Subretinal fluid accumulation in a patient with polycythemia vera after receiving a prostaglandin I2 analogue treatment

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ABSTRACT

Purpose: To report a case of polycythemia vera (PV) with subretinal fluid accumulation after the administration of prostaglandin I2 (PGI2) analogue.

Observations: A 57-year-old woman diagnosed as having PV was referred to our department for the evaluation of severe metamorphopsia in the left eye, which gradually progressed after the initiation of oral administration of PGI2 mimetics. At the first visit, the patient’s best-corrected visual acuities (BCVAs) were 20/20 OD and 20/30 OS. Fundus examination and optical coherence tomography revealed the presence of subretinal fluid (SRF) in the left eye and multiple serous pigment epithelial detachments (PEDs) in both eyes. Fluorescein angiography revealed central serous chorioretinopathy (CSC)-like lesions, consisting of dye pooling corresponding to the PEDs in both eyes and dye leakage in the left eye. Indocyanine green angiography and laser speckle flowgraphy revealed dilated choroidal veins and reduced choroidal blood flow, respectively. The central choroidal thickness (CCT) measured at the first visit showed a relatively thickened choroid in the left eye. Laboratory data showed mild pancytosis. The patient was diagnosed as having CSC associated with a background of PV, presumably triggered by the PGI2 analogue. One month after cessation of drug administration, the patient’s BCVA improved, the CCT slightly decreased, and serous retinal detachment and PED disappeared in the left eye.

Conclusions and importance: Our case of PV presenting with CSC-like lesions after PGI2 analogue administration indicates the possible risk of SRF accumulation by PGI2 analogues in patients with PV.

1. Introduction

Polycythemia vera (PV) is a rare, acquired myeloproliferative neoplasm (MPN) with a prevalence of 2.3–2.8/100,000 persons/year. 1 Patients with PV present with erythrocytosis, thrombocytosis, neutrophil leukocytosis, reduced serum erythropoietin levels, splenomegaly, and transformation to myelofibrosis or acute myeloid leukemia. 2 Gain-of-function somatic mutation of the tyrosine kinase Janus kinase 2 (JAK2), which increases the activation of the JAK2/signal transducer and activator of transcription (STAT) signaling pathway, is responsible for the pathogenesis in approximately 95% of patients with PV. 3 Moreover, constitutive activation of JAK2/STAT signaling leads to cell proliferation and clonal expansion of myeloproliferative malignant cells, 4 which subsequently increase the risk of thrombotic and hemorrhagic predispositions in the body. Ocular manifestations of patients with PV, including central retinal artery occlusion, 5,6 central retinal vein occlusion, 7 and anterior ischemic optic neuropathy, 8 all of which were presumably caused by the increased blood viscosity, have been reported to date.

Prostaglandin (PG) analogues are the most potent ocular hypotensive medications for the treatment of open-angle glaucoma. PG analogues have become the first-choice therapy for open-angle glaucoma and has improved intraocular pressure control in patients with most forms of glaucoma. However, there are several reports regarding the association between PGF2 alpha analogue latanoprost and serous choroidal effusion, 9,10 indicating that PG analogues potentially participate in the accumulation of subretinal fluid (SRF) under certain circumstances.

Here, we report a case of PV complicated with SRF accumulation after systemic administration of beraprost sodium, a stable analogue of PGI2.

2. Case report

A 57-year-old woman was diagnosed as having PV and was treated by phlebotomy. The patient developed deep vein thrombosis with an

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intractable cutaneous ulcer, and oral administration of beraprost sodium was initiated to improve blood flow to the lower extremities. Systemic corticosteroids were not administered. Ten days after the initiation of beraprost sodium administration, she complained of progressive metamorphopsia affecting her left eye, and she was referred to our department approximately 1 month later. Written informed consent was obtained from the patient for the publication of this case report. At the first visit, the patient’s best-corrected visual acuities (BCVAs) were 20/20 OD and 20/30 OS. The results of anterior-segment slit-lamp examination were unremarkable except for mild cataract OU, and the intraocular pressure was within the normal range. Fundus examination revealed the presence of serous pigment epithelial detachment (PED) temporal to the fovea in the right eye and SRF at the fovea with multiple PEDs in the left eye (Fig. 1). Fundus fluorescein angiography (FA) revealed dye pooling corresponding to the PEDs in both eyes and dye leakages at the superotemporal quadrant of the macula in the left eye.

