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Near-complete vision recovery from bilateral serous retinal detachment associated with thrombotic thrombocytopenic purpura

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SUMMARY

Ocular manifestations of thrombotic thrombocytopenic purpura (TTP) are uncommon, and bilateral retinal detachment is a rare presentation of TTP. We report a rare case of bilateral retinal detachment from underlying TTP in a patient presenting with vision loss. A 56-year-old man presented with a 4-day history of bilateral vision loss. Bilateral serous retinal detachment was confirmed using dilated ophthalmoscope examination. Laboratory results were significant for severe thrombocytopenia, peripheral smear revealed numerous schistocytes and ADAMTS13 activity of less than 1%. The patient was treated with plasma exchange (PLEX), prednisone, rituximab and caplacizumab. This case report highlights that prompt treatment of TTP with PLEX, prednisone, rituximab and caplacizumab could result in significant vision recovery.

BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening condition originally described in 1924 and characterised by the pentad of thrombocytopenia, microangiopathic haemolytic anaemia, neurologic symptoms, renal failure, and fever.¹ The pentad of TTP is present in only 5% of patients. Moreover, presence of all of these signs indicates late presentation which is associated with high mortality and can be avoided with early diagnosis and prompt treatment. The dysregulation of von Willebrand (vWF)-dependent platelet adhesion causes microvascular thrombosis in multiple organs and is the feature of TTP.² The common laboratory abnormalities include decreased platelet count, elevated lactate dehydrogenase, negative direct antiglobulin test and schistocytes on peripheral smears. Elevated creatine is seen with renal involvement. In contrast to disseminated intravascular coagulation, TTP has a normal coagulation panel. Furthermore, testing of ADAMTS13 levels will be abnormally low. The presence of thrombocytopenia and microangiopathic haemolytic anaemia and the absence of alternative causes should be treated empirically as TTP prior to the ADAMTS level resulting as its mortality exceeds 90% if left untreated.¹

Ocular involvement is an uncommon manifestation of TTP, occurring in 14%–20% of patients reviewed.^{3–6} It is suspected that injury occurs from a combination of haemorrhagic and vaso-occlusive microangiopathy due to intravascular coagulation. Percival published the first case report of a patient

who presented with bilateral exudative retinal detachment and TTP.⁶ Ocular manifestations of TTP were further delineated based on whether they are caused by more focal ocular lesions versus systemic microangiopathic involvement.^{4–6} The former category includes retinal detachment, choroidal bleeding and homonymous hemianopsia secondary to haemorrhagic lesions at the occipital poles. In the latter category, hypertensive retinopathy, chemosis, subconjunctival bleeding and retinal bleeding are associated with systemic manifestation of TTP. There are few case reports of bilateral retinal detachment as the initial manifestation of TTP. More commonly, retinal haemorrhages and serous macular degeneration were noted as primary ophthalmologic manifestation of TTP.^{3–5–7–13} The wide range of reported vision complaints and variable ophthalmologic findings make TTP easy to overlook in the absence of additional systemic manifestations or laboratory evidence. To the best of our knowledge, we report the first case of TTP treated with plasma exchange (PLEX), prednisone, rituximab and caplacizumab with significant improvement of the patient's vision loss.

CASE PRESENTATION

A 56-year-old man presented with a 4-day history of bilateral vision loss, reported as curtains of red and black across his vision in both eyes. There were no other associated visual symptoms including ocular pain, focal weakness, recent illness or fever. He noted intermittent gum bleed while brushing his teeth for a few days prior to arrival. Other review of system was negative for mouth ulcers, joint pain, shortness of breath, hematochezia or melena or chest pain but was remarkable for a skin rash in the dorsal and ventral surfaces of both hands and hair loss of eyebrows and hairline for the past few months. His medical history was significant for hypertension and the recent diagnosis of biopsy-proven psoriasiform dermatitis of his hands and scalp. His medications included amlodipine and triamcinolone ointment. He had a history of daily drinking (six beers/day) but denied history of any illicit drug use. Family history was negative for malignancy or autoimmune disease.

