INTRODUCTION

Lymphomas are unusual malignant neoplasms that affect the lymphoreticular system and take up about 14% of all head and neck malignancies [1]. These tumours are morphologically divided into two groups: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), out of which, 97% are NHL [2]. Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of NHL, which commonly occur in men rather than in women, especially in middle-aged to elderly. It is a fast-growing lesion, aggressive and fatal if left untreated, but with early diagnosis and appropriate treatment, around two-thirds of the patient affected can be cured.

Despite that, DLBCL is often clinically ‘misdiagnosed’ or being a ‘missed diagnosis’. The manifestation often mimic other common illnesses such as infections or other benign lesions. Radiologically the radiolucent area may resemble endodontic lesion, periodontal pathology including odontogenic cyst and tumour.

Diagnosis of chronic oral ulceration is always challenging and has been the source of difficulty because of the remarkable overlap in their clinical presentations, thus biopsy of the lesion is a mandatory to establish a diagnosis [3].

CASE PRESENTATION

A 22-year-old gentleman, a college student with no known medical illness, presented with complaint of three-month painful ulcer over the right soft palate, which was aggravated by opening of the mouth during talking and chewing food. It was also associated with bilateral neck swelling which had similar onset with the sore throat. The symptoms worsened with odynophagia and poor oral intake for the past week at which he was
unable to tolerate a solid diet, and only taking semi-solid and fluids. He also had an intermittent, low-grade fever which not associated with chills, rigours or night sweats and resolved after taking paracetamol. There was no significant family history of malignancy, no weight lost or any history of prolonged cough. He was a non-smoker and there was no high-risk behaviour.

On general examination, he was found to be moderately built adult with good hydration, not anaemic nor septic looking. Vital signs were within normal limits with no signs of anaemia. There were multiple bilateral cervical lymph nodes palpable, largest was in right level II, measuring 3 x 3 cm. No axillary and inguinal lymph nodes palpable. All cranial nerves were intact.

Intraoral examination revealed an ulcer with irregular edge over the right soft palate, measuring 3 x 3 cm with uvula deviated to the left. The edge of the ulcer was sloping with the centre lesion being perforated through and through (Figure 1). Palpation revealed the ulcer to be tender with no discharge and no contact bleeding. Right tonsil was enlarged grade 2 and extend inferiorly to the base of the tongue. The flexible nasopharyngolaryngoscopy was normal.

Chronologically prior to his presentation to our centre, the patient was managed in another hospital nearby his college. After 2 weeks of admission, he requested to be transferred to our hospital due to logistic reason. Patient was investigated before for bilateral non-exudative tonsillitis with infected ulcer of the soft palate. Infectious mononucleosis was one of the differential diagnosis that was highly suspected due to his age, clinical history and presentation, thus he was given 2 weeks course of antibiotics intravenously with analgesics to reduce the symptoms of sore throat and odynophagia. However, due to the persistent ulcerative lesion over the soft palate, biopsy was taken from the right soft palate and histopathological examination (HPE) showed diffused infiltrates of malignant cells in the subepithelial stroma, large in size, hyperchromatic and amphophilic cytoplasm. There were apoptosis, frequent mitosis and necrosis present. However, no Hodgkin cell or Reed Sternberg cells were seen. Epstein-Barr virus (EBV) test was negative and tumour cells are positive for B-cell markers (CD20 and CD79a), hence the interpretation was DLBCL.

Nevertheless, because of the patient’s clinical presentations that appear well and responded with initial antibiotic given, the physician had requested for a second opinion from our in-house pathologist. The revised diagnosis was made cautiously as consistent with prominent B-cells proliferation, possible secondary to viral infection, advising for a close follow up of the patient and to repeat biopsy for re-confirmation of the diagnosis.

His blood investigations were normal except for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were both high; 16mg/L and 120mm/h respectively. His infectious screening such as Hepatitis B/C and HIV were non-reactive and serum lactate dehydrogenase (LDH) was not high (198 U/L).

During his subsequent follow-up, the symptoms reduced, however, both ulcer and the neck swelling did not resolve. He also developed other new swellings in the right neck level II and III. In view of the lymph node enlargements, another biopsy was discussed and arranged with other radiological investigations.

