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CLINICAL RECORD

Plasmablastic lymphoma of the larynx: report of two cases

K STEPHENSON[1], S PEER[1], D GOVENDER[2], J J FAGAN[1]

Divisions of [1]Otorhinolaryngology and, [2]Anatomical Pathology, University of Cape Town, South Africa

Abstract

Objective: To report two cases of laryngeal plasmablastic lymphoma, a rare and relatively recently described form of non-Hodgkin's lymphoma. It has not previously been described in the larynx, nor associated with upper airway obstruction.

Case reports: We describe the clinicopathological features of two such cases in human immunodeficiency virus positive patients, and we discuss their unusual presentations and diagnostic features.

Conclusion: When evaluating a laryngeal tumour, plasmablastic lymphoma and other non-Hodgkin's lymphomata should be considered as differential diagnoses, particularly in the setting of a high prevalence of human immunodeficiency virus infection. Biopsy with detailed histopathological and immunohistochemical evaluation is recommended to ensure correct diagnosis and optimal management.

Key words: Larynx; Plasmablastic Lymphoma; Lymphoma, Non-Hodgkin's; Lymphoma, B-Cell; Human Immunodeficiency Virus

Introduction

Plasmablastic lymphoma is a rare and relatively recently described form of non-Hodgkin's lymphoma. It has not previously been described in the larynx, nor associated with upper airway obstruction. In this paper, we describe the clinicopathological features of two cases of plasmablastic lymphoma occurring in the larynx, and we highlight the unusual presentation and diagnostic features.

In 1997, Delecluse *et al.* were the first to describe a new, distinct subtype of B-cell lymphoma of the oral cavity, in a series of 16 patients.[1] Following this initial report of oral tumours, a number of extra-oral sites have been described; these include the paranasal sinuses, skin and soft tissue, lung, and anorectal region.[2] Plasmablastic lymphoma has an aggressive nature and a particularly poor prognosis.[3]

Plasmablastic lymphoma may present a significant diagnostic challenge. Distinct morphological and clinical features have been recognised, and a clear association between immunosuppression and plasmablastic lymphoma has been identified. In a recent review of 228 cases of plasmablastic lymphoma, approximately 70 per cent of cases were described in individuals infected with human immunodeficiency virus (HIV).[4] Plasmablastic lymphoma accounts for an estimated 2.6 per cent of all HIV-associated non-Hodgkin's lymphoma.[5] An estimated further third of HIV-negative plasmablastic lymphoma patients have been found to be otherwise immunodeficient, for example, as a result of steroid therapy or solid organ transplantation.[6] Non-Hodgkin's lymphoma is classified as an acquired immune deficiency syndrome (AIDS) defining condition; furthermore, the risk of non-Hodgkin's lymphoma in HIV-infected persons is increased in those with more advanced immunodeficiency.[7] Meta-analysis of cohort studies has also confirmed that the incidence of HIV-related non-Hodgkin's lymphoma has decreased since the advent of highly active anti-retroviral therapy (HAART).[8]

The pathogenesis of plasmablastic lymphoma is poorly understood. In common with other HIV-related non-Hodgkin's lymphomas, Epstein–Barr virus is suspected to be involved, and potential mechanisms have recently been suggested.[9] A recent meta-analysis found that 74 per cent of HIV-associated plasmablastic lymphoma patients showed the presence of Epstein–Barr virus, detected by *in situ* hybridisation and/or polymerase chain reaction in more than 90 per cent of cases.[3] A potential association between plasmablastic lymphoma and human herpes virus 8 (Kaposi sarcoma herpes virus) was initially suspected due to confusion between plasmablastic lymphoma and the now recognised, separate entity of multicentric Castleman's disease, which contains Kaposi sarcoma herpes virus; increasing evidence currently indicates that most plasmablastic lymphomata do not contain this virus.[10]

Case reports

Case one

A 49-year-old, HIV-positive man presented with vocal change and odynophagia of two months' duration, together with a one-month history of multiple small, subcutaneous, nodular masses on the anterior chest and abdominal wall. He had been receiving HAART for six months and anti-tuberculosis treatment for five months. His absolute cluster of differentiation 4 glycoprotein ('CD4') level was

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49×10^6/l, and his erythrocyte sedimentation rate (ESR) was 126 mm/hour.

Clinical evaluation revealed an underweight man with a muffled voice. Signs of upper airway obstruction were not present. At flexible nasendoscopy, a bulky, exophytic lesion of the supraglottic larynx was found, with pooled salivary secretions (Figure 1). The ENT examination was otherwise unremarkable, with no cervical lymphadenopathy of note. Further examination revealed multiple firm, nontender, subcutaneous masses ranging from 1 to 3 cm in greatest dimension and extending across the anterior chest and abdominal wall (Figure 2).

The laryngeal mass was biopsied under local anaesthesia. Fine needle aspiration of the anterior abdominal wall and chest masses revealed an atypical lymphoid population which was suspicious for lymphoma. Excision biopsy of a subcutaneous nodule was subsequently performed under local anaesthesia. Histological sections of the laryngeal mass and subcutaneous nodule showed similar features, i.e. solid, diffuse infiltrates of large, round to oval, neoplastic cells with a paranuclear hof imparting a plasmacytoid appearance. The nuclear chromatin was coarse and the nucleolus prominent. There were frequent mitotic figures. The significant immunohistochemical results were negativity for cluster of differentiation (CD) 20 protein and positivity for plasma cell markers (i.e. CD 138 protein and MUM1 protein), an immunoprofile consistent with plasmablastic lymphoma (Table I).

Case two

A 41-year-old, HIV-positive woman receiving HAART presented with a 9-month history of vocal change, dysphagia and odynophagia. The patient had a past history of pulmonary tuberculosis (TB). Severe upper airway obstruction necessitated an emergency tracheostomy under local anaesthesia. She had an absolute CD4 level of 57×10^6/l and an ESR of 126 mm/hour, in addition to macrocytic anaemia.

At endoscopy, we found synchronous tumours of the supraglottic larynx (involving the laryngeal surface of the epiglottis) and the post-nasal space. Biopsy of both tumours revealed neoplastic infiltrates composed of large, round to oval cells with amphophilic cytoplasm and a discernible paranuclear hof in some cells (Figure 3a). Nuclei had stippled chromatin and the nucleolus was prominent. The neoplastic cells were positive for CD 138 protein (Figure 3b), MUM1 protein and VS38c but negative for CD 20 protein, an immunoprofile consistent with plasmablastic lymphoma.

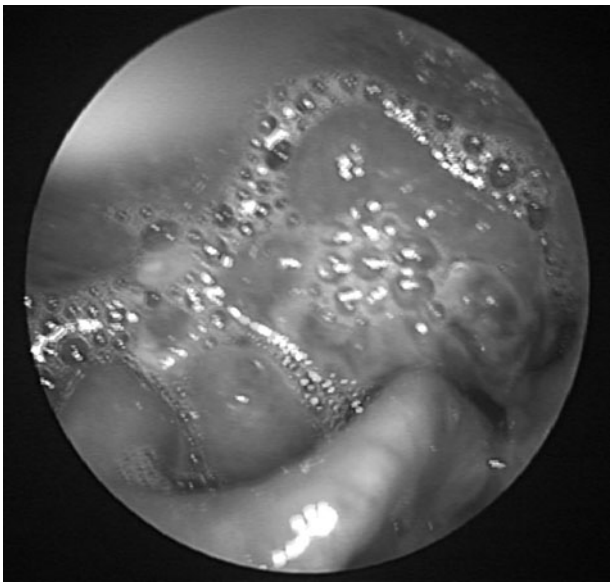

FIG. 1
Nasendoscopic photograph of supraglottis of case one.

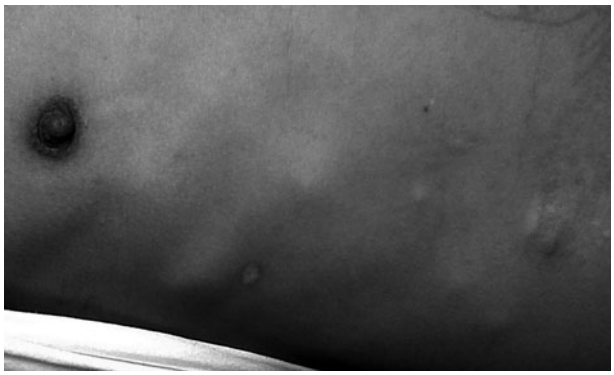

FIG. 2
Clinical photograph of anterior chest and abdomen of case one.

Both patients were treated with cyclophosphamide, doxorubicin, vincristine and prednisone (the 'CHOP' regimen), and their HAART was also continued.

Both patients were alive one year after diagnosis of plasmablastic lymphoma.

Discussion

Clinicians and pathologists should have a high degree of awareness of plasmablastic lymphoma occurring in unusual sites in HIV-infected individuals. The cases described above demonstrate that plasmablastic lymphoma is not necessarily confined to the oral and nasal cavities but may occur lower in the respiratory tract.

Clinical and microscopic features may not be sufficient to distinguish plasmablastic lymphoma from other

TABLE I
IMMUNOHISTOCHEMISTRY

Parameter	Result	
	Case 1	Case 2
CD45*	+	Weak +
CD138	+	+
MUM1	+	+
Ki67 (%)	60	70
CD3	–	–
CD10	–	ND
CD20	–	–
CD56	–	–
CD79a	ND	+
MNF114	–	ND
VS38C	ND	+
EMA	ND	–
EBV LMP1	–	–

*Also known as leukocyte common antigen. CD = cluster of differentiation (glyco)protein; + = positive; – = negative; ND = not done; EMA = epithelial membrane antigen; EBV LMP1 = Epstein–Barr virus latent membrane protein 1