INVESTIGATIONS

The patient's vitals on presentation were notable for blood pressure of 153/88 and heart rate of 104. Physical examination was remarkable for



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erythematous and eroded papules on bilateral dorsal and ventral hands. There was no evidence of mucosal bleed or purpura. Ophthalmology service was consulted for acute painless bilateral vision loss. Visual acuity test noted 20/200 in the left eye and 20/400 in the right eye, with no improvement with correction or on pinhole testing. Intraocular pressure of the right eye by tonopen was 22 mm Hg and that of the left eye was 24 mm Hg. Anterior segment examination revealed conjunctival injection, 3+ anterior chamber white blood cell and 1+ flare consistent with intraocular inflammation in both eyes. In the fundus examination, they noted a cup-to-disc ratio of 0.5, no oedema and yellow/white patchy subretinal lesions in the bilateral posterior pole, along with the presence of inferior subretinal fluid extending into the macula that exhibited a shifting pattern with patient positioning, suggestive of serous retinal detachment. There was absence of retinal holes, tears or breaks on peripheral examination. There were minimal cotton wool spots and intraretinal haemorrhages.

Laboratory studies were significant for platelets of less than 5 ($160\text{--}383 \times 10^9/L$), haemoglobin of 8.1 g/dL with baseline haemoglobin of 12 ($13\text{--}17$ g/dL), lactate dehydrogenase of 1018 ($135\text{--}225$ units/L), undetectable haptoglobin, total bilirubin of 3.7 ($0.2\text{--}1.3$ mg/dL) with indirect bilirubin of 1.2 ($0\text{--}0.3$ mg/dL) and international normalized ratio (INR) of 1.4. Rapid plasma reagin (RPR) was non-reactive. Peripheral smear had numerous schistocytes per high-power field. Creatine was 0.92 mg/dL with baseline of 0.64. ADAMTS13 antibody was more than 104 (≤ 15 units/mL) and ADAMTS activity was less than 1% ($40\text{--}130\%$). French Score was 2. Further work up revealed erythrocyte

sedimentation rate (ESR) of 110 ($0\text{--}20$ mm/hour), C-reactive protein (CRP) of 2.1 ($0\text{--}0.5$ mm/dL), C3 level of 62 ($90\text{--}180$ mg/dL), C4 level of 9 ($10\text{--}40$ mg/dL), negative antinuclear antibody, negative double stranded DNA antibody and anti-Smith antibody of 4.2 ($0\text{--}0.9$ AI). Additionally, human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C antibody were non-reactive. Vitamin B₁₂ level was within range. Screen for malignancy with CT scan of the chest, abdomen and pelvis was unrevealing.

The patient's presentation was suggestive of lupus-related TTP given positive anti-Smith antibody, low complements, elevated ESR/CRP and rash consistent with subacute cutaneous lupus erythematosus versus discoid lupus.

TREATMENT

The patient was promptly started on prednisone 1 mg/kg and PLEX. He completed eight cycles of PLEX. Additionally, rituximab 375 mg/m² was started on day 4 and given weekly for a total of four doses. Caplacizumab 11 mg was given daily subcutaneously starting day 5, when his ADAMTS13 antibody came back positive, for a total of four doses due to slow platelet recovery. The patient was discharged after his platelet count improved to normal level. He did not require further treatment after finishing the fourth dose of rituximab at day 28.

OUTCOME AND FOLLOW-UP

The patient had improvement in his vision starting from day 3 of hospitalisation. His platelet count was normal by day 8 (figure 1)

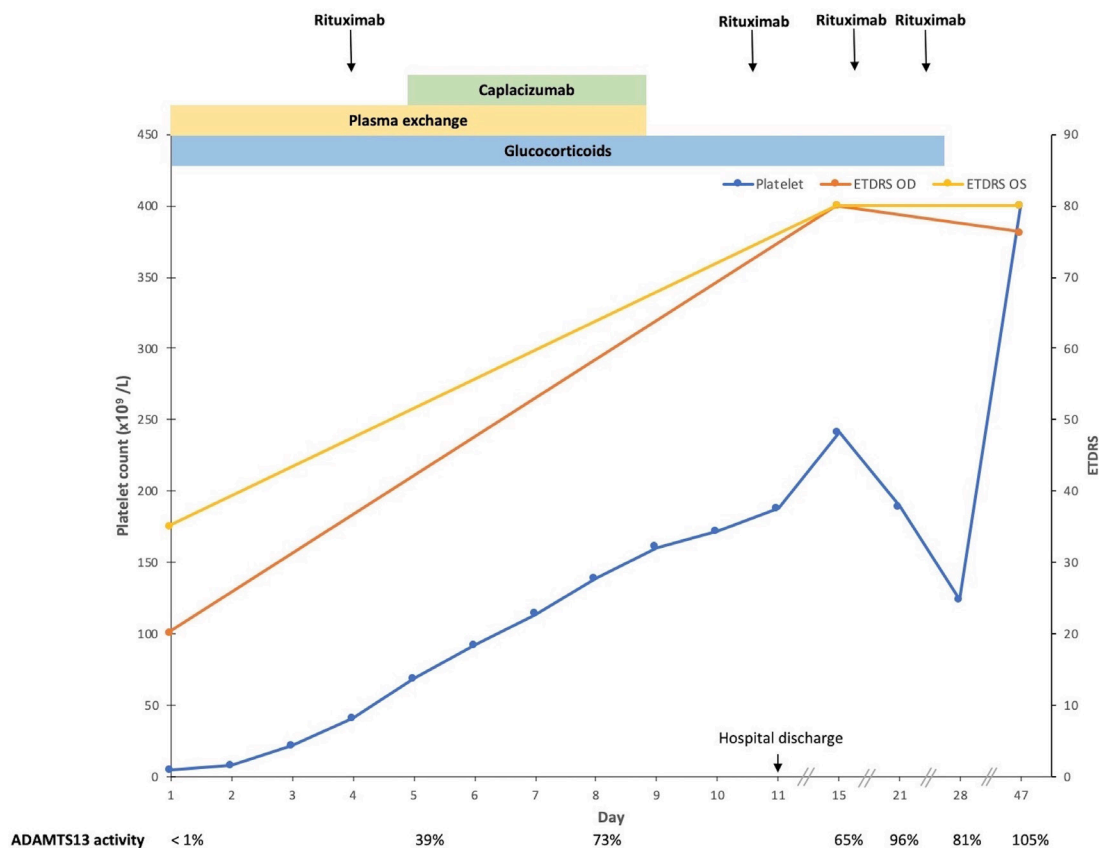


Figure 1 Treatment response. Response of platelet count (normal range $160\text{--}383 \times 10^9/L$), Early Treatment Diabetic Retinopathy Study (ETDRS) chart and ADAMTS13 activity (normal range $40\%\text{--}130\%$) are shown. Data are presented from day 1 of treatment (day of admission) to day 47. The patient received glucocorticoids (day 1 to day 28), plasma exchange (day 1 to day 8), rituximab (days 4, 11, 21 and 28) and caplacizumab (day 5 to day 8). OD, right eye; OS, left eye. Authors will have permission to retain the image.

and his creatine improved to baseline. Follow-up with ophthalmology demonstrated remarkable improvement of linear visual acuity to 20/25 bilaterally on day 14. Optical coherence tomography imaging of the macula demonstrated residual subretinal fluid in the subfoveal region of both eyes confirming bilateral serous retinal detachment. Fluorescein angiography indicated some patchy staining in the macula from residual inflammatory damage but no major dye leakage that would indicate vasculitis. Linear visual acuity in the right eye was 20/30 and in the left eye was 20/25 on day 49. The patient continued receiving outpatient care for his cutaneous lupus erythematosus.

DISCUSSION

In 1991, the TTP-associated mortality had reduced from 50% to 22% with PLEX compared with plasma infusion. As such, PLEX has become the mainstay therapy for TTP.^{1 14 15} PLEX removes circulating antibodies and immune complexes from the patient's plasma. Within one study, out of 15 patients treated with PLEX, complete and lasting remission was noted in 9 instances.¹⁵ Additionally, rituximab, a chimeric mouse-human monoclonal antibody targeted against CD20, has also been used in the management of TTP. CD20 is a transmembrane protein found on B lymphocytes. Once rituximab binds to the CD20 ligand, it induces cell death by multiple modalities including antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity and apoptosis. It also works to rapidly reduce the production of antibodies thereby modulating CD4+ T lymphocytes and regulatory T cells. In a cohort study of UK patients, all 25 patients with refractory or relapsing TTP reached remission within 11 days of starting rituximab.¹⁶ Additionally, patients treