Case Report

Cephalic and ocular manifestations of EBV-associated plasmablastic lymphoma: Clinical and radiological response to bortezomib, EPOCH, and intrathecal methotrexate [☆],[☆☆]

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ABSTRACT

Plasmablastic lymphoma (PBL) is a rare and aggressive type of lymphoma, particularly affecting HIV-positive and immunocompromised individuals, with a median diagnosis age of 49 years. Cases of this malignancy in HIV-negative individuals are less common and rarely involve the bone marrow. While traditional chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) were previously utilized in the management of such malignancy, the National Comprehensive Cancer Network currently recommends more intensive approaches. We present a rare stage IV Epstein–Barr virus (EBV)-positive PBL with a nasal cavity tumor extending into the left orbital sinus and encapsulating segments of the optic nerve in a 38-year-old young immunocompetent adult, without a significant past medical history. Treatment consisted of 6 cycles of Bortezomib in combination with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and intrathecal methotrexate which exhibited significant clinical and radiological improvement suggesting the potential efficacy of this regimen. Vision returned to baseline, the mass size reduced significantly, and headaches improved. Given this outcome, it is highly encouraged to emphasize the need for further exploration of this treatment in larger clinical trials.

Introduction

Plasmablastic lymphoma (PBL) is an aggressive subtype of diffuse large B-cell lymphoma with male predominance and median age of 49 years [1]. It was originally described in the oral cavity of Human Immunodeficiency Virus (HIV) patients [2]. More recently, PBL cases have been reported in HIV-negative individuals including those with Epstein-Barr Virus (EBV), [1,3] receiving immunosuppressive therapy, and rarely in immunocompetent patients [1,4]. Most commonly, this lymphoma presents with abdominal/gastrointestinal complaints, localized mass or swelling, and oral/nasal symptoms (e.g., ulcer, epistaxis, rhinorrhea, sinusitis). While lymph node involvement is identified in about 70% of cases, extranodal disease is also common with the oral/nasal cavity and gastrointestinal tract being the most involved in extranodal sites [1].

Regardless of immune status, there seems to be an association between PBL, EBV infection and MYC gene aberrations [5]. From a pathological standpoint, PBL is identified by the absence of CD20 expression and the presence of plasma cell markers like CD38 and MUM-1, along with a notably high proliferation index (Ki-67) [6]. The cellular origin of PBL is the plasmablast, an activated B-cell undergoing plasmacytic differentiation but not yet transformed into a quiescent plasma cell. Prognostically, PBL consistently exhibits poor outcomes with conventional chemotherapy regimens, resulting in an overall survival period of 12 months [7]. Here, we present our experience with a case of immunocompetent EBV-positive stage IV PBL responsive to combination of bortezomib, dose-adjusted EPOCH (etoposide, prednisone, doxorubicin, vincristine, and cyclophosphamide) and intrathecal methotrexate.

Case report

History: A 38-year-old male with a recent diagnosis of plasmablastic lymphoma presented to the emergency department to start chemotherapy following his oncologist recommendation. One month prior, patient presented to an outside facility with a new onset tearing left-sided headaches and progressive left-sided vision loss for the past 2 weeks. No other symptoms were presented. CT imaging revealed a large soft tissue mass in the left maxillary sinus extending to the ethmoid sinus and invading into the orbit and left sphenoid sinus (Fig. 1A). Outpatient soft tissue biopsy of the mass showed EBV-positive B-cell lymphoma with high Ki-67, consistent with Plasmablastic lymphoma. Considering the pathology results, the patient was advised to proceed to the hospital for chemotherapy treatment.

Patient's vision continues to progressively worsen since previous hospitalization. On admission, he was unable to identify objects and was only able to see flickering of light and movement of objects. Headaches continued to be present, and relieved by ibuprofen. Patient was not taking any medications and denied any chest pain, shortness of breath, fever, chills, sore throat, abdominal pain, nausea, vomiting, neuropathy, or rashes. Other than this illness, patient reported no significant past medical history. Patient denied any surgical history and admitted to family history of breast cancer in both mother and grandmother. He stopped drinking alcohol and smoking marijuana since his diagnosis, as he used to drink 12 (12 oz) beers/day. Patient was not working and lives at home with his wife.

