Don’t lose sight: rare extramedullary involvement of myeloid/lymphoid neoplasm with *ETV6:ABL1* translocation in blast phase

A 34-year-old male with a past medical history of ankylosing spondylitis, presented with acute onset of fever and a sore throat. Blood count revealed significant leukocytosis, with a white blood cell (WBC) count of 37×10^9/L, accompanied by neutrophilia and monocytosis, without eosinophilia or basophilia. Additional findings included anemia (hemoglobin 75 g/L), thrombocytopenia (47×10^9/L), elevated liver enzymes (X5 the upper limit normal [ULN] with a cholestatic pattern), direct hyperbilirubinemia (34.0 µmol/L, ULN <5.1 µmol/L), and increased lactate dehydrogenase (LDH).

The patient’s clinical condition rapidly deteriorated with persistent fever, hypotension, and hypoxemia while WBC count continued to rise to 123×10^9/L. He required intensive care unit (ICU) management, including high-flow nasal cannula (HFNC) oxygen therapy and vasopressor support. Considering the above, along with elevated ferritin (4,202 µg/L) and soluble IL-2 receptor levels (5,872 kU/L), a diagnosis of hemophagocytic lymphohistiocytosis (HLH) was made, consistent with secondary HLH.[1] Direct bilirubin continued to rise and peaked at 213.4 µmol/L prompting a liver biopsy that revealed extramedullary hematopoiesis without evidence of leukemia or hemophagocytosis. A thorough infectious and immunological workup was unrevealing. Bone marrow (BM) assessment at presentation showed less than 2% blasts on aspirate smear while BM biopsy demonstrated a hypercellular marrow (>90% cellularity) with signs of hemophagocytosis and increase in reticulin fibers. Cytogenetic analysis revealed an abnormal karyotype with the t(9;12)(q34;p13) translocation, but no additional findings were noted in somatic genetic testing, including negative results for *BCR-ABL1*, *JAK2*, *c-KIT*, *PDGFRA* and *CALR* mutations. High-dose dexamethasone (20 mg once a day [QD]) and broad-spectrum antibiotics were initiated, resulting in prompt clinical and laboratory improvement. Shortly after initial recovery, the patient was readmitted with extensive joint pain accompanied by worsening thrombocytopenia and emergence of myeloid blasts in the blood and marrow. BM demonstrated 20% myeloid blasts positive for MPO and lysozyme, CD13, CD33, CD117, CD34, and HLA-DR. A hypercellular marrow (>90%) with severe erythroid hypoplasia, numerous immature megakaryocytes, and prominent eosinophilia was noted. Optical genome mapping (OGM) confirmed the previously identified cytogenetic findings, including an *ETV6:ABL1* insertional translocation (Figure 1A), as well as a *MECOM (EVI1):GEMIN5* translocation and additional complex chromosomal rearrangements.

The patient was diagnosed with a myeloid/lymphoid neoplasm with eosinophilia and *ABL1-ETV6* translocation, progressing to blast crisis.[2]

ETV6-ABL1 fusion is a rare but recurrent genetic alteration resulting from a complex chromosomal translocation involving *ETV6* (formerly known as *TEL*) and *ABL1*, with the translocation occurring at 9q34 and 12p13. Alternative splicing produces two distinct fusion transcripts: type A, which lacks *ETV6* exon 5, and type B, which includes it. Both variants lead to continuous activation of a chimeric tyrosine kinase[3] that was shown to be sensitive to specific tyrosine kinase inhibitors (TKI).[4] A myeloproliferative (MPN) presentation with frequent progression to blast phase resulting in an overall poor prognosis was previously reported. Zaliova *et al.* reported on 44 patients with *ETV6-ABL1*-driven leukemias including 22 patients with acute lymphoblastic leukemia (ALL) (13 children and 9 adults) and 22 patients with a myeloid neoplasm (18 with MPN and 4 with acute myeloid leukemia [AML]). Notably, eosinophilia was detected in all MPN and AML cases but only in some ALL patients. In adults, acute leukemias were associated with a poor prognosis, with a >80% of evaluable patients succumbing to disease progression or relapse. MPN blast crisis was reported in five of 18 MPN patients and was associated with high mortality (4 of 5 patients) despite early introduction of TKI to therapy.[5]

The occurrence of HLH in the context of a myeloid neoplasia as seen in our patient was previously reported. In one series of 343 patients with AML undergoing intensive chemotherapy, 32 patients (9.3%) had evidence of HLH. Compared to patients without HLH, those affected showed hepatomegaly, liver abnormalities, reduced platelet counts, elevated C-reactive protein levels, and extended pancytopenia. In addition, patients with HLH had worse prognosis with a significantly shorter median overall survival (14.9 months) compared to those without HLH (22.1 months; *P*=0.0016) and higher rates of induction failure, primarily due to deaths during aplasia.[6]

The patient presented herein received induction therapy (7+3; cytarabine/daunorubicin), along with dasatinib 100 mg QD on days 8-21 and achieved complete remission (CR). Two additional consolidation cycles with high- dose cytarabine and dasatinib were administered.

After the second consolidation, the patient presented with progressive leukocytosis and new disseminated skin nodules (Figure 1B) confirmed by biopsy as myeloid sarcoma (Figure 1C, D). BM aspiration showed 8% myeloid blasts,

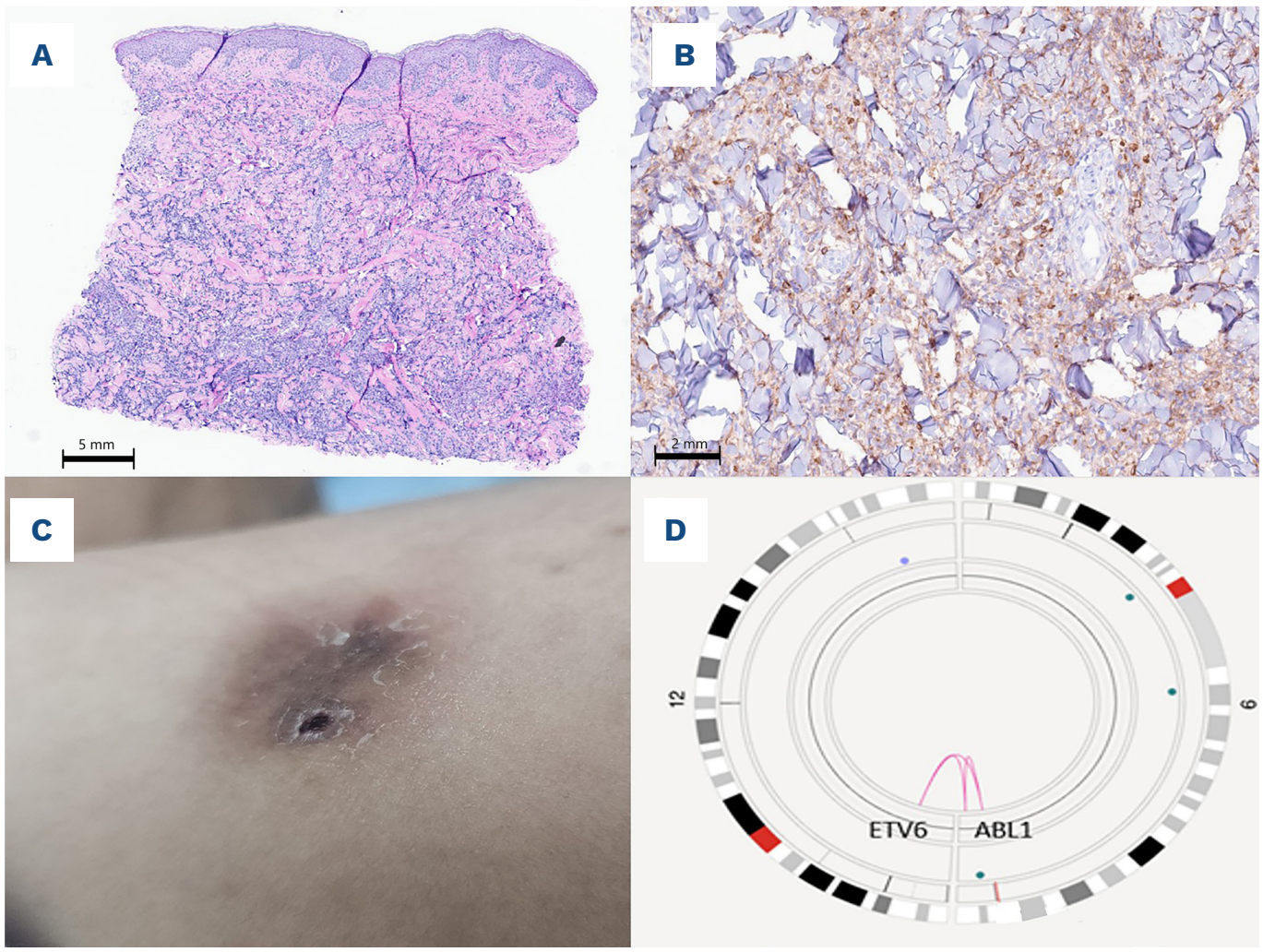

Figure 1. Histopathological, clinical, and genetic features of disease presentation. (A) Skin of right forearm, punch biopsy: myeloid sarcoma. The histological sections demonstrate an infiltrate of immature mononuclear cells dispersed between dermal collagen fibers (hematoxylin and eosin stain 4x magnification). (B) The myeloid blasts were positive for myeloperoxidase (20x magnification), weakly positive for CD117, partially positive CD34, negative for CD20, CD3, CD15. (C) Skin nodules (left arm). (D) Optical genome mapping findings.

OGM analysis of the marrow confirmed persistence of *ETV6:ABL1* translocation. The patient was diagnosed with primary refractory leukemia with extramedullary cutaneous involvement (EMD). Shortly after, the patient complained of blurred vision of his left eye. Initial ophthalmologic examination revealed uncorrected visual acuity of 20/20 in the right eye and 20/25 in the left eye. Right fundus examination showed normal optic disc and retina while left fundus examination demonstrated 2+ vitreous cells, diffuse pallid disc edema with obscured and multiple hemorrhages (Figure 2A). Visual field testing revealed a superior altitudinal defect and an inferior temporal quadrant scotoma in the left eye (Figure 2B). Optical coherence tomography (OCT) of the optic nerve demonstrated diffuse thickening of the peripapillary retinal nerve fiber layer in the left eye. Macular OCT identified subretinal fluid in the PMB and foveal regions, along with intraretinal and subretinal hyperreflective dots suggestive of leukemic cell infiltration. Additional findings included retinal folds, inferior retinal detachment, and multiple vitreous cells. Brain and orbital magnetic resonance imaging demonstrated T2-hyperintense signal in the left posterior sclera with gadolinium enhancement (Figure 3A, B). A poorly demarcated enhancing mass was seen in the infero-temporal aspect of the left orbit with extra-conal and intra-conal components. The orbital lesion's characteristics were most consistent with myeloid sarcoma (Figure 3C, D). The patient underwent *pars plana* vitrectomy of the left eye. Cytology and flow cytometry from undiluted vitreous samples were negative. CSF analysis showed nine WBC negative for myeloid markers.

The patient received salvage treatment with FLAG-IDA in combination with venetoclax (FLAG-IDA-VEN: fludarabine, cytarabine, filgrastim, idarubicin, and venetoclax). Intrathecal methotrexate 12 mg and radiation therapy directed to the left orbital mass (total dose of 23 Gray) were added to the regimen. Dasatinib 100 mg QD was initiated after recovery of the blood count. Post-salvage marrow examination demonstrated a CR. The skin nodules completely regressed without residual EMD on positron-emission tomography/computed tomography. Imaging of the left orbit showed a reduction in lesion size. The patient continues dasatinib maintenance and is currently being evaluated for consolidative allogeneic transplantation.

EMD is a well-recognized manifestation of AML. It can be detected at diagnosis, or on relapse, and occurs alone or as part of a systemic disease. Ganzel *et al*. demonstrated that EMD can be detected in almost one-quarter of newly diagnosed patients with AML without a clear negative prognostic effect.[7,8]

Leukemic optic neuropathy is a very rare form of central nervous system (CNS) involvement in AML[9] and has been previously described in case-reports at diagnosis and during relapse.[10,11] The optic nerve functions as a leukemic sanctuary site with limited penetration of chemotherapeutic agents across the blood-brain barrier, resulting in treatment resistance. The typical presentation is acute painless

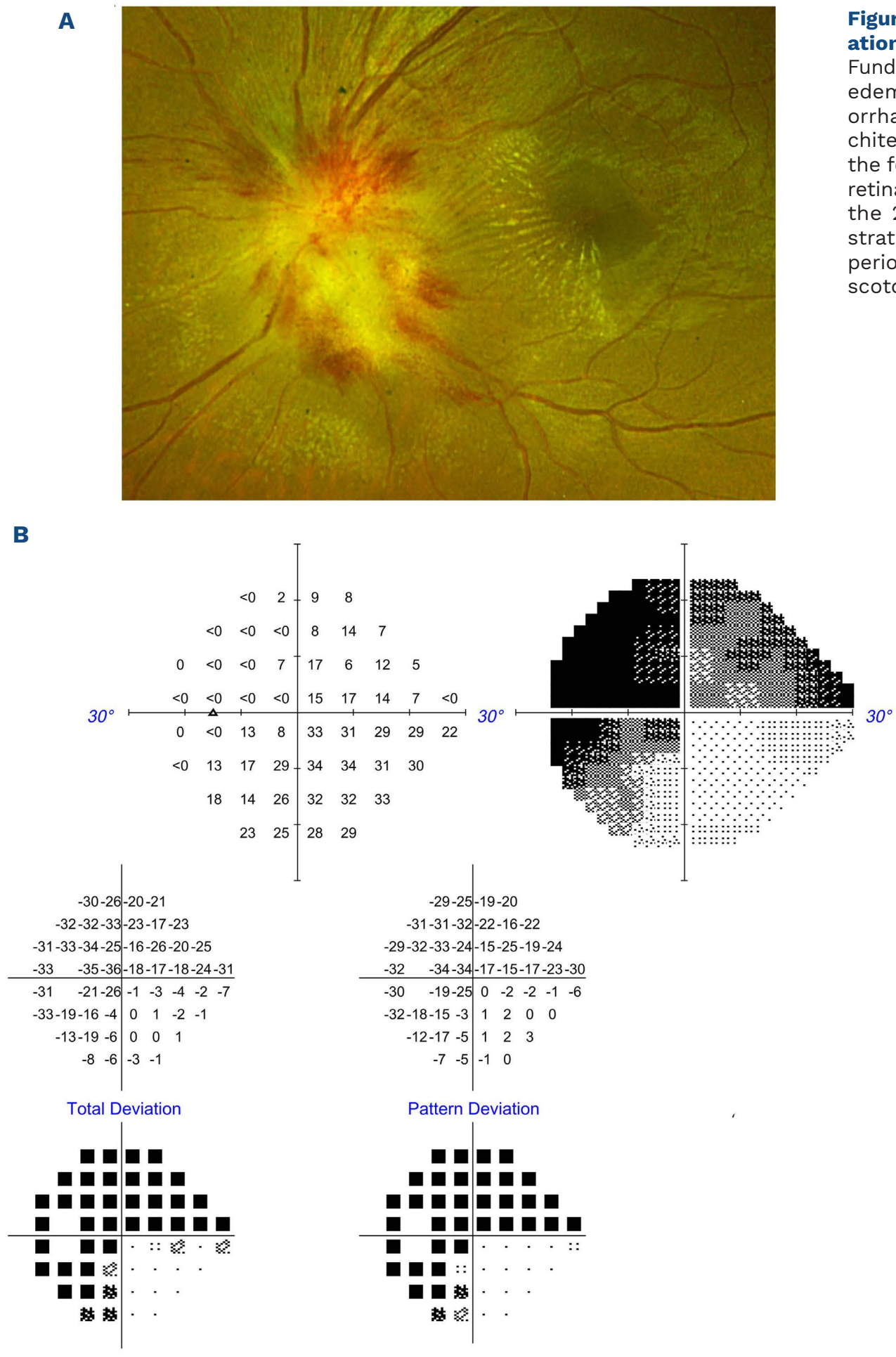

Figure 2. Diagnostic ophthalmologic evaluation revealing leukemic retinopathy. (A) Fundus photography reveals severe optic disc edema with associated exudates and hemorrhages, leading to loss of normal disc architecture. Radial white streaks surrounding the fovea, forming a "macular star," indicate retinal exudation. (B) Visual field testing with the 24-2 SITA-Fast test strategy demonstrates complete visual field loss in the superior half and an inferior temporal quadrant scotoma in the left eye.

monocular vision loss, though a subacute course may occur. Visual acuity and visual field deficits vary significantly on examination. Fundoscopy typically reveals severe optic disc edema with diffuse white exudation, obscuration of adjacent retinal vessels, and peripapillary hemorrhages. Leukemic cells are frequently present in the vitreous.

Leukemic infiltration of the optic nerve is a neuro-oncologic emergency requiring urgent intervention.[12] As the optic nerve is a white matter tract of the central nervous system, leukemic optic neuropathy inherently indicates CNS leukemic infiltration. However, diagnosis lacks consensus criteria and is often presumptive. Magnetic resonance imaging with gadolinium typically shows optic nerve enhancement, though up to 43% of cases demonstrate normal findings.

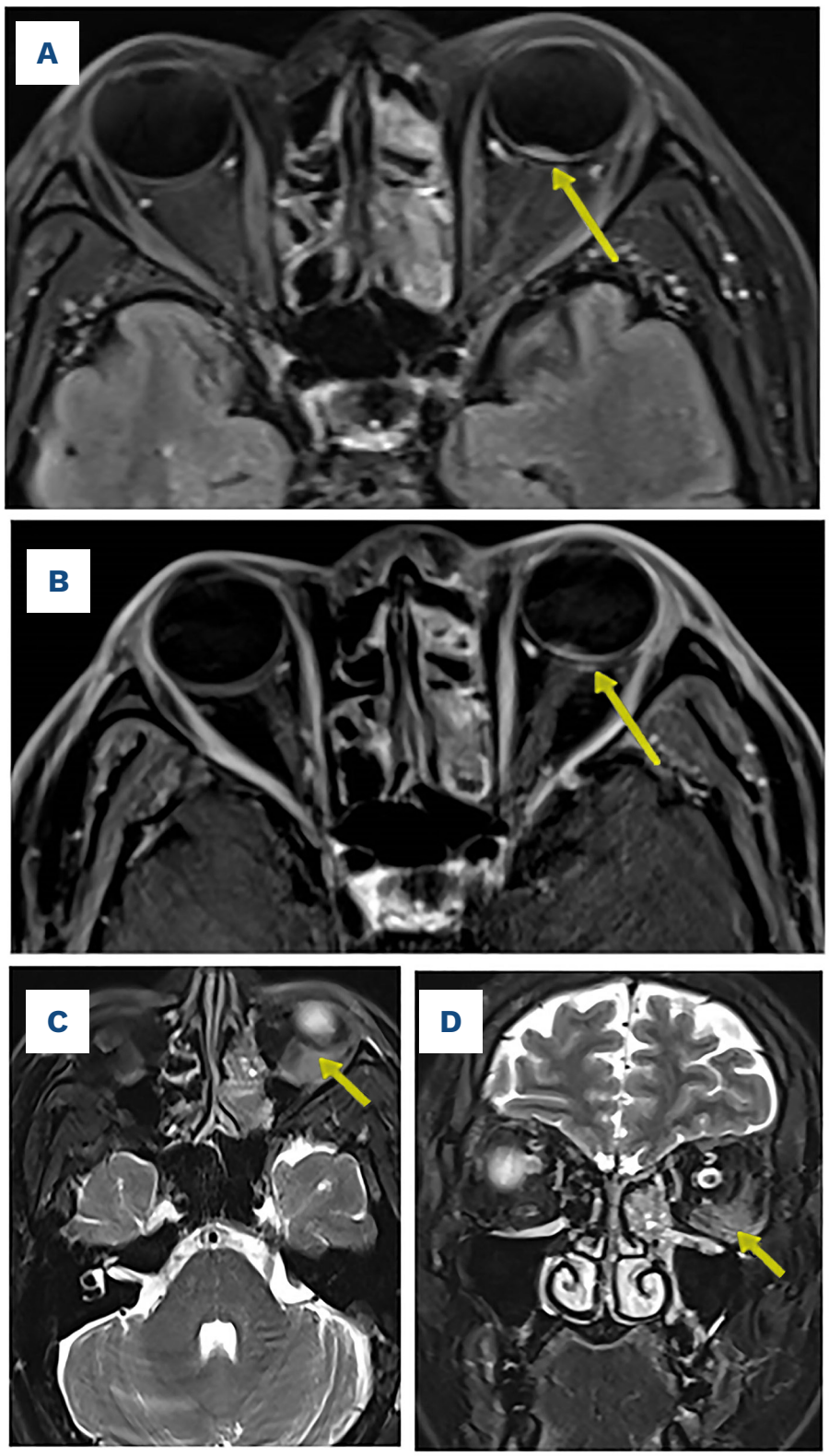

Figure 3. Orbital magnetic resonance imaging demonstrating orbit involvement. (A) Axial FLAIR sequence reveals a hyperintense signal in the left posterior sclera at the optic nerve insertion into the globe (yellow arrow). (B) Axial T1-weighted sequence with fat suppression after gadolinium injection demonstrates contrast enhancement of the left posterior sclera (yellow arrow). (C, D) Axial and coronal T2-weighted sequences, respectively, show a hyperintense, poorly demarcated orbital lesion located posterior and inferior to the left globe (yellow arrows), most consistent with an orbital chloroma.

Initial diagnostic approach involves lumbar puncture (LP), although the diagnostic yield remains low. Vitreous cytology offers an alternative diagnostic pathway and may be the sole positive finding.[13] While needle vitreous tap is feasible, small-gauge *pars plana* vitrectomy under local anesthesia is preferred due to its minimal perioperative risk. Optic nerve biopsy may be considered in cases of severe vision loss but serves as a last resort given its destructive nature. Systemic chemotherapy remains the cornerstone of treatment, in conjunction with intrathecal chemotherapy. Radiation therapy may be considered for localized disease control. Visual recovery has been documented with CNS-penetrating systemic chemotherapy, repeated intrathecal chemotherapy, and fractionated orbital radiation as single or combined modalities.[14] However, systemic and optic nerve disease frequently recur, resulting in a dismal prognosis, mainly due to resistant systemic relapse. This report has been approved by the institutional review board and the patient has signed an informed consent.

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Disclosures

No conflicts of interest to disclose.

Contributions

NS, PR and OW supervised the study. NS, AR, ASA, PR and OW collected clinical data and managed patient care. OB contributed to ophthalmologic assessment and interpretation. SY and RTM conducted genetic analysis. AS performed pathology analysis. NS and OW wrote the manuscript with input from all authors.

Data-sharing statement

For original data, please contact the corresponding author.

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