HPE of right cervical lymph nodes showed a diffuse pattern of medium-to-large sized neoplastic cells having moderately pleomorphic, round to oval vesicular irregular nuclei with 1-2 nucleoli and moderate clear cytoplasm. Sprinkled amongst them are larger cells with hyperchromatic irregular nuclei.
Mitoses and apoptotic bodies are easily seen. The neoplastic cells are immunoreactive to CD45, CD20, CD79a (strong), BCL6, c-myc, CD30, CD10 and MUM1 (weak). They are negative to CKAE1&AE3, BCL2 and T-cell markers. The proliferative index (Ki67) is about 90%. There are scattered reactive T cells in the background (Figure 2). The interpretation was aggressive B-cell lymphoma with differential diagnoses include CD30+ DLBCL NOS or high-grade B-cell lymphoma, double expressions (BCL2-/BCL6+/c-myc+). Molecular testing for double/triple hits high-grade lymphoma was not available in our centre.

Contrast-enhanced computed tomography scan (CECT) brain, neck, thorax, abdomen and pelvis revealed bilateral enlargement of tonsils with irregular right tonsil and presence of air pockets at the peritonsillar region, enlarged adenoid with hypodense lesion within, multiple enlarged cervical lymph nodes with necrotic centre at bilateral level II and III, largest at the right level II measuring 3.5 x 3 cm (Figure 3). Subcentimeter submental nodes and posterior cervical nodes also noted.

Bilateral parotid and submandibular glands were normal. There were no other nodal group or extra-nodal involvement seen. No other suspicious lesion was seen in the brain, bones and others.

**Figure 2** Diffuse, medium to large sized neoplastic lymphoid cells, having irregular nuclei, prominent nucleoli and moderate cytoplasm. Many mitoses are present. Also seen here are atypical large cells with hyperchromatic nuclei (H&E 400x). Inset is CD20 immunohistochemistry (400x)

**Figure 3** The CECT neck patient in axial (3a) and coronal (3b) views. 3a) The red arrow showing an irregular right tonsil with an enlarged hypodense right cervical lymph node level II measuring 3.5 x 3cm indicated by yellow arrow. 3b) The white arrow showing the presence of air pockets in the right hypodense peritonsillar region with hypodense lesion of the right tonsil shown by the black arrow.
A final diagnosis of DLBCL Stage 2E (oropharynx) was made and patient was subsequently started with six cycles of R-CHOP regimen in every three weeks (21 days). Follow-up examination of his oral cavity after completion with 6 cycles of chemotherapy revealed completely healed ulcer with profound fibrosis of right soft palate causing narrowing of the fauces over the affected side and slight uvula deviation to the left (Figure 4). His symptoms were much improved and he was able to tolerate orally well since then. Currently, he is disease-free on regular surveillance follow-up.

![Figure 4](image)

**Figure 4** A completely healed ulcer with fibrosis on the soft palate causing narrowing of the fauces (red arrow) and slight uvula deviation to the left (black arrow) post-completion 6 cycles of R-CHOP.

**DISCUSSION**

Lymphomas are solid malignant neoplasms that have a wide spectrum of clinical and pathological features. There are 2 types of lymphoma; HL and NHL, both respond to treatment differently. Two-thirds of the NHL cases presenting as lymph nodes enlargement (cervical, axilla, groins and elsewhere that are part of the immune system) while the remaining one-third of the NHL cases has been reported in the extranodal sites such as Waldeyer’s ring, oral cavity, oropharynx, gastrointestinal tract, testes, thyroid, skin, breast, bone, brain or any essential organ in the body. Head and neck are the second region most stricken by NHL after the gastrointestinal tract. The involvement of the oral cavity is rare and accounts for less than 3.5% of the cases reported. Although rare, they are the second mostly common malignancy in the mouth, constituting 2.2% of head and neck tumours [4].

Oral lesions of NHL can develop in the soft tissues or within the jaws. They appear as non-tender swellings usually affecting the vestibule, gingiva or posterior hard palate and develops slowly, mimicking a dental abscess of endodontic or periodontal origin [5]. In our case, the patient was diagnosed with extranodal NHL DLBCL stage 2E (oropharynx) which is considered rare manifestation of DLBCL.

