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LETTER TO THE EDITOR

Plasmablastic lymphoma of visceral cranium, cervix and thorax in an HIV-negative woman

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Dear Editor,

We would like to report a case of aggressive plasmablastic lymphoma (PBL) in an HIV-negative individual, characterised by a unique combination of unusual clinical and immunophenotypic features.

A 67-year-old woman presented with a 20-day history of a painless mass lesion in the left supraclavicular fossa. She was also complaining of blurred vision and a continuous mild retrosternal pain. She denied fever, night sweats or weight loss. Her past medical history was negative for diseases or treatments associated with immunodeficiency. On physical examination, she had diplopia on upward gaze. A painless firm mass 3×4 cm in size was palpated in the left supraclavicular fossa. There was no peripheral lymphadenopathy, organomegaly or other remarkable findings.

Laboratory investigations showed a normal full blood count and serum biochemical profile, including normal lactate dehydrogenase levels. No paraprotein was present on serum and urine electrophoresis. Enzyme-linked immunosorbent assay testing for HIV antibodies was negative. Computerised tomography (CT) imaging studies revealed a mass with soft tissue density occupying the left sphenoid sinus and infiltrating the ethmoid sinus and ipsilateral concha with associated areas of bone destruction. The mass was extending to the left orbit with thickening of the left inferior rectus muscle. There was also an evidence of tumour invasion of the left maxillary antrum and mandibular ramus. Furthermore, soft tissue masses compatible with multiple lymph node enlargement and block formation were present in the inferior frontolateral cervical region with extension to the anterior upper mediastinum. CT imaging of abdomen was negative for lymphadenopathy or organomegaly. A bone marrow biopsy was negative for neoplastic invasion.

Biopsy of the cervical mass revealed a neoplasm causing complete effacement of nodal architecture and extending to the adjacent adipose tissue. The neoplastic tissue consisted of diffusely growing large- and medium-sized cells with polymorphic nuclei, frequent mitoses and moderate-to-large amount of eosinophilic or amphiphilic cytoplasm (Fig. 2a). Immunohistochemical investigation using markers of epithelial (Ker HMW, Ker LMW, Ker7, Ker20, EMA, Cam 5-2), lymphoid (CD3, CD20, CD45RO, CD45, CD30, CD21, CD79a, CD8, CD56, CD138, kappa and lambda chains, immunoglobulins), mesenchymal (S-100, vimentin, actin, desmin, CD31, CD34, GFAP (glial fibrillary acidic protein)), histiocytic (CD68), melanocytic (HMB-45) differentiation and various others (Bcl-2, CD99, neuron-specific enolase [NSE]) revealed only a strong expression of vimentin and a small percentage of cells with moderate positivity for NSE. Blind biopsies from the nasopharynx indicated only non-specific immunologic stimulation of the lymphoid tissue.

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In view of the very poor immunophenotypic data in the presence of a morphologically and clinically aggressive tumour, empirical chemotherapy for head and neck cancer was administered. The patient received a course (six cycles) of cisplatin–5-fluorouracil–leukovorin chemotherapy without significant clinical response. Four weeks after the cessation of chemotherapy, the disease progressed with enlargement of the cervical mass and emergence of a subcutaneous mass in the thoracic wall over the sternum, thought to represent extension of mediastinal disease (Fig. 1c,d). Histological examination of biopsy specimens from the subcutaneous mass showed neoplastic infiltration by cells with the morphological features described above. Surprisingly, immunophenotyping with the same panel of differentiation markers showed 100% positivity for CIgD (λ) (Fig. 2c,d). Further investigation revealed that these cells were positive for MUM-1 (100%; Fig. 2b), bcl-2pr (50%) and MIB1 (80%), and negative for CD3, CD5, CD10, CD20, CD30, CD45, CD45RO, CD56, bcl-6, bcl-2, CD79a and CD138. Genotypic analysis, by semi-nested polymerase chain reaction (PCR), of DNA extracted from the biopsy material demonstrated a specific Ig_H rearrangement, thus confirming B cell monoclonality. Based on the morphologic, immunohistochemical and molecular genetic findings, a diagnosis of diffuse large-cell B cell non-Hodgkin's lymphoma of plasmablastic type was made. A

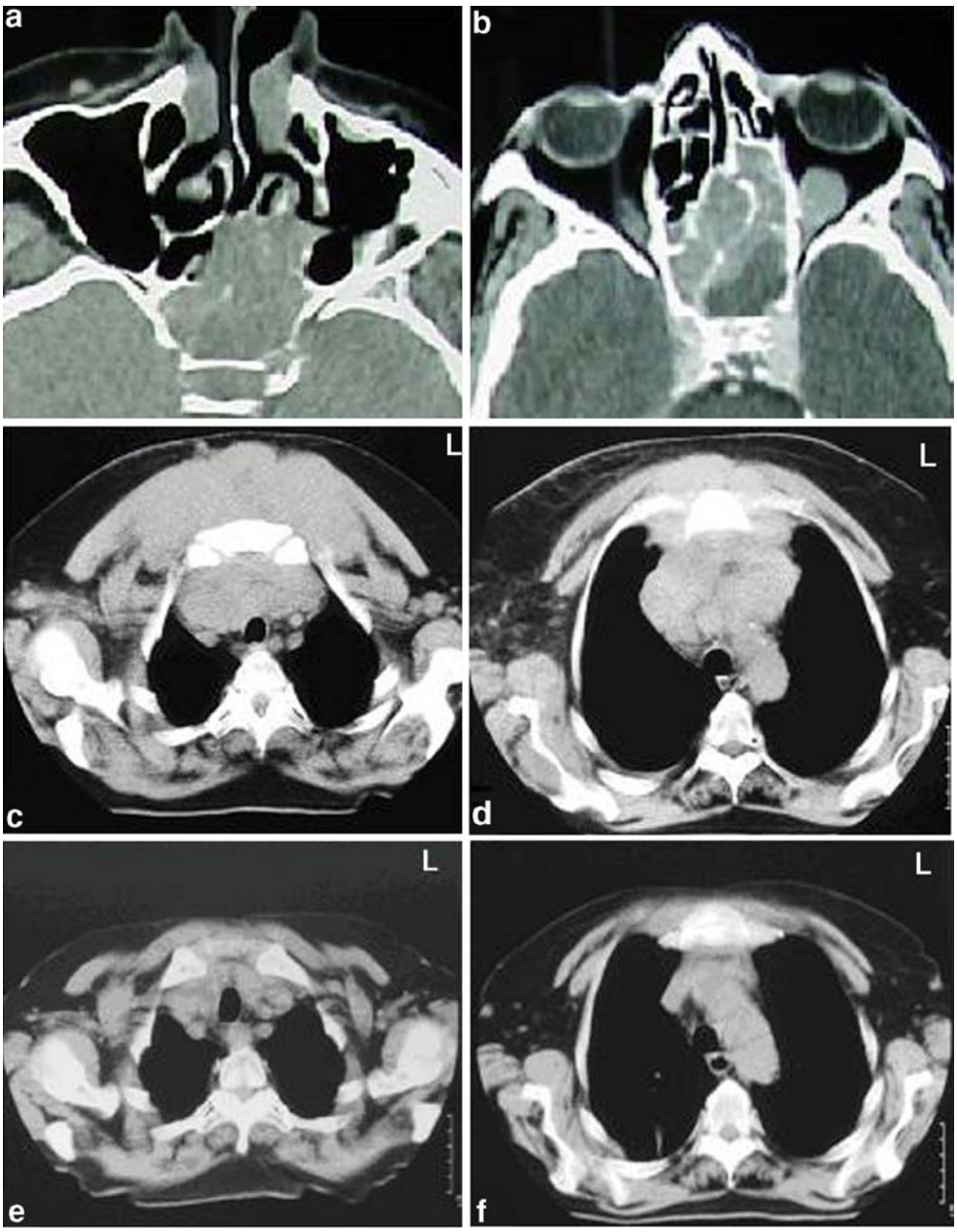

Fig. 1 CT images of visceral cranium and thorax. **a** Tumour occupying the left sphenoid sinus and ethmoidal air cells with associated bone destruction. **b** Extension of tumour into left orbit. Tumour masses in anterior upper (**c**) and middle (**d**) mediastinum with extension to anterior thoracic wall. Complete regression of tumour after chemoradiotherapy (**e**, **f**)