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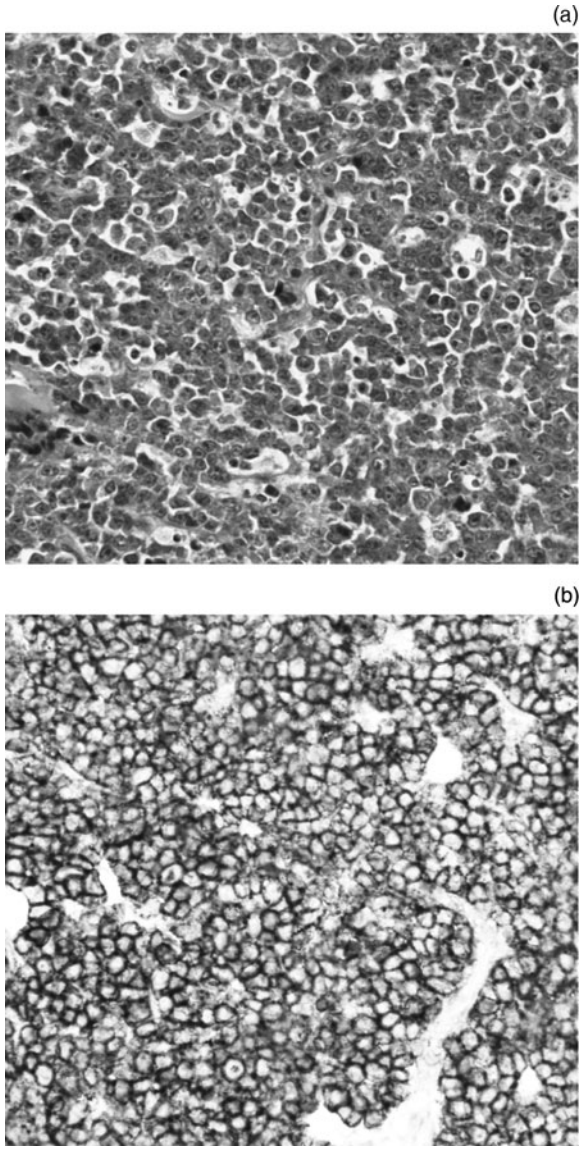

FIG. 3

Photomicrographs for case two showing: (a) diffuse infiltration of round neoplastic cells with eccentric nuclei and paranuclear hofs (H&E; × 20); and (b) neoplastic cells with diffuse membrane immunoreactivity for CD 138 protein (×).

malignancies of the head and neck such as undifferentiated carcinoma, other lymphoproliferative diseases, and malignant melanoma. Infective pathology, such as TB, is an important clinical differential diagnosis, particularly in regions with a high prevalence of TB and HIV.

Biopsy with detailed histopathological and immunohistochemical evaluation is recommended to ensure correct diagnosis and optimal management. Microscopically, plasmablastic lymphoma may resemble diffuse large B-cell lymphoma with immunoblastic morphology; however, in this situation testing for CD 20 protein would be positive. In some cases, plasmablastic lymphoma may resemble undifferentiated carcinoma and melanoma, but in both these instances immunohistochemistry is a very useful means of arriving at the correct diagnosis. Epstein–Barr virus has been demonstrated in plasmablastic lymphoma by Epstein–Barr virus encoded RNA *in situ* hybridisation; however, immunohistochemical detection of Epstein–Barr virus latent membrane protein 1 is usually negative.[11]

- **Plasmablastic lymphoma is a rare, aggressive form of non-Hodgkin's lymphoma**
- **A strong association with immunosuppression exists**
- **Most tumours are oral, but may also be extra-oral**
- **Laryngeal tumours may occur, with upper airway obstruction**
- **Detailed histopathological and immunohistochemical evaluation is required**

Optimal treatment of plasmablastic lymphoma has not yet been clearly defined. Chemotherapy has been the mainstay of treatment in the vast majority of cases reported.[2] The most commonly used regimen is a combination of cyclophosphamide, doxorubicin, vincristine and prednisone; however more intensive regimes have also been explored.[12] The relapse rate is high and overall survival rates are poor: a median overall survival of 14 months with a 5-year overall survival rate of 31 per cent have been estimated.[5] It is notable that these data reflect a variety of therapeutic approaches in a heterogeneous patient population. Furthermore, an early meta-analysis has suggested that HAART in addition to chemotherapy and/or radiotherapy may improve prognosis and survival.[13]

Conclusion

When evaluating head and neck mucosal lesions, plasmablastic lymphoma and other non-Hodgkin's lymphomata are important differential diagnoses to be considered, particularly in the setting of a high prevalence of HIV.

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Address for correspondence:
Dr Kate Stephenson,
Division of Otorhinolaryngology,
University of Cape Town,
H-53 Old Main Building,
Groote Schuur Hospital,
Observatory, Cape Town 7925, South Africa

E-mail: katestephenson@doctors.org.uk

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