Despite being aggressive in nature, DLBCL is considered potentially curable, whereby 3 out of 4 people are disease-free after treatment and about half are cured [6]. There are several subtypes of DLBCL, depending on histopathological characteristic, origins, EBV related as well as their genetic and immunophenotyping characteristic. Nevertheless, the cause of DLBCL is still not well understood [7-8].

In our case, the history and clinical presentation did not fit in any common presentation of DLBCL. The patient is young and immunocompetent, non-smoker with no family history of malignancy. He also denied any of B symptoms (Night sweats, unexplained weight loss, persistent fatigue) which highly suggestive of malignancy and his serum LDH was normal, hence the suspicion of malignancy is not prioritized. During the initial presentation, he had been treated with antibiotics and the symptoms showed some improvement. At that time, the working diagnosis was more of infectious in origins such as infectious mononucleosis, histoplasmosis, syphilitic ulcer or even intra-oral tuberculosis, although the later occurrence is quite rare.

However, the dilemma kicks in after the initial HPE of tissue biopsy from right soft palate revealed as DLBCL, although clinically and histologically not strongly suggestive. The initial HPE of the right soft palate in this patient only revealed immunopositivity in few markers (CD20 and CD79a) which are non-sufficient to diagnose DLBCL. DLBCL characteristically expresses CD45 and more pan-B cell markers such as CD19, CD20, CD22, CD79 and PAX5,
with other markers such as CD10, Bcl6, Bcl2, Ki67, CD43, CD5, CD30, IRF4/MUM1 and p53. Due to the large number of subtypes of lymphomas, their heterogenous nature as well as their complex relationships, the diagnosis and classification of lymphomas continue to be a challenge histologically [9]. Hence, a multi-disciplinary team discussion was made among hemato-oncologist, surgeons and pathologist. Eventually, the decision to take the second sample from the right cervical lymph nodes concluded the final diagnosis and treatment were commenced accordingly.

Since DLBCL is very progressive in nature and can advance immediately, prompt treatment is required. A combination of chemotherapy and the monoclonal antibody rituximab, can conduce to disease remission in great number of patients, with or without radiation therapy [9]. A combination regimen known as R-CHOP (rituximab [Rituxan], cyclophosphamide [Cytoxan], doxorubicin [Adriamycin], vincristine [Oncovin], and prednisone) is widely used and remain the treatment of choice for DLBCL. The R-CHOP regimen is usually given for an average of 6 cycles, in 21-day cycles (once every 21 days). Nevertheless, the length and number of cycles given can differ based on the patient’s individual disease and health status. In certain cases, 14-day cycles can be used, and for limited stage disease (Stage I or II) 3-4 cycles can be used followed by radiation therapy. As for this case, R-CHOP were commenced for 6 cycles with no radiotherapy and repeated CT scan showed good remission in terms of reduction of cervical lymph nodes with no new lymph nodes or extranodal solid organ involvement. In assessing the response assessment based on CT scan, the repeated CT scan likely represent partial respond to treatment (>50% reduction in size), which indicate a non–progressive disease that required regular surveillance [10].

CONCLUSION

Every non-healing ulcer persisted more than 3 weeks should raise high suspicion for malignancy. Regardless of the history, clinical presentation and investigations are being benign in origin, one must have a high index of suspicion of malignancy if the ulcer shows no sign of healing, as squamous cell carcinoma still being the most common oral malignancy to date. Thus, an urgent referral should be made. Many solitary non-healing ulcers appear quite similar in presentation and may pose a challenge to the diagnostician, thus a histological analysis of suspected oral lesions is always mandatory.

Conflict of Interest
Authors declare none.

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Authors’ contribution
Ahmad Izani Mohd Safian drafted the article. Sarah Zulkarnain and Faazahtul Arbaeyah Hussain incorporated the pathology aspect. Azlan Husin contributed the hematology point. Azliana Aziz involved in the critical revision, while Irfan Mohamad integrated all the inputs and approved the final version.

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