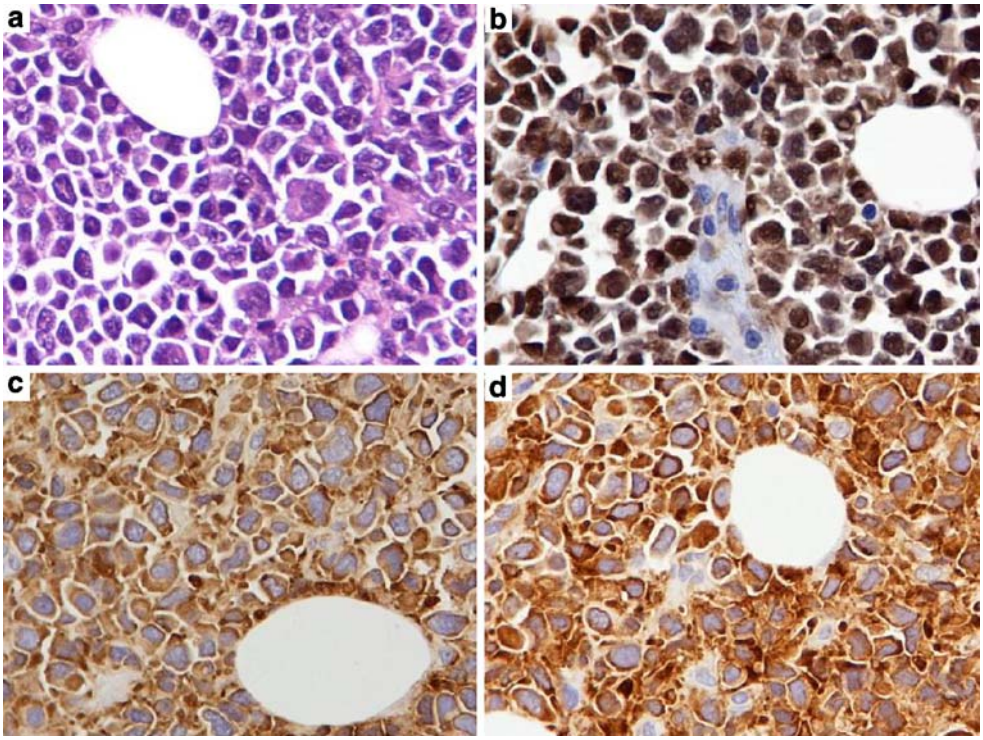

Fig. 2 Tumour biopsy material. **a** Haematoxylin–eosin stain. **b**, **c**, **d** Immunohistochemical stains for MUM1, IgD and lambda light chains, respectively, employing a PAP technique. See text for details

search for Epstein–Barr (EB) virus DNA in the neoplastic tissue was negative using a PCR technique. Immunostaining for human herpesvirus-8 (HHV-8) antigen employing a peroxidase–anti-peroxidase technique was also negative.

The patient was clinically staged as Ann Arbor IV E and was given six monthly cycles of cyclophosphamide–oncovin–adriamycin–dexamethasone (CHOP) chemotherapy at conventional doses. After the first cycle, a total dose of 2,000 Gy consolidative locoregional radiotherapy was delivered to the cervix and mediastinum. After completing the chemoradiotherapy, reevaluation CT revealed complete remission of disease in the cervix and mediastinum (Fig. 1e,f), but no change in the mass occupying the sinuses. Over the following months, there was an increase in the size of the latter mass with further extension into the left orbit resulting in exophthalmos, which responded satisfactorily to local irradiation. Despite further chemotherapy in the form of CHOP–bleomycin, the disease progressed with local recurrence in the cervix as well as development of intraabdominal lymphadenopathy and widespread subcutaneous deposits in the trunk. The patient succumbed to advancing lymphoma 23 months after her initial presentation.