Fig. 1. Color fundus photography. Serous pigment epithelial detachments (PEDs) temporal to the fovea (arrows) and serous retinal detachment involving the fovea with multiple PEDs (arrows) are present in the right eye and the left eye, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2. Fluorescein angiography. In the late phase, hyperfluorescence and dye pooling corresponding to the pigment epithelial detachments (arrows) were present in both eyes. Dye leakage (yellow arrowhead) was detected in the superotemporal quadrant of the macula. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
Indocyanine green angiography revealed hypofluorescent spots representing serous pigment epithelial detachments (arrows) and dilated choroidal veins (yellow arrowhead) were visualized. In the late phase, choroidal vascular hyperpermeability were remarkable. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Laser speckle flowgraphy (LSFG) revealed a diffuse cold-color pattern of the color map in the macular area bilaterally, indicating a reduction in choroidal blood flow (Fig. 4). Since macular LSFG color map is largely derived from the choroid, diffuse cold color pattern in the macular area indicated a reduction in the choroidal blood flow of the present case. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Indocyanine green angiography revealed hypofluorescent spots representing serous PEDs, choroidal vein dilatation in the early phase, and multiple choroidal vascular hyperpermeability in the late phase (Fig. 3). Laser speckle flowgraphy (LSFG) revealed a diffuse cold-color pattern of the color map in the macular area bilaterally, indicating a reduction in choroidal blood flow (Fig. 4). Enhanced depth imaging optical coherence tomography revealed the presence of PED temporal to the fovea in the right eye and SRF at the fovea with PED in the left eye (Fig. 5A). The central choroidal thicknesses (CCTs) measured at the fovea were 309 μm OD and 462 μm OS, demonstrating a relatively thickened choroid in the left eye (Fig. 5). Laboratory data showed mild pancytosis: a red blood cell count of $6.41 \times 10^6/\mu l$, white blood cell count of 20,300/μl, platelet count of 53.4 $\times 10^4/\mu l$, and hematocrit level of 39.3%.

On the basis of the findings and short-term onset of metamorphopsia after beraprost sodium administration, the patient was diagnosed as having central serous chorioretinopathy (CSC) associated with a back-ground of PV, presumably triggered by beraprost sodium. One month after the cessation of drug administration, the patient’s BCVA improved to 20/20 OU, and serous retinal detachment and PED disappeared in her
posterior segment of the eye, such as central retinal artery occlusion, ocular manifestations of PV are related to thrombotic obstruction in the ability and abnormal red cell adhesion, the most commonly described-
left eye (Fig. 5). The CCTs slightly decreased to 294 μm and 445 μm in the right and left eyes, respectively (Fig. 5B).

3. Discussion

In the present case, a patient with PV who showed a thickened choroid developed CSC-like lesions after the administration of beraprost sodium; however, the lesions disappeared rapidly after the cessation of drug administration. To the best of our knowledge, this is the first report demonstrating the possible risk of SRF accumulation by a PGI2 analogue in patients with PV.

Erythrocytosis, the prevailing characteristics of PV, elevates the hematocrit level and causes hyperviscosity, which plays a major role in the pathogenesis of both microcirculatory disturbances and thrombosis. Because of the hyperviscosity, resulting in reduced red cell deformability and abnormal red cell adhesion, the most commonly described ocular manifestations of PV are related to thrombotic obstruction in the posterior segment of the eye, such as central retinal artery occlusion, central retinal vein occlusion, anterior ischemic optic neuropathy, and choroidal infarction. In addition to the thrombotic events, several studies have indicated the presence of blood flow congestion due to hyperviscosity in the retina and choroid in patients with PV. It has been shown that macular venous blood velocity increased in the retina of patients with MPN when there was complete hematological remission after treatment, suggesting that retinal blood flow velocity decreased in the acute stage of MPN. Furthermore, the arm-to-choroid filling time, defined as the beginning of choroidal filling with dye after injection into the right brachial vein upon FA, was significantly longer in patients with PV than in control subjects. In concordance with the previous reports, LSFG revealed a diffuse cold-color pattern in the macular area in the present case, indicating delayed choroidal blood flow. This case and previous studies clearly demonstrate the presence of congestion of choroidal blood flow in patients with PV.

Thus far, it has been hypothesized that blood flow congestion is related to choroidal thickening in ocular disorders. In CSC which is characterized by serous detachment of the neurosensory retina, congestion of choroidal outflow was identified as a contributing factor to the pathogenesis of the disease. As choroidal vessel dilatation correlates with choroidal thickening in CSC eyes, it is most likely that choroidal congestion is at least one of the triggers causing choroidal thickening and subsequent SRF accumulation in the eye. In fact, it was experimentally elucidated that choroidal vessel congestion induces choroidal thickening with choroidal vessel dilatation. In addition, SRF accumulation and PED formation in a patient with hyperviscosity syndrome were reported. In patients with PV, it was demonstrated that choroidal thickness showed a positive correlation with hematocrit levels, indicating that uncontrolled erythrocytosis is an aggravating factor of choroidal thickening in PV. Taken together, several lines of evidence indicate that choroidal blood flow congestion is implicated in the increase of choroidal thickness and potentially leads to SRF accumulation in cases of PV.

However, neither SRF accumulation nor PED formation in cases of PV has been reported, implying that choroidal thickening alone due to blood flow congestion is insufficient to cause fluid accumulation in the subretinal space of PV cases. There are several possibilities accounting for the unusual SRF accumulation and PED formation in the present case of PV, in which the onset and their resolution completely coincided with the initiation and discontinuation of the PGI2 analogue. First, in the present case, a PGI2 mimetic was used for the treatment of cutaneous ulcer in the lower extremities. Within the vasculature, PGI2 inhibits platelet aggregation as a major inhibitory prostaglandin and serves as a potent vasodilator; therefore, a stable analogue of PGI2 was administered in the present case. It has been previously reported that PGI2 elicits vasorelaxation as a downstream molecule of nitric oxide in the choroid and increases retinal and choroidal blood flow. Hence, it is possible that the PGI2 mimetic boosted the SRF accumulation caused by choroidal blood flow congestion in the present case. Thus far, the association between serious choriorretinopathy and PGI2 alpha analogue, latanoprost, has been documented. As PG analogues, it is possible that the PGI2 mimetic, beraprost sodium, also caused the SRF accumulation in the present case of PV. However, to the best of our knowledge, neither subretinal detachment nor serious choriorretinopathy caused by PGI2 analogue alone has been reported. Therefore, it may be true that PGI2 analogue per se was not a sufficient condition to induce SRF accumulation and the choroidal congestion or hyperviscosity due to PV. Second, another possibility is that pachychoroid characteristics existed originally in the present case, independent of the use of PGI2 mimetics. As OCT examination was not performed in our patient before the first visit, this possibility could not be excluded. However, representative cases of CSC related to the pachychoroid characteristics showed a warm-color pattern of the color map in LSFG, indicating the choroidal blood flow elevation. Since the present case showed a cold-color pattern of the color map in LSFG, it is likely that administration of PGI2 mimetics was the trigger to boost the SRF accumulation and PED formation in the present case. Nonetheless, our case report is limited by the challenges common to studying rare diseases. Further clinical experience is warranted to elucidate the causal association between PGI2 mimetics and SRF accumulation in patients with PV.

4. Conclusions

In summary, we encountered a case of PV presenting with CSC-like lesions after PGI2 analogue administration. While PGI2 analogues contribute to the improvement of systemic symptoms in patients with

Fig. 5. Enhanced depth imaging optical coherence tomography (EDI-OCT) before and after administration of prostaglandin I2 (PGI2) mimetics. (A) At the first visit, EDI-OCT revealed the presence of pigment epithelial detachment (PED) temporal to the fovea in the right eye and diffuse subretinal fluid accumulation at the fovea with PED in the left eye. (B) One month after the withdrawal of PGI2 mimetics, choroidal thickness slightly reduced in both eyes. In addition, serous retinal detachment and PED disappeared in the left eye, while PED remained in the right eye. Using EDI-OCT horizontal-scan images through the fovea, CCT was manually measured as the distance from the outer border of the hyporeflective line corresponding to the RPE, to the outer border of the choroid beneath the fovea.
PV, it is also likely to increase the choroidal circulation due to vasodilator effects. Our case indicates the possible risk of SRF accumulation by PG12 analogues in patients with PV.

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Declaration of competing interest
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