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Case Report

Extraosseous plasmacytoma with an aggressive course occurring solely in the CNS

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Extraosseous (extramedullary) plasmacytoma is a relatively indolent neoplasm that constitutes 3–5% of all plasma cell neoplasms. Rare cases have been reported to truly occur in the CNS and not as an extension from a nasal lesion. EBV expression in plasma cell neoplasms has been reported in very few cases that are mainly post-transplant or occurring in severely immunosuppressed patients. We report a case of extraosseous plasmacytoma with an aggressive course in an HIV-positive individual that occurred solely in the CNS, showing EBV expression by *in situ* hybridization, and presenting as an intraparenchymal mass as well as in the CSF.

Key words: aggressive, central nervous system (CNS), Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), plasmacytoma.

INTRODUCTION

Plasma cell neoplasms refer to a group of true plasma cell disorders that include plasma cell myeloma, plasmacytoma, primary amyloidosis, and light and heavy chain deposition diseases.¹ Extraosseous (extramedullary) plasmacytomas constitute 3–5% of all plasma cell neoplasms, arise in tissues other than bone, and have a relatively indolent course with only 15% of cases progressing to plasma cell myeloma.^{1,2} A slight male preponderance has been reported with a mean age at diagnosis of 55 years.¹ The vast majority of the reported cases occur in the upper respiratory tract with very few cases reported to occur in the CNS.^{1,2} Traditionally, CNS involvement can be subdivided into the presence of a localized intraparenchymal lesion, the presence of solitary cerebral plasmacytoma, or as a CNS myelomatosis, which is

defined as the presence of monoclonal plasma cells in the CSF during the course of plasma cell myeloma.³ In addition, few cases of extraosseous plasmacytomas involving the nasal septum or sinuses have been reported to extend into the CNS.⁴ Given that involvement of the CNS as the initial and sole presentation of plasma cell neoplasms is exceedingly rare and their association with EBV has not previously been well-documented, we present an unusual case of extraosseous plasmacytoma expressing EBV and presenting in the CNS of a 40-year-old HIV-positive man.

CASE REPORT

A 40-year-old HIV-positive Hispanic man was admitted to the Emergency Room for altered mental status, fever, vomiting and diarrhea that had started 1 day prior to admission. He was diagnosed with HIV infection 3 years prior and since that time he was also diagnosed with cryptococcal meningitis, recurrent herpes simplex virus (HSV) infection, anal condyloma, and hepatitis C infection. Four days prior to admission the patient was seen at the infectious disease clinic in our institute and was noted to have shingles on the right shoulder. On admission, the patient's HIV-1 RNA viral load was 307 copies/mL, CD4:CD8 ratio: 0.15 and his CD4 count was 74/ μ L. The patient's medications included zidovudine, ritonavir, fluconazole, acyclovir and trimethoprim–sulfamethoxazole.

In the Emergency Room, CT and MRI scans showed meningeal and dural enhancement with multiple nodular lesions within the frontal region, around the left cavernous sinus, and laterally around the left sphenoid ridge (Fig. 1). CT scans of the chest, abdomen and pelvis were unremarkable except for mild hepatomegaly. Lumbar puncture and a subsequent flow cytometry of the CSF identified kappa-restricted plasma cells that expressed CD38 and CD138 and were estimated at 65% of all cells. No evidence of a monoclonal B-cell population was noted and the CSF was reported as consistent with a plasma cell neoplasm. A subsequent brain biopsy of the mass located at the right middle frontal gyrus showed sheets of plasma cells that

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were positive for CD138, IgG, and kappa by immunohistochemistry but negative for all B-cell markers (Fig. 2). Most of the neoplastic plasma cells showed normal morphology with no atypical features except for a small focal area,

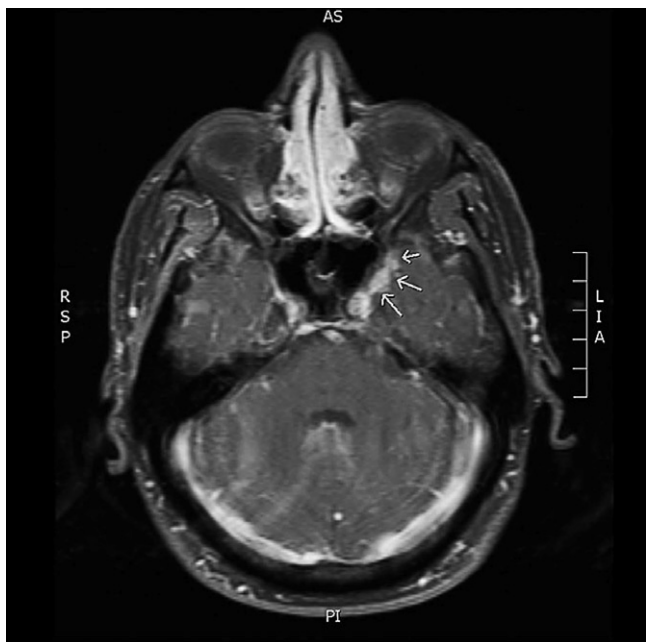


Fig. 1 MRI of the head and neck shows multiple nodular lesions (arrows) along the left cavernous sinus and laterally along the sphenoid ridge and skull base.

which contained highly atypical plasma cells with plasmablastic features exhibiting open chromatin, prominent nucleoli, and a higher proliferative activity. Of interest, the neoplastic plasma cells, whether atypical or not, demonstrated expression of EBV-encoded small RNA (EBER) by *in situ* hybridization (Fig. 2). The EBV-latent membrane protein 1 (LMP1) immunostain showed negative results for both areas. All immunostains were performed on formalin-fixed tissue. Cryptococcal infection was noted as well on the biopsy sections. The patient's serum was positive for cryptococcal antigen, while screens for histoplasmosis and syphilis were negative. At that time, 3 weeks after admission, the patient's HIV-1 RNA viral load was 55 copies/mL, CD4:CD8 ratio: 0.29 and his CD4 count was 101/ μ L. No lytic bone lesions, hypercalcemia, or renal failure were noted. A bone marrow biopsy showed a normocellular marrow with active trilineage hematopoiesis and no evidence of a plasma cell neoplasm. Cytogenetic studies performed on the bone marrow aspirate showed a normal male karyotype. No monoclonal bands were detected by serum and urine protein electrophoresis.

Intrathecal chemotherapy with thiotepa was initiated via installation of an Ommaya reservoir. Subsequent samplings of the CSF showed no significant decrease in the number of neoplastic plasma cells and the patient's mental status continued to deteriorate. After consultation with the patient and family members, the patient was put into a "Do not resuscitate (DNR)" status and placed on comfort care.

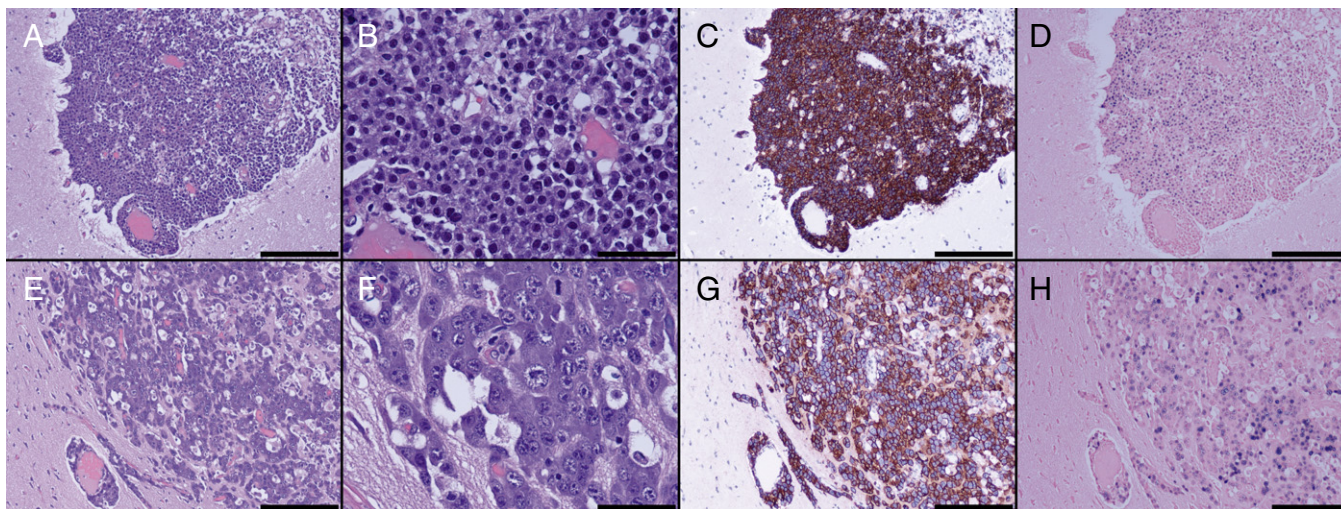


Fig. 2 The composite picture represents two different fields from the frontal gyrus mass. The upper half shows sheets of neoplastic plasma cells that show no atypical features, which is representative of the majority of plasma cells seen in the different sections of the specimen. (A) Low-power magnification ($\times 10$) of the plasma cells. (B) high-power magnification ($\times 40$). (C) CD138 expression by plasma cells ($\times 10$). (D) EBV-encoded small RNA (EBER) expression (EBV by *in situ* hybridization) ($\times 10$). The lower half of the composite picture shows clusters of plasma cells with atypical and plasmablastic features and a high proliferative activity, which represents a small focal area within the entire specimen. (E) Low-power magnification ($\times 10$) of the atypical plasma cells, (F) high-power magnification ($\times 40$). (G) CD138 expression by atypical plasma cells ($\times 10$), (H) EBER expression ($\times 10$). Scale bars represent 200 μ m (A, C, D, E, G and H) and 50 μ m (B and F).

The patient was then transferred to hospice care 10 weeks after admission and subsequent follow-up was not available to us at that point.

DISCUSSION

Neurological symptoms in patients diagnosed with a plasma cell neoplasm are not uncommon but they are mainly attributed to hypercalcemia, hyperviscosity, medullary compression, or deposition of amyloid; however, true CNS involvement is rare with an overall incidence of approximately 1% of all patients with plasma cell neoplasms.^{3,5} To diagnose true CNS involvement, pathologic and cytologic examinations are the gold standard and cannot be substituted by CSF protein electrophoresis, as the identification of a monoclonal paraprotein may be due to the passage of immunoglobulins into the CSF as a result of alterations to blood–brain barrier permeability.⁶ Within all categories of plasma cell neoplasms, CNS involvement is likely common to occur during the course of plasma cell myeloma rather than as an isolated plasmacytoma confirmed by the recent review of 109 previously reported cases of patients with a plasma cell neoplasm that have CNS involvement, where only 13 patients (12%) represented an extraosseous plasmacytoma with no evidence of concurrent or subsequent plasma cell myeloma history.³

The exact pathogenesis of CNS involvement in patients with plasma cell neoplasms remains unknown; however, several theories about a possible etiology have been reported that include possible contiguous spread from an eroded lytic lesion of the skull,⁷ hematogenous spread seen in patients with plasma cell leukemia,³ or continuous growth of plasma cells during the treatment course as most drugs used in plasma cell myeloma therapy cannot cross the blood–brain barrier.⁸ A number of studies hypothesized that infectious agents such as HIV, EBV, hepatitis C virus, and human herpes virus 8/ Kaposi sarcoma-associated herpes virus (HHV-8/ KSHV) may play a role in the pathogenesis of plasma cell neoplasms, particularly plasma cell myeloma.^{9–12} Plasma cell myeloma is significantly more common in HIV-infected individuals compared to the general population, which may be due to increased opportunistic infections in HIV-infected individuals.¹³ EBV latent protein LMP-1, as well as HHV-8, stimulates cellular proliferation through induction of interleukin-6 (IL-6), which is a potent growth factor for plasma cells, especially in the setting of immunosuppression.¹⁴ Others have postulated that CNS myelomas represent a unique subset of plasma cell neoplasms with extremely poor prognosis that are associated with high-risk chromosomal abnormalities, such as abnormalities of chromosomes 11 and 13, hypodiploidy, and deletions of chromosome 17 involving the P53 gene.¹⁵

The patient in our case was a young HIV-positive individual who presented with a rapidly progressive extraosseous plasmacytoma that presented both as an intraparenchymal mass, as well as in the CSF. EBV expression was noted by *in situ* hybridization but no expression of HHV-8 immunostain was seen. Cases of primary CNS extraosseous plasmacytomas have been rarely reported, even in the setting of HIV infection, which is more commonly associated with a full-blown plasma cell myeloma. The EBV association is of interest given that it was clearly and diffusely detected by *in situ* hybridization (EBER), while it was repeatedly negative for the LMP-1 protein by immunohistochemistry. This is discordant with the previously mentioned hypothesis of LMP-1 being the culprit for the neoplastic transformation by induction of IL-6 and subsequent plasma cell proliferation, and may be supportive of a more restrictive pattern of expression of EBV latent encoded proteins similar to that seen in Burkitt lymphoma, as an example.¹⁶ Moreover, the presence of a small focal area of plasma cells exhibiting atypical and plasmablastic features in the brain mass but not in the CSF may be related to EBV expression as others have hypothesized that the detection of EBV expression in plasma cell neoplasms is significantly associated with plasmablastic morphologic features, suggesting that these tumors may have been driven by EBV to gain such atypical morphologic features, as well as a higher proliferation rate.¹⁷ Given the immunosuppressive status of the patient, we speculate that EBV, although through alternate pathways other than the LMP-1 protein, may be responsible for the highly aggressive plasma cell proliferation seen in our case as well as for the plasmablastic morphology detected in a very small subset of the plasma cells.

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