PBL is a rare, highly malignant variant of diffuse large B cell lymphoma (DLBCL) with unique immunohistological features, including absent expression of the leucocyte common antigen (LCA, CD45) as well as of the pan-B cell antigen CD20, combined with strong expression of various plasma-cell-related antigens and variable expression of cytoplasmic immunoglobulin. The first case of a diffuse large-cell lymphoma with plasmablastic features was reported as early as 1978 [1], but it was the description of a series of 16 cases by Delecluse et al. [2] in 1997 that prompted the inclusion of PBL as a distinct variant of DLBCL in the World Health Organization classification of lymphomas. Although the vast majority (15 of 16) of patients in the original series were HIV positive, it was shown in subsequent case reports that similar tumours could be encountered in immunocompetent individuals. In a recent series of 12 consecutive cases of PBL, six were recorded in HIV-negative patients, four of which had no known cause of immune deficiency [3]. As the number of reported cases increased, it became clear that PBL should not be regarded as a single pathological entity but rather as a heterogeneous group of neoplasms with different aetiologies and clinicopathological characteristics [3, 4]. The members of this group are PBL of oral mucosa type, PBL with plasmacytic differentiation, primary effusion lymphoma (PEL), Kaposi's sarcoma-associated herpesvirus-positive solid lymphoma/extracavitary PEL/HHV-8-associated DLBCL and DLBCL expressing anaplastic lymphoma kinase. An association of PBL with EB and HHV-8 infection has been frequently reported [2, 5–7], although there is no conclusive evidence for a pathogenetic role of these viruses.

The cardinal clinical feature of PBL is its extra-nodal localisation. Although the oral cavity is the usual site of disease in HIV-positive patients, involvement of various other sites including nasal cavity, cervical nodes, stomach, colon, liver, lungs, testicles, bone and skin has been reported in both HIV-positive and HIV-negative patients [3, 8–15]. An apparently immunocompetent patient with aggressive,

treatment-refractory PBL presenting with a neck mass and bony destruction of sinuses has been described by Teruya-Feldstein et al. [3]. Our patient had unusually extensive disease involving the left half of the visceral cranium from the orbit to the mandible, with an associated left cervical mass extending to the mediastinum and anterior thoracic wall by continuity of tissue. This pattern of disease has not been reported previously in the setting of PBL.

From a pathological viewpoint, the importance of PBL lies mainly in the fact that the frequent involvement of extranodal sites combined with the lack of CD20 and LCA expression can mistakenly lead to the exclusion of lymphoma from the differential diagnosis. This is highlighted in the case presented here, where negativity for the commonly used plasmacytic marker CD138, combined with lack of cytoplasmic immunoglobulin staining in the initial biopsy specimen, resulted in delayed diagnosis. In the largest series (50 cases) published to date, Colomo et al. showed that PBL is characterised by marked morphological and immunophenotypic heterogeneity, with MUM1 being the only consistently positive marker [4]. MUM1 is a lymphocyte-specific member of the interferon regulatory factor family of transcription factors, and its expression is thought to denote the final step of germinal centre B cell differentiation [16]. Our patient falls into Colomo's "oral cavity" type of PBL [4], where the unusual CD138−/MUM1+ phenotype may be encountered, probably signifying that histogenetically different subsets of disease exist within this PBL type. Interestingly, 52% of cases with this type of PBL show absence of cytoplasmic immunoglobulin light chain expression [4].

There was no evidence of HHV-8 or EB virus involvement in the pathogenesis of PBL in this case. This is in keeping with published data indicating lack of a consistent association of either of these viruses with PBL, irrespective of HIV status [3, 4, 17].

The poor response to treatment and survival of only 23 months observed in our patient is in accordance with published experience. In a recent study, HIV-negative patients with PBL appeared to have a worse prognosis (median survival 12 months) compared to their HIV-positive counterparts receiving highly active antiretroviral therapy (median survival not reached at 22 months of follow-up) [3]. It is worth noting that, in the case of our patient, substantial remission was seen only at disease sites subjected to radiotherapy. The role of this treatment modality in the setting of PBL needs to be better defined in future studies.

In conclusion, the case reported here broadens the spectrum of the protean clinical presentations of PBL and highlights the importance of performing extensive immunophenotyping, including multiple markers of terminal B cell differentiation in the setting of CD20/LCA-negative large-cell tumours.

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