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Ocular involvement in TEMPI syndrome

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ABSTRACT

Purpose: We report the first case of ocular involvement in TEMPI syndrome, a rare disease characterized by telangiectasias, elevated erythropoietin with erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intra-pulmonary shunting.

Observations: A 64-year-old Caucasian man with history of TEMPI syndrome presented with subacute bilateral painless vision loss. Ocular examination showed chronic retinal ischemia with microvascular damage, which was likely associated with the chronic systemic hypoxemia, and spontaneous wax and wane of cystoid macular edema, presumedly related to the systemic bortezomib treatment.

Conclusions and importance: Our case demonstrates that pathologic retinal vascular changes could be seen in association with TEMPI syndrome and suggests that a comprehensive ophthalmological examination may be beneficial for these patients.

1. Introduction

TEMPI syndrome is a rare disease characterized by telangiectasias, elevated erythropoietin (EPO) level with erythrocytosis, monoclonal gammopathy, perinephric fluid, and intra-pulmonary shunting.[1] To the best of our knowledge, this syndrome has never been associated with any ocular manifestations. In this report, we presented the first case of ocular involvement in TEMPI syndrome.

2. Case report

A 64-year-old Caucasian man with a history of TEMPI syndrome presented to the Wilmer Eye Institute for evaluation of subacute bilateral painless vision loss.

3. Summary of medical presentation

Prior to his diagnosis with TEMPI syndrome, the patient had an eighteen-year history of presumed polycythemia vera, diagnosed based on elevated hematocrit and managed with therapeutic phlebotomies by a local hematologist. Two years prior to his presentation to our center, he developed worsening symptomatology, including an unintentional 20 pounds weight loss and shortness of breath. A never smoker, he developed worsening dyspnea requiring 4 liters of supplemental oxygen at rest. He was also diagnosed with chronic kidney disease, although laboratory testing for antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, hepatitis C, hepatitis B, complement components C3, and anti-phospholipase A2 receptor antibodies were all unremarkable.

He subsequently sought a second opinion at the Johns Hopkins Hospital, and underwent an extensive hematologic work up that revealed a hematocrit of 55.0%, hemoglobin of 15.3 g/dL, erythropoietin (EPO) level of 2062.0 mU/mL, ferritin of 5 μg/L, and negative JAK2 comprehensive mutation analysis. Gammopathy studies revealed an IgG kappa M-spike of 0.6 g/dL, IgG of 1800 mg/L with a serum free kappa to lambda light chain ratio of 3.0, and minor proteinuria of 30 mg/dL with a small IgG kappa κ monoclonal band on immunofixation. The bone marrow biopsy revealed a hypercellular bone marrow with maturing trilineage hematopoiesis, erythroid and megakaryocytic hyperplasia, and an 8% clonal kappa restricted plasmacytosis. Myeloma fluorescence in situ hybridization and cytogenetics were normal. Bone imaging was negative for lytic lesions.

Transthoracic echocardiogram and ventilation/perfusion scan revealed an intra-pulmonary shunt of >20%. He endorsed chronic

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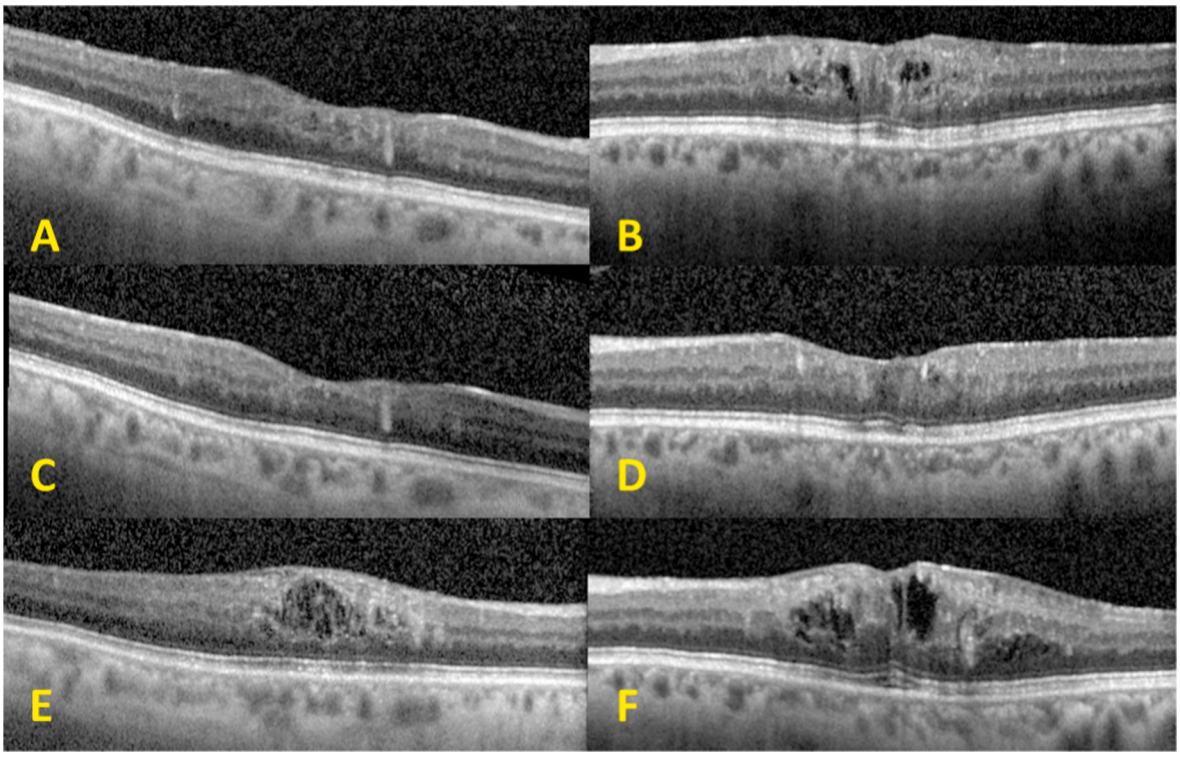