Vitals and Physical Exam: All vitals were within normal range. On physical exam, patient was in no acute distress. Head was normocephalic and atraumatic. There was a small amount of blood in the left nares with minimal purulent discharge. The oropharynx was clear with tacky mucous membranes. No palpable neck mass or lymphadenopathy was noted. The cardiorespiratory examination was unremarkable as there was no evidence of rashes, wounds, or bruising. Patient was alert, oriented, and responded to questions appropriately. There was markedly reduced vision in the left eye otherwise no other focal neurological symptoms. His gait was intact.

Hematology laboratory values:

Table 1 – Hematology laboratory values on admission.

Parameter	Result	Reference range	Parameter	Result	Reference range
WBC	33.5 (H)	(4.8-10.8 K/mm^3)	Band Neutrophils %	21.9 (H)	(0%-6%)
RBC	3.90 (L)	(4.6-6.2 M/mm^3)	Lymphocytes %	8.6 (L)	(25%-40%)
Hgb	12.1 (L)	(13-18 gm/dL)	Neutrophils Count	30.1 (H)	(2.0-8.1 K/mm^3)
Hct	35.9 (L)	(38%-54%)	Lymphocytes Count	3.1	(1.2-3.4 K/mm^3)
MCV	92.0	(80-99 fL)	Monocytes Count	0.1	(0-2 K/mm^3)
MCH	31.1	(27-34 pg)	Eosinophils Count	0.2	(0-0.7 K/mm^3)
MCHC	33.8	(32-36.9 g/dL)	Basophils Count	0.1	(0-0.5 K/mm^3)
RDW	12.3	(11%-14.5%)	Vacuolated Neutrophils	Present	
Plt Count	255	(150-400 K/mm^3)	Smudge Cells	2.9	
MPV	9.70	(7.4-10.4 FL)	Platelet Estimate	Adequate	
Seg Neuts %	69.5 (H)	(57%-68%)	RBC Morphology	Normal	

Hgb, Hemoglobin; Hct, Hematocrit; MCV, Mean Corpuscle Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; Plt, Platelet; MPV, Mean Platelet Volume; RBC, Red Blood Cells; RDW, Red cell Distribution Width; Seg Neuts, Segmented Neutrophils; WBC, White Blood Cells.
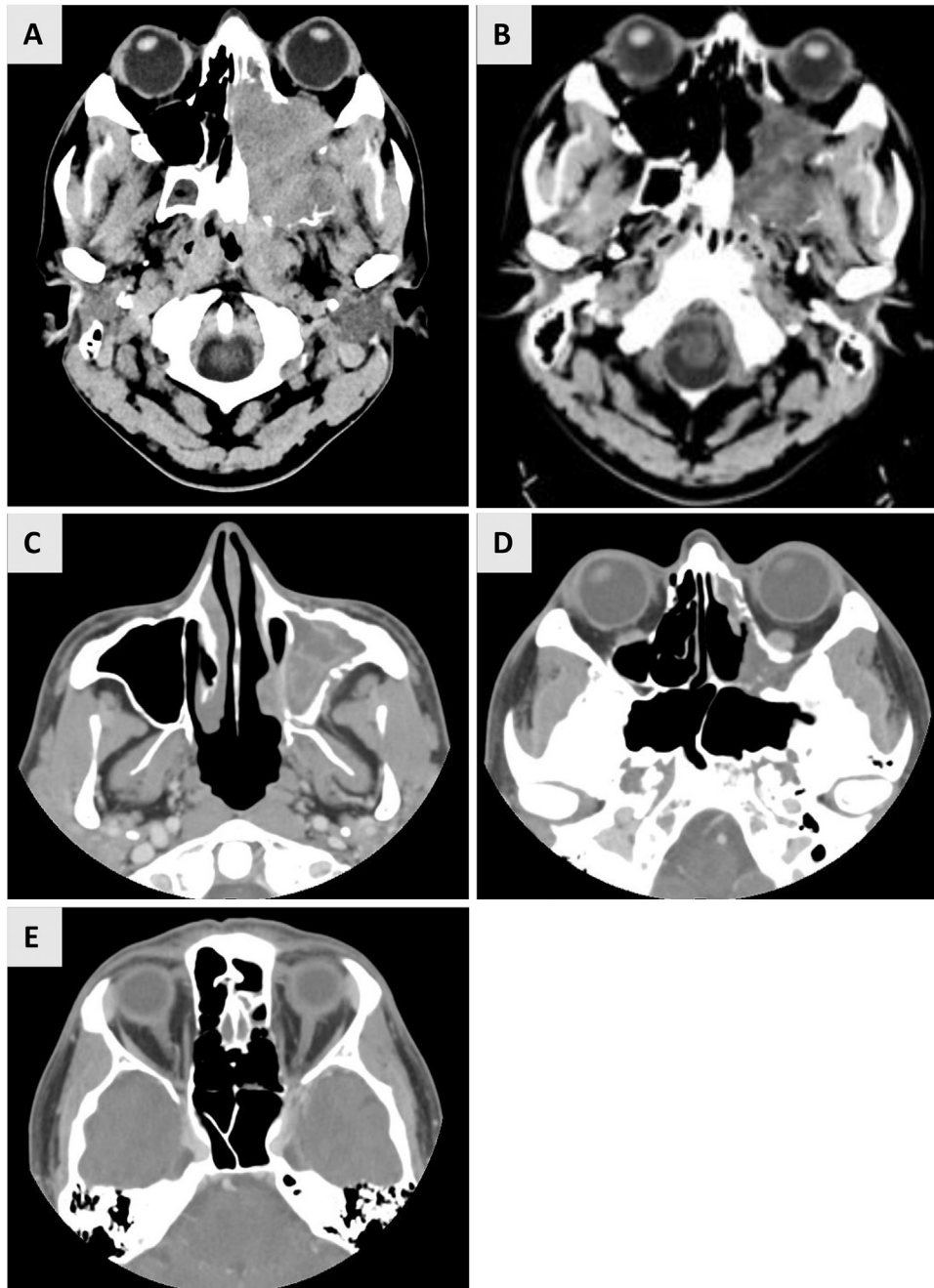
Fig. 1 – A series of axial noncontrast head/maxillary CT studies at different timeframes of treatment. (A) On admission, there is 6.5 x 4.2 cm soft tissue mass centered in the left paranasal ethmoid/sphenoid and maxillary sinuses with erosive changes, cortical breakthrough, and invasion of the left retrobulbar orbit and right ethmoid sinus. There is left extraocular muscle displacement and retrobulbar narrowing. (B) After 1 cycle of chemotherapy, CT head shows notable reduction in the size of the mass. There is no involvement of the right ethmoid sinus and less involvement of the left sphenoid sinus and orbital cavity. (C-E) CT maxillary post fifth chemotherapy cycle revealed a significant reduction in the size of the mass. The mass continues to involve the left maxillary and ethmoid sinuses. No involvement of the left sphenoid sinus, orbit sinus, or optic nerve was noted in image.

Diagnostic Imaging: CT head and neck without contrast (Fig. 1A) showed a 6.5 × 4.2 cm hyperdense soft tissue mass centered within the left maxillary sinus with invasion and osseous destruction of the nasal cavity, left ethmoid sinus, and left sphenoid sinus. The mass extends posteriorly to abut the

left cavernous sinus and anteriorly to the left cervical internal carotid artery. There is additional extension to the posterior aspect of the left medial orbit.

As seen in Fig. 2, brain MRI without contrast shows a heterogeneously hyperintense infiltrative mass centered within
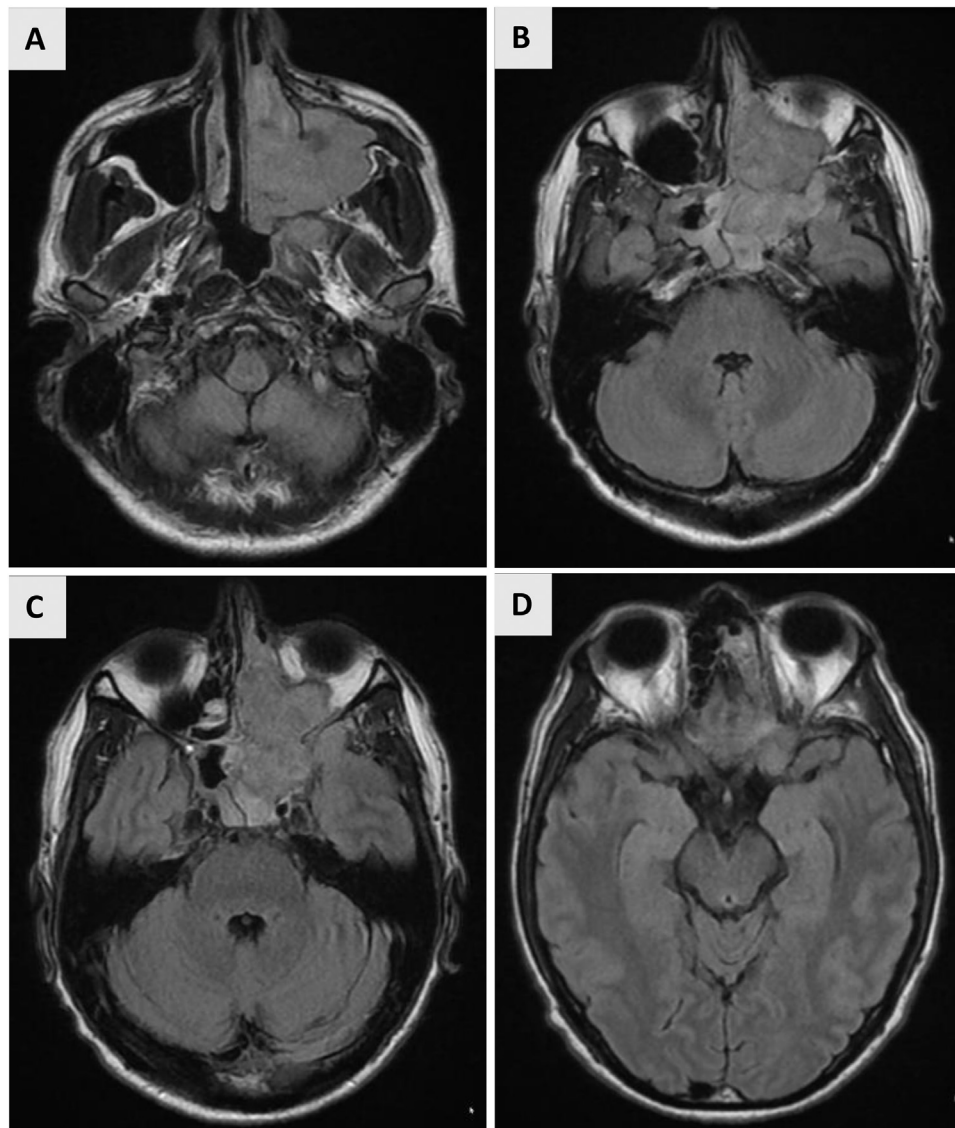
Fig. 2 – Axial noncontrast MRI cross sectional study of the head on admission. (A) The mass is centered within the region of the left pterygopalatine fossa extending into the left nasal cavity, left maxillary sinus, left anterior and posterior ethmoid air cells left sphenoid sinus, and left retromaxillary region. (B) The mass extends through the nasal septum to the right ethmoid sinus. (C) The intra-orbital left optic nerve has been compressed by the mass. (D) The intra-canicular optic nerve has also been compressed while the intracranial and chiasmal segments of the left optic nerve are intact.

the region of the left pterygopalatine fossa extending into the left nasal cavity, left maxillary sinus, left anterior and posterior ethmoid air cells left sphenoid sinus, and left retromaxillary region. The mass spans approximately $5.4 \times 4.2 \times 6.5$ cm (anterior to posterior by medial to lateral by superior to inferior. The mass abuts the left frontal lobe without associated invasion. There is leftward shift of the cisternal segment of the left optic nerve. There is partial encasement of the left cavernous sinus. CT abdomen and pelvis with and without contrast showed no evidence of metastasis or inflammatory disease.

Pathology: On histology, multiple small sinonasal samples revealed abnormal dense sheet-like infiltrate of enlarged lymphoid cells with a morphologic spectrum varying from cells resembling immunoblasts to cells with more obvious plasmacytic differentiation associated with brisk mitotic activity, apoptosis, and necrosis. Immunohistochemistry (IHC) stain stains show that the abnormal lymphoid cells have a very high Ki-67 proliferative index of >90% and are negative for both CD20 and PanKeratin. In addition, there was restricted expression of kappa light chain; overexpression of c-MYC (>90%); positive for CD10, CD38, CD138, MUM1, BCL2, CD30 (small subset/focal); negative for CD3, CD5, CD43, CD45, CD56, CD79a, PAX5, Cyclin D1, BCL6, ALK, lambda light chain, synaptophysin; and p53 was not expressed (<20%). The background CD3+ T-cells are composed predominately of CD8+ T-cells

with only a small subset of CD4+ T-cells observed (markedly reversed CD4:CD8 ratio), raising the suspicion for HIV infection. In situ hybridization for EBER is positive, supporting involvement of tumor cells by Epstein-Barr Virus (EBV).

Cytogenetic analysis of right iliac bone marrow showed an abnormal karyotype of 46, XY, t(8;14) (q24;q32) [3] and 46, XY [17] out of the 20 analyzed metaphase cells. This reciprocal translocation between the long arms of chromosomes 8 and 14 in 3 of the 20 analyzed metaphase cells, with juxtaposition of MYC oncogene at 8q24 to IgH locus at 14q32, is a classical cytogenetic abnormality found in Burkitt's lymphoma, its leukemic counterpart (L3-ALL), and diffuse large B-cell lymphoma. EBER in situ hybridization stain is positive in the atypical plasmacytoid infiltrate, supporting the involvement of plasmablastic lymphoma. IHC of the atypical plasmacytoid infiltrate is positive for CD38, CD71, CD138 and negative for CD3, CD20, CD30, CD56, PAX5, and EMA.

Medical Management: As surgical management is not indicated for such malignancy [8], patient was scheduled for 5-day 6 cycles of EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) in combination with bortezomib at a dose of 2.16 mg administered subcutaneously (SQ) on days 1-5 of each cycle. Supportive therapy consisted of daily 1000 mg valacyclovir PO for herpes zoster prophylaxis and daily 300mcg Tbo-Filgrastim SQ for neutropenic fevers caused by chemotherapy. Intrathecal methotrexate 12 mg was administered on last day of each cycle. Prior to the first intrathecal injection, 6-10 cc of cerebrospinal fluid was obtained and was unremarkable.

Follow-up Imaging and Pathology: After completing first cycle of chemotherapy, patient received a CT head study to rule out any intracranial hemorrhage prior to intrathecal methotrexate injection. As seen in Fig. 1B, there is a notable reduction to the size of the mass by exhibiting no involvement in the right ethmoid sinus and less involvement in the left orbital and ethmoid sinus. CT maxillary/face (Fig. 1C-E) following the fifth chemotherapy cycle revealed a significant reduction to the size of the mass. No involvement of the left sphenoid sinus, orbit sinus, or optic nerve was noted. The mass continues to involve the left maxillary and ethmoid sinuses. Left iliac bone marrow biopsy post fifth chemotherapy cycle demonstrated normocellular bone marrow with trilineage hematopoiesis with negative morphological, immunophenotypic, or flow cytometry evidence of lymphoproliferative disease (Table 1).

Discussion

PBL is a rare lymphoma and more prevalent in HIV-positive and other immunocompromised individuals. The median age for diagnosis typically stands at approximately 50 years. HIV-positive individuals tend to present the condition at a younger age, with a median age of 40 years, in contrast to non-HIV patients, whose median age at presentation exceeds 50 years. This lymphoma usually presents with extranodal involvement of the nasal/mucosal layers and gastrointestinal symptoms [1]. PBL cases in HIV-negative individuals are less common and do not typically involve the bone marrow [9]. Rarely,

does it present as stage IV EBV-positive malignancy with a nasal cavity tumor extending into the orbital sinus and encapsulating segments of the optic nerve, especially in a 38-year-old young immunocompetent adult without a significant past medical history.

The presence of MYC translocations in EBV-positive PBL is highly prevalent, and the identification of an IGH/MYC translocation in this context leans towards a diagnosis of plasmablastic lymphoma rather than EBV-positive diffuse large B-cell lymphoma (DLBCL) [10]. PBL usually shows expression of CD38, CD138, and MUM1, along with frequent positivity for EMA, CD30, and cytoplasmic light chain. There may be expression of CD79A, CD 56, or CD10, but PBL is generally negative for CD20, CD45, and PAX5. The proliferation rate, as indicated by Ki67, exceeds 90%. Dual infection with EBV and human herpesvirus 8 (HHV-8) has been demonstrated in PBL [11]. While the majority of cases exhibit positivity for EBV through in situ staining (EBER), they are negative for HHV-8, distinguishing them from primary effusion lymphoma.

With a positive bone marrow involvement, Ann Arbor staging revealed stage IV of such lymphoma.

While cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) previously served as the standard therapeutic chemotherapy regimen, the National Comprehensive Cancer Network (NCCN) now recommends a more intensive approach [12]. This includes regimens such as cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC); infusional etoposide, vincristine, and doxorubicin with bolus cyclophosphamide and prednisone (infusional EPOCH); and hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyper-CVAD). Patients with PBL who were not treated with chemotherapy invariably died with a median survival of 3 months [12].

Due to disappointing CHOP response and survival rates, the NCCN guidelines advocated for more intensive regimens like infusional EPOCH, hyper-CVAD, or CODOX-M/IVAC [13]. However, Castillo and colleagues assessed treatment outcomes in patients undergoing CHOP, CHOP-like, and more rigorous regimens. They found no statistically significant difference in overall survival between the less intensive and more intense treatment protocols, although only a quarter of the reported patients in the literature had been treated with regimens more intensive than CHOP.

A newly emerged treatment option for PBL involves bortezomib, a proteasome inhibitor widely used in myeloma therapy and the management of relapsed or refractory mantle cell lymphoma [14]. Several studies suggest that bortezomib, either as a standalone treatment or in combination with chemotherapy, may exhibit an antitumor effect in PBL. In recently published PBL cases, bortezomib has shown promising results [14–19]. Although most of these responses were not sustained, bortezomib represents a new therapeutic option for PBL. Despite initial promising results, the drugs were used at case report level and the response with the new agents was transient and should be further explored in larger clinical trials [12,20].

Patient was scheduled for a total of 6 cycles. After completing the first V-EPOCH cycle with intrathecal methotrexate,

there was notable clinical and radiological improvement observed in this patient. Vision substantially recovered, almost reaching its preillness state, and CT imaging indicated a significant reduction in the size of mass. While headaches did not fully resolve, there was marked improvement compared to the pretreatment state. Following fifth chemotherapy session, vision was completely recovered, and headaches continue to be mild. There was a significant reduction to the mass without involvement of the left sphenoid sinus, orbital sinus, or optic nerve (Fig. 1E). Involvement of the left maxillary and ethmoid sinuses was noted (Fig 1C and D). The favorable results observed here carry significant promise, prompting consideration for a more extensive investigation of the outcomes associated with this regimen in treating such malignancies at a broader clinical-trial scale.

Ethical approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration. Informed consent was obtained from the patient for being included in this study.

Consent for publication

Written informed consent was signed by the patient and collected for publication of this case report.

Availability of data and materials

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Data sharing statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

All authors reviewed the literature, evaluated the discussion, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Patient consent

We have obtained written consent from this patient.

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