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Young immunocompetent patient with oropharyngeal plasmablastic lymphoma

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Abstract. *Young immunocompetent patient with oropharyngeal plasmablastic lymphoma. Background:* Plasmablastic lymphoma (PBL) is a rare tumour that most commonly occurs in the oral cavity in immunocompromised patients.
Case report: A 35-year-old man presented with symptoms suggesting obstructive sleep apnoea syndrome (OSAS). Fiberoptic nasopharyngoscopy, contrast-enhanced computed tomography, and drug-induced sleep endoscopy revealed a mass in the oropharynx that completely obstructed the upper airway. Direct laryngoscopy was performed, and the lesion was excised using a CO_2 laser. Anatomopathological examination and flow cytometric differentiation established a diagnosis of plasmablastic lymphoma (PBL). Postoperative chemotherapy resulted in complete response.
Conclusions: Extra-oral PBL is very rare. This is the first published report of oropharyngeal PBL in an immunocompetent patient. This case emphasizes the importance of considering PBL as a differential diagnosis when an oropharyngeal tumour is present. Clinical ENT examination should include fiberoptic nasopharyngoscopy to detect any head and neck mass that may cause OSAS-related symptoms.

Introduction

In 1997, Delecluse *et al*.[1] first described a rare variant of diffuse large B-cell lymphoma, which was named plasmablastic lymphoma (PBL) in reference to its blastoid morphology and immunophenotypic features. In 2008, PBL was recognized as a new entity and distinct subtype of non-Hodgkin B-cell lymphoma.[2] This cancer type usually occurs in the oral cavity, and is most common in patients with human immunodeficiency virus (HIV). PBL diagnosis is challenging because of its rarity, and because features of PBL overlap with other malignant tumours.[3] PBL is associated with poor outcome, showing a median overall survival (OS) of 8-19 months and a five-year OS rate of 30-40%.[4]

Here we report a rare case of PBL, originating in the oropharynx of a 35-year-old immunocompetent male who initially presented at the ENT outpatient clinic with symptoms suggestive of obstructive sleep apnoea syndrome (OSAS). OSAS is a common chronic condition characterized by the inability to maintain a patent upper airway during sleep.[5] Cardinal OSA symptoms include socially disturbing snoring, excessive daytime somnolence, and apnoea witnessed by a partner. Without treatment, OSAS can cause a number of adverse cardiovascular, neurocognitive, and daytime consequences, leading to substantial morbidity and related mortality.[5]

Case report

A 35-year-old male was referred to the ENT outpatient clinic due to a history of snoring and witnessed apnoeas. The patient consumed alcohol weekly, was overweight (BMI: 28.2 kg/m^2), and had quit smoking six months earlier. The patient had previously undergone functional endoscopic sinus surgery for chronic sinusitis. No abnormalities were found upon physical and clinical ENT examination, including neck palpation. However, fiberoptic nasopharyngoscopy revealed an obvious mass in the oropharynx arising from the right epiglottic vallecula.

An intravenous contrast-enhanced computed tomography (CT) scan of head and neck revealed a non-contrast-enhancing exophytic mass in the oropharynx, involving the right epiglottic vallecula (Figure 1). The mass was 1.5 × 1.8 × 2.7 cm in size. Adhesion to the surrounding tissues was

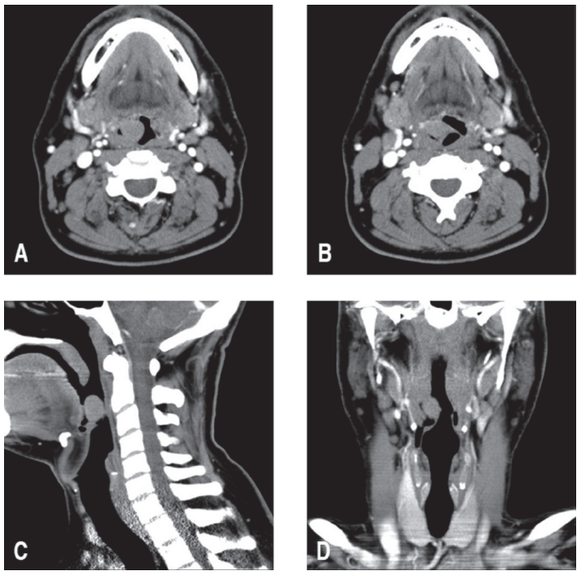

Figure 1
Contrast-enhanced computed tomography scans of the head and neck revealed a non-contrast-enhancing exophytic mass in the oropharynx, with a size of 1.5 × 1.8 × 2.7 cm (A). The mass arose from the right epiglottic vallecula (B, C). Images were acquired in the axial plane (A, B), sagittal plane (C), and coronal plane (D). There was no obvious invasion of the epiglottis or the epiglottic vallecula, although adhesion to the surrounding tissues was suspected. The mass caused partial airway obstruction (A) and posteroinferior deviation of the epiglottis (B, D).

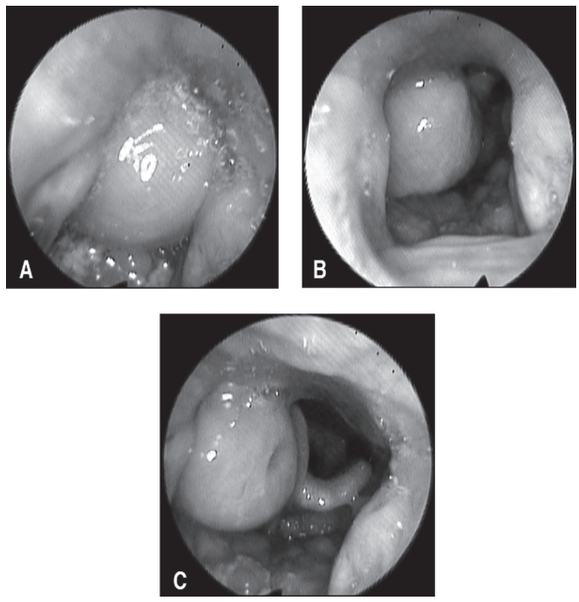

Figure 2
A, Drug-induced sleep endoscopy revealed a right-sided mass in the oropharynx, which resulted in complete obstruction. B, During inspiration, the mass was aspirated and pushed the epiglottis posteroinferior, leading to collapse and generating a snoring noise. C, During expiration, the tumour was blown upwards, diminishing the pressure on the epiglottis, resulting in sudden anterosuperior displacement of the epiglottis.

suspected, but no obvious invasion of the epiglottis or the epiglottic vallecula was observed. The mass partially obstructed the airway (Figure 1A), and caused posteroinferior deviation of the epiglottis (Figure 1B, D). In agreement with the clinical examination, no pathological lymph nodes were observed in the head and neck region.

Supporting the CT and fiberoptic nasopharyngoscopy findings, drug-induced sleep endoscopy (DISE)[5] revealed a mass in the oropharynx, which completely obstructed the upper airway (Figure 2A). During inspiration, the mass was aspirated and pushed the epiglottis posteroinferior, resulting in collapse and generating a snoring noise (Figure 2B). During expiration, the mass was blown upwards, diminishing the pressure on the epiglottis, and resulting in the sudden anterosuperior displacement of the epiglottis (Figure 2C).

Direct laryngoscopy exposed a pedunculated mass at the base of the tongue and the lateral pharynx. Since the tumour was easily accessible and obstructive, complete macroscopic resection was performed using a CO_2 laser. The specimen was sent for anatomopathological classification and flow cytometric differentiation.

Pathological results revealed densely expanded lymphoid tissue, with increased large blastic cells that were positive for cluster of differentiation (CD) 138 and multiple myeloma oncogen-1 (MUM1), and negative for CD20, immunoglobulin light chain restriction, c-myc oncogene rearrangements, and Epstein-Barr virus (EBV)-encoded RNA (EBER). CD56 immunohistochemistry was faintly positive, and the Ki-67 proliferation index was 70%. The differential diagnoses included plasma cell myeloma and atypical marginal zone lymphoma. However, based on the cytomorphologic and immunophenotypic features, a diagnosis of PBL was established.

Complete blood count, liver enzymes, kidney function, calcium, serum protein electrophoresis, and serum immunoglobulin levels were normal. Serology was negative for HIV, EBV, hepatitis B virus, hepatitis C virus, and *Treponema pallidum*. Bone marrow biopsy and aspiration showed no invasion.

Tumour staging was performed using 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and PET-CT scanning. The FDG-PET scan revealed a diffuse increase of metabolic activity in the bilateral jugulodigastric and left cervical lymph nodes, and focally increased FDG uptake in the distal oesophagus. Gastroscopy revealed no abnormalities apart from the diagnosis of mild-to-moderate reflux oesophagitis (grade B). CT of the thorax-abdomen revealed no abnormalities.

The patient was diagnosed with Ann Arbor pathological stage 1EA PBL. Treatment was initiated with six courses of CHOP chemotherapy at three-week intervals: cyclophosphamide (750 mg/m², day 1), doxorubicin (50 mg/m², day 1), vincristine (1.4 mg/m², day 1), and prednisone (50 mg/m², days 1–5). After treatment, FDG-PET scanning confirmed a complete response. Follow-up revealed no disease recurrence for up to three years.

Discussion

The introduction of highly active antiretroviral therapy has been accompanied by a dramatically decreased incidence of HIV-related lymphomas. The present annual incidence of HIV-related non-Hodgkin lymphoma is 194 per 100,000, which is ten times higher than the non-Hodgkin lymphoma incidence in the general population.[6] It is estimated that PBL constitutes approximately 2% of all HIV-related lymphomas.[7] However, due to its rarity, the exact incidence of PBL is unknown.

PBL is most often found in the oral cavity of HIV-infected patients. However, recent reports describe several cases of PBL among HIV-negative patients. Many of these cases have emerged in immunodeficient patients following solid organ transplantation or steroid therapy.[3] Patients with autoimmune diseases, lymphoproliferative disorders, and solid tumours are also more susceptible to PBL.[2,8] PBL has also been reported in immunocompetent patients, particularly elderly individuals, with the majority of these tumours located at the classical oral cavity region.[2]

PBL in the oropharynx is extremely rare, with only two such cases reported to date. In one case, the tumour was localized in the oropharynx and arose from the gingivobuccal sulcus of an HIV-positive patient.[9] In the other case, the tumour was localized at the base of the tongue in a patient with unknown HIV serology.[10] To our knowledge, the present case is the first described oropharyngeal PBL in an immunocompetent patient.

PBL occurs mainly in adult males and is associated with EBV infection and c-myc gene rearrangements.[3] Based on EBER expression, Morscio *et al*.[4] demonstrated that EBV infection was more common among HIV-positive patients (75%) than in immunocompetent patients (50%). They also reported that c-myc gene rearrangements were more strongly associated with HIV-positive patients (78%) than with immunocompetent patients (44%). Although the pathogenesis of PBL is not completely understood, it appears that EBV infection and c-myc gene rearrangements play important roles.[3] Fluorescent in situ hybridization analysis revealed that the present case was negative for both EBER and c-myc gene rearrangements, which is an atypical presentation of PBL.

PBL is usually associated with a poor prognosis, with a systematic review of 277 cases showing a median OS of eight months. More specifically, the median OS was seven months among post-transplant PBL patients, ten months among HIV-positive PBL patients, and eight months among HIV-negative immunocompetent PBL patients.[4] Several factors were associated with better prognosis, including young age (<60 years), early stage at diagnosis, complete response to chemotherapy, and a lack of c-myc gene rearrangements. The prognostic value of EBER expression remains unclear, as several studies have reported contradictory results. Compared to oral involvement, extra-oral location is more commonly associated with advanced stage. Swerdlow *et al*.[2] reported that 55% of patients with extra-oral PBL were at stage IV at the time of diagnosis.

No standard PBL treatment has been described. Half of the reported cases have been treated with CHOP or CHOP-like chemotherapy. Due to the disappointing survival rates, current National Comprehensive Cancer Network guidelines recommend intensive chemotherapy regimens, such as CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and high-dose cytarabine), EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), or hyper-CVAD (fractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone).[11]

However, several studies report a lack of survival benefit associated with intensive chemotherapy regimens among patients with PBL. Castillo *et al.*[12] compared CHOP/CHOP-like chemotherapies with more intensive regimens, and found that median progression-free survival was 12 and 6 months, respectively, and median OS was 15 and 8 months, respectively. Recent assessment of the role of stem cell transplantation (SCT) suggests that patients with chemotherapy-sensitive PBL might benefit from autologous SCT.[3] However, only some cases were treated with radiotherapy (isolated or in combination with chemotherapy), and information about the exact radiotherapy regimens was lacking. Therefore, no conclusion can be drawn. Other treatment options include surgery, chimeric antigen receptor T-cell therapy, and the proteasome inhibitor bortezomib.[3]

The patient in the present case was diagnosed with Ann Arbor pathological stage 1EA PBL. Complete macroscopic resection of the tumour was achieved using endoscopic laser surgery, and then CHOP chemotherapy was started. After therapy, PET-CT revealed a complete response. The present case included several factors that are associated with better prognosis, including younger age, complete response after therapy, and immunocompetence. Close follow-up remains necessary. To date, no recurrence has been detected at three years after the initial diagnosis.

Tumours in the upper airway can cause OSAS. In 1981, Moses *et al.*[13] described the first case of a patient with OSAS secondary to a tumour, specifically a nasopharyngeal carcinoma. Since then, there have been occasional reports of new cases of head and neck cancer (HNCa) causing secondary OSAS. Compared to the normal population, patients with HNCa show a higher incidence of OSAS, both before and after treatment.[14] Notably, OSAS may sometimes remain undiagnosed in HNCa patients since they are treated with the aim of preventing tumour recurrence.

Initially, the presently reported patient was referred to an ENT specialist for further examination of the socially disturbing snoring and witnessed apnoeas described by his partner. Fiberoptic nasopharyngoscopy of the upper airway revealed a suspected mass that was found to be a PBL lesion. Indeed, the literature confirms that HNCa is a rare cause of OSAS, as in the present case. Mayer Brix *et al.*[15] examined the frequency of pathological ENT findings among OSAS patients and found that only 3 of 336 patients were diagnosed with pharyngeal tumours. The present case report highlights the importance of performing fiberoptic nasopharyngoscopy during an initial ENT outpatient visit for complaints suggesting OSAS, to detect any potential tumour in the upper airway.

Conclusion

Extra-oral PBL is very rare, which hinders clinical differentiation. This is the first published case report of an oropharyngeal PBL in an immunocompetent patient. The present case illustrates that PBL must be considered as a differential diagnosis in cases of oropharyngeal tumour. Moreover, this report reinforces the importance of including fiberoptic nasopharyngoscopy in the clinical ENT examination to ensure detection of any head and neck mass that may be causing OSA-related complaints or other symptoms in the ENT and head and neck region.

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