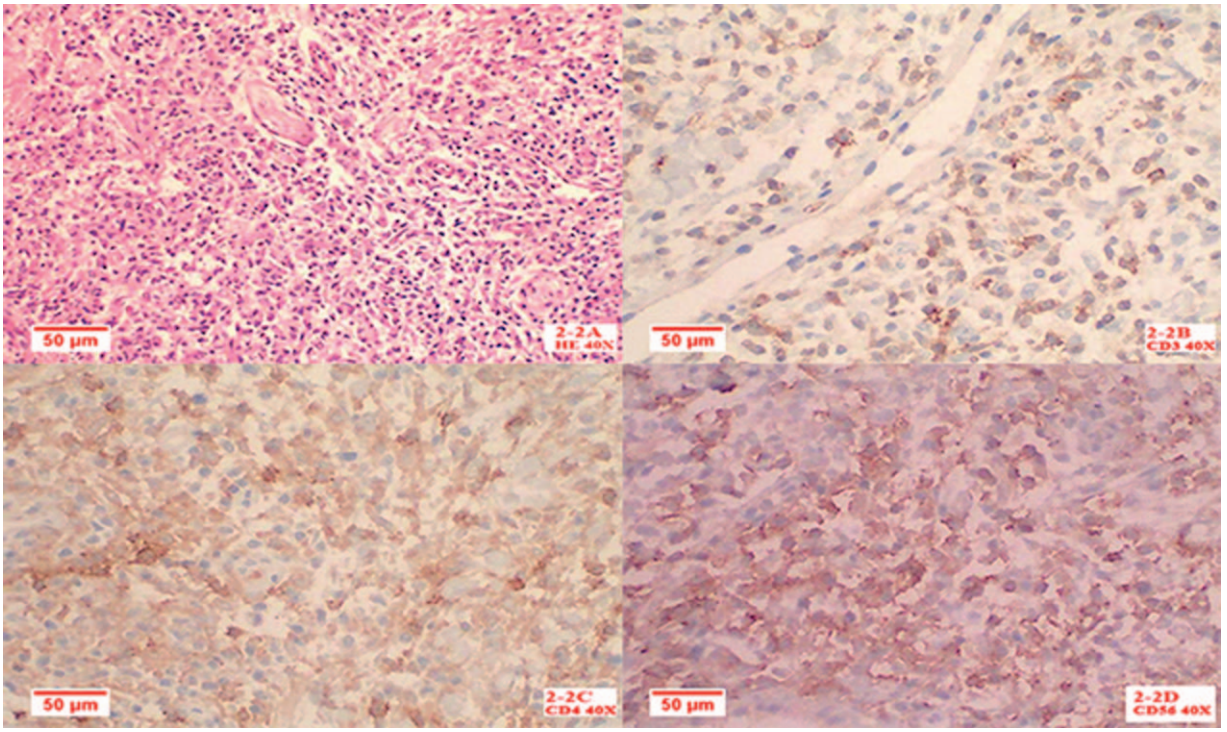

Figure 4. Pathological images. HE staining showing medium-sized neoplastic cells with abundant cytoplasm, invading some of the epithelial area (A, ×40). The neoplastic cells are positive for CD3 (B, ×40), CD4 (C, ×40), and CD56 (D, ×40) on IHC. IHC = immunohistochemical.

3.4.5. Pathological diagnosis. Extranodal NK/T-cell lymphoma, nasal type.

3.4.6. Treatment and outcome. The patient was treated with surgical excision of the palatal and skin lesions followed by CHOP chemotherapy. He was alive without relapse of disease at the final follow-up 24 months after diagnosis.

4. Discussion

4.1. Clinical manifestations

Local swelling, mass, ulceration, tooth mobility, skin lesion, pain, and lymphadenopathy were seen in our cases as are cited in literature as the most commonly seen symptoms of NHLs.[4,6,8–10] Radiologically, the most often cited imaging findings on CT scanning include hypodense lesions with diffuse boundaries, bone resorptions, and tooth displacements.[4] Bone destruction, which is seen in our Case 4, is also strongly indicative of aggressive malignancies such as ENKTL-NT.[11] The involved lymph nodes, if any, are often isodense[12] and homogenous on plain CT films, with a variable degree of enhancement following the injection of contrast.[13] On magnetic resonance imaging, imaging features of lymph nodes which are most characteristic of malignancies such as central necrosis and extracapsular neoplastic spread (ENS) are also often seen with incidence rates varying in different subtypes.[14] The elevation of serum lactate

Figure 5. Clinical findings. An ulceration covered with whitish pseudomembrane located on the left floor of the mouth (A) and multiple lymphadenopathies of the submental and submandibular regions (arrow in B) are shown.

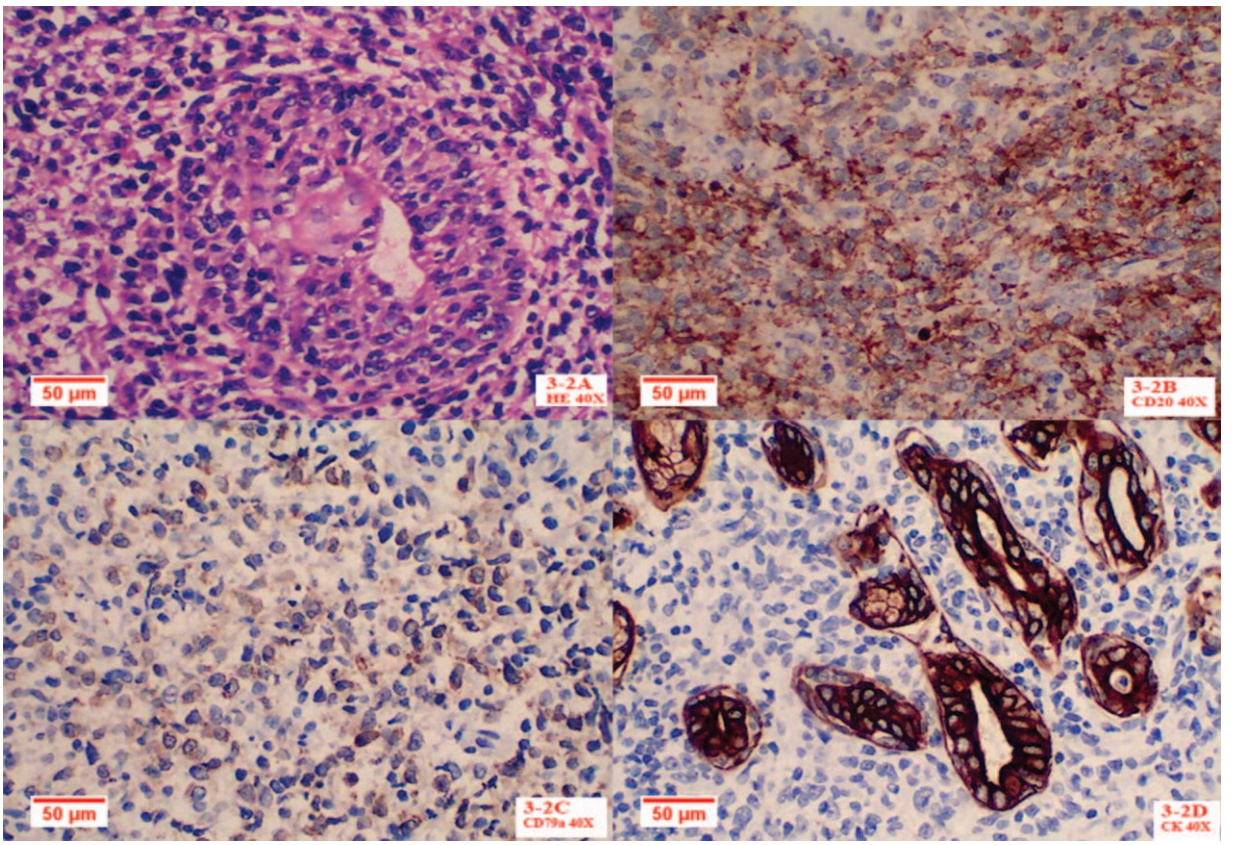

Figure 6. Pathological images. Small-sized atypical lymphoid cells with irregular nucleic types were diffusely distributed in the neoplastic tissue on HE (A, ×40). The neoplastic cells are positive for CD20 (B, ×40) and CD79a (C, ×40) but negative for CK (D, ×40).

dehydrogenase (LDH) is also frequently seen in lymphoma patients, which is not only a clue of lymphoma but also an indicator of a worse prognosis.[15]

4.2. Delay of diagnosis

In spite of all the clinical and radiological features mentioned above, none of them is specific for lymphoma, especially when the lesions are still small or solitary with a short history. Thus, patients with early NHLs are often misdiagnosed and treated with non-neoplastic diseases, such as infection and common skin disease as is the case with our patients. In fact, delay in the diagnoses of NHLs is not uncommonly reported in the literature, with a time interval from the onset of disease to the confirmation of pathology varying from months to decades,[16–18] within which our data fall (2 months in 2 cases and 1 year in the other 2 cases). Due to the lack of earlier clinical data, it is now impossible to know whether the initial appearances of the lesions of our patients were "aggressive" enough to remind their initially consulted doctors to take biopsies. The treatments for non-neoplastic diseases were also applied on these patients. The poor response could also have warned the need of biopsy taking. Besides, none of the 4 patients were tested for serum LDH at primary consultations, which, if done, could have reminded the doctors the possibility of malignant neoplasms in need of biopsy.

Above all, an oral lesion presented with an aggressive growth pattern (e.g., extensive swelling or ulceration, necrosis, bone destruction, and etc.), elevated serum LDH and/or poor response to treatments of non-neoplastic diseases (such as inflammations and/or infections) should be biopsied as soon as possible.

4.3. Biopsy methods

Although methods such as fine needle aspiration biopsy (FNA) and core needle biopsy (CNB) biopsy have been proved adequate enough for further pathological examinations,[13,19,20] for exposed skin or mucosa lesions, punch biopsy is logically the most convenient, for it can be done under a direct visual without a need of ultrasound guide. Excisional biopsies, such as tonsillectomy, submandibulectomy, and lymphadenectomy,[13,21,22] are also useful. Although 3 of our 4 patients underwent excisional biopsies, it is not appropriate to emphasize the role of surgery as a "treatment." Instead, it should only be preserved as the last shot when pathological diagnosis cannot be established due to extensive necrosis and/or diffuse infiltration of inflammatory cells in the samples obtained by needle aspiration or punch biopsy. The extension of surgical excision must also be limited so that it does not cause severe damage to organs or sacrifice of important functions.

4.4. Limitations of our study

There has been a large quantity of literature discussing the clinical features, pathology, treatment, and prognosis of oral and maxillofacial (OMF) lymphoma. However, the small number of patients involved in our study made it insufficient to compare the outcome with the literature. We provided these cases because OMF lymphoma is not quite so often seen in our department and we did see worrisome delay in biopsy and diagnosis of these patients, so that it is a very good lesson for oral and maxillofacial surgeons to learn.

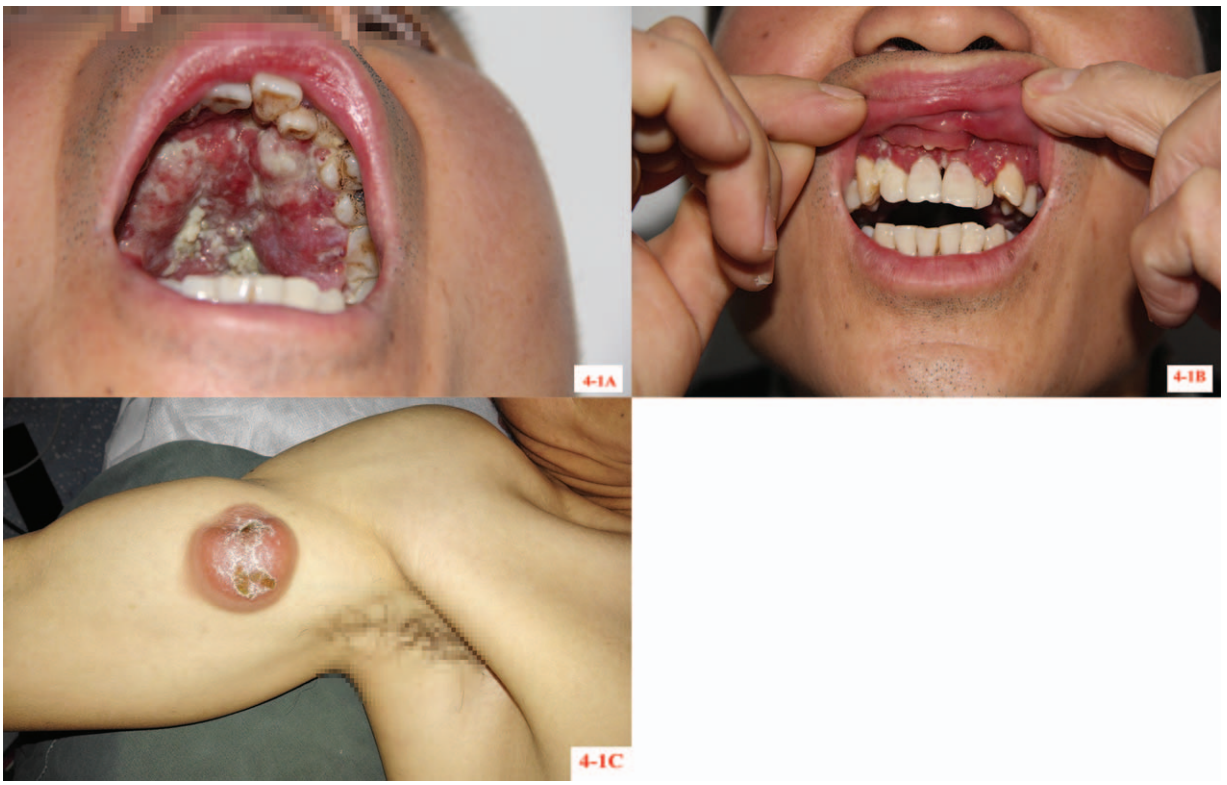

Figure 7. Clinical findings. A, Extensive swelling and ulceration of the mucosa of the hard palate covered by whitish pseudomembrane with an ill-defined margin. B, The involved anterior upper gingival mucosa with a slice-shaped neoplasm at the labial side. C, A well-bordered round skin erythema covered with yellowish crust at the area of the right brachial biceps.

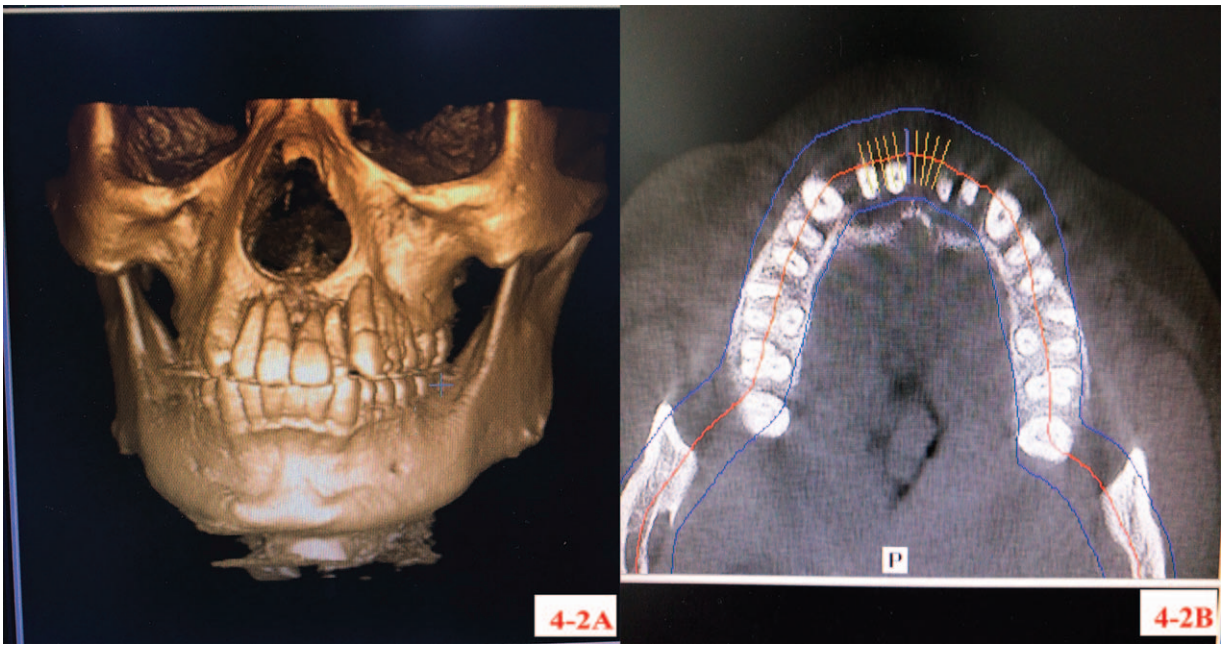

Figure 8. CT images. A and B, Exposure of the upper anterior dental roots due to destruction of the maxillary alveolar bone.

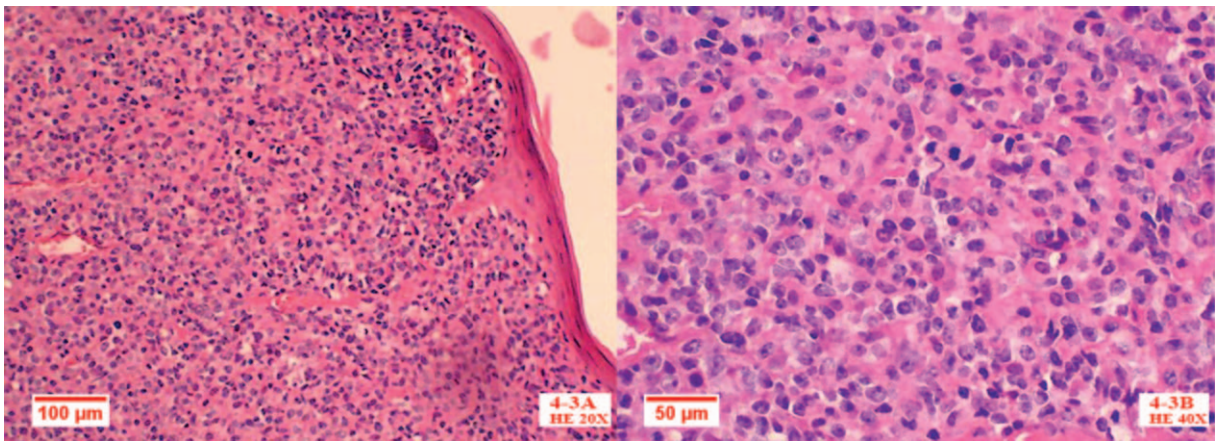

Figure 9. HE staining. Infiltration of abundant inflammatory cells and atypical lymphoid cells (ALC) arranged in an angiocentric pattern. A, HE staining (×20) with dilated vessels observed (black arrow heads). B, HE staining (×40) showing the infiltration of small-to-medium sized cells with irregular nuclei.

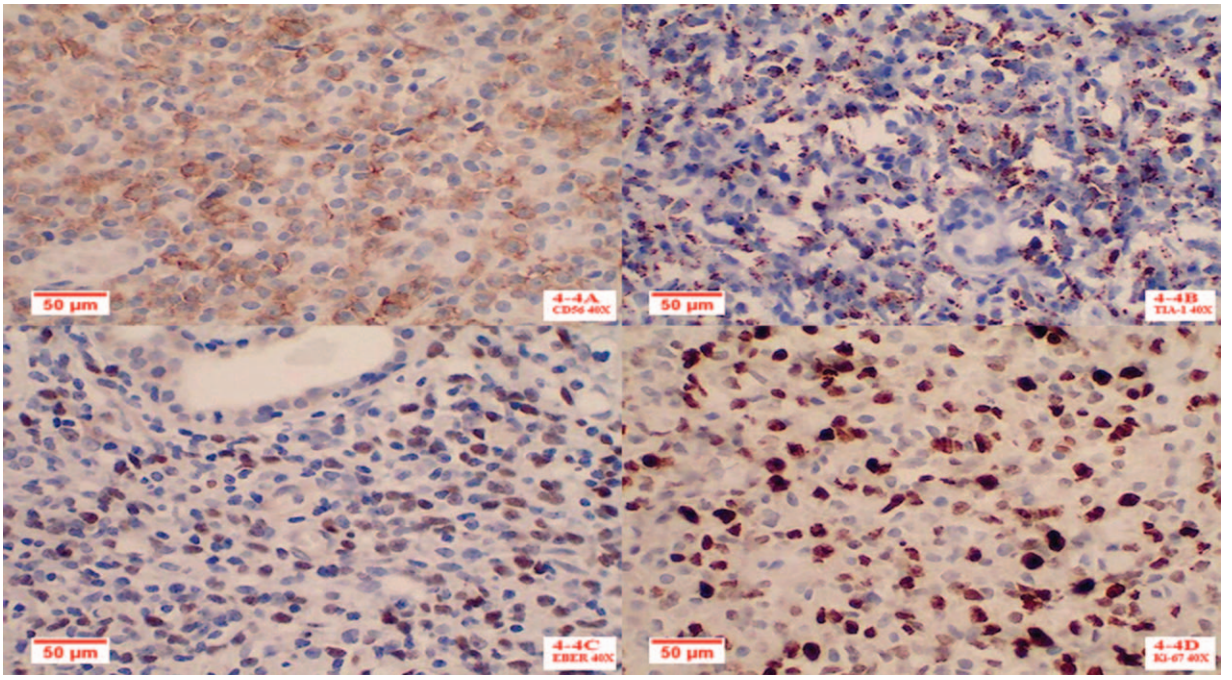

Figure 10. Immunohistochemical staining. Immunohistochemical staining (×40) with positive CD 56 (A), TIA-1 (B), EBER (C), and a labeling index of about 50% of Ki-67 (D).

5. Conclusion

Oral lesions with aggressive growth patterns, multiple lymphadenopathies and comorbid systemic skin lesions, elevated serum LDH, and poor response to medical therapies should warn the doctors of the possibility of malignancy and the necessity of biopsy. Excisional biopsy without sacrificing organs or functions should be preserved for patients whose pathological diagnoses cannot be established through aspiration or punch biopsy.

Acknowledgments

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