Fig. 1. Optical coherence tomography images at presentation (A, OD; B, OS), 1-week follow up (C, OD; D, OS), and 2-month follow up (E, OD; F, OS), showing spontaneous waxing and waning of cystoid macular edema.

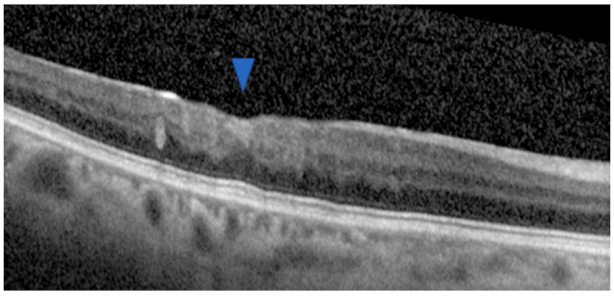

Fig. 2. Optical coherence tomography of the right eye showed focal inner retinal thinning, consistent with prior retinal ischemia (blue arrow head). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

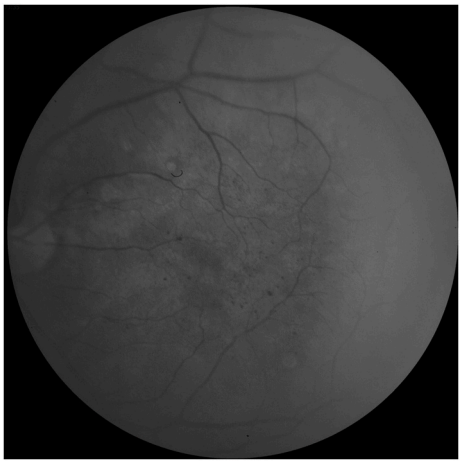

Fig. 3. Red free photograph of the left eye showed numerous parafoveal microaneurysms.

epistaxis, and rigid nasal endoscopy revealed telangiectasias over nasal septum and turbinates. He was then diagnosed with TEMPI syndrome on the basis of skin and mucous membrane telangiectasias, erythrocytosis, monoclonal gammopathy, and intra-pulmonary shunting.

He was subsequently initiated on bortezomib-based therapy with a partial hematological response. His M spike decreased from 0.6 g/dL to 0.3 g/dL, but the light chain ratio remained stable at 3.0. Initially, his EPO level decreased from 2400 to 1077 mU/mL. He was ultimately switched to salvage daratumumab with lenalidomide and dexamethasone, to which he had an outstanding hematologic and end organ response with resolution of the gammopathy, reduction of EPO level to 50 mU/mL, and elimination of the need for supplemental oxygen. Patient has since moved and is now managed at another institution.

4. Ocular presentation

The patient's ocular symptoms of subacute bilateral painless vision loss began a few months prior to his presentation to our institution, when he had no known ocular history. His Snellen visual acuity (VA) on presentation was 20/63 in the right eye and 20/80 in the left eye. The anterior segment exam was unremarkable. The funduscopic examination revealed bilateral retinal microaneurysms (MAs) and bilateral cystoid macular edema (CME) in the central macula, which was worse in the left eye (Fig. 1). Optical coherence tomography (OCT) of the right eye showed scattered areas of focal inner retinal thinning, consistent with prior retinal ischemia (Fig. 2). Red free photograph showed parafoveal microaneurysms in both eyes, which were more obvious in the left eye (Fig. 3). Fluorescein angiography (FA) of the right eye showed microaneurysms and diffuse leakage, and FA of the left eye revealed an enlarged foveal avascular zone, areas of retinal non-perfusion, parafoveal microaneurysms, vascular anastomoses, and vascular leakage in the macula (Fig. 4). The retinal veins were not tortuous and there were no

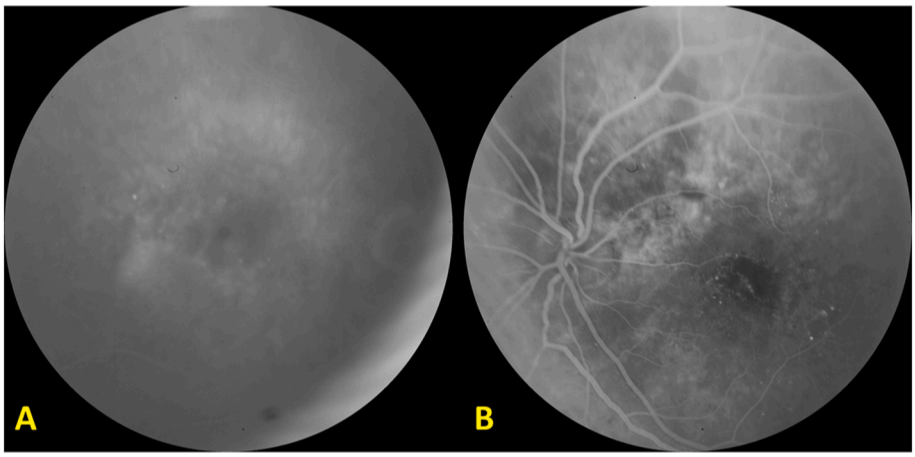

Fig. 4. Fluorescein angiography of the right eye (A) showed microaneurysms and diffuse leakage, while the left eye (B) showed an enlarged foveal avascular zone, areas of retinal non-perfusion, vascular anastomoses, and diffuse leakage.

intraretinal hemorrhages in the peripheral retina to suggest a prior retinal vein occlusion. His clinical examination and retinal imaging were consistent with retinal microvascular damage and chronic ischemia.

The patient was offered off-label treatment with intravitreal anti-vascular endothelial growth factor (VEGF) injections, but he opted for observation. In the absence of ocular medication, repeated OCT imaging showed both spontaneous resolution and recurrence of CME over the next 2 months (Fig. 1).

5. Discussion

TEMPI syndrome was first described in 2011 and is a rare multi-system disease characterized by telangiectasias, elevated EPO level with erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intra-pulmonary shunting.[1] While the pathophysiology of TEMPI syndrome remains unclear, some TEMPI patients showed complete or partial response to treatments with plasma cell directed therapy, including bortezomib,[2–4] daratumumab,[5] and lenalidomide,[6] with resultant normalization of serum EPO level, eradication of monoclonal gammopathy, and resolution of other signs, implicating that either the monoclonal antibodies or the monoclonal plasma cells are involved in the pathophysiology of TEMPI syndrome.[7] This is further supported by hematologic and clinical responses following autologous stem cell transplantation.[8]

Our patient showed clear signs of chronic retinal ischemia and microvascular damages, as evidenced by focal inner retinal thinning on OCT imaging and various findings on FA, including vascular shunting, retinal microaneurysms, and capillary drop out. Given he did not have diabetes mellitus, his hypertension was well controlled, and his retinal examination was not consistent with previous retinal vein occlusions, the retina ischemic changes were likely TEMPI related. While it was impossible to identify the exact causal pathways, the retinal microvascular changes likely resulted from chronic systemic hypoxemia status caused by intra-pulmonary shunting. Although pathologic retinal vascular changes due to gammopathy-related syndromes, such as Waldenstrom's macroglubulinemia and multiple myeloma, have been reported in the past,[9–11] we do not believe chronic vascular plugging is a likely etiology for our patient's retinal findings. Our patient did not have IgM gammopathy, and the size of the M spike was much smaller compared to what is usually seen in hyperviscosity.[12]

While CME can develop as a result of various pathologic processes, it is well known that retinal ischemia increases the VEGF level within the retina, which in turn increases the endothelial permeability of retinal capillaries and leads to the accumulation of CME.[13–19] Therefore, we believe the CME seen in our patient was VEGF-driven in response to chronic retinal ischemia. The spontaneous waxing and waning of CME in the absence of ocular interventions in this case was also intriguing, and we hypothesize that it could be related to our patient's systemic bortezomib treatment, as bortezomib has been shown to inhibit hypoxia-inducible factors, which in turn down regulates VEGF.[19–24]

To date, a total of 23 cases of TEMPI syndrome have been described worldwide,[25] and to our knowledge, none of the TEMPI cases reported pathologic ocular findings. Not only did our patient had pathologic retinal microvascular damages, these pathologic changes were also visually significant, as both CME and macular ischemia adversely affect vision. Moreover, chronic untreated retinal ischemia could lead to blinding complications, such as proliferative retinopathy, vitreous hemorrhage, tractional retinal detachment and neovascular glaucoma, and early identification of the retinal pathologies is crucial for the patient's visual outcome.

6. Conclusions

In conclusion, our case demonstrates that pathologic retinal vascular changes could be seen in association with TEMPI syndrome and suggests that a comprehensive ophthalmological examination, with particular attention to the retina with multimodal imaging, may be beneficial for these patients.

Patient consent

Written consent to publish this case has been obtained from the patient. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

No conflicting relationship exists for any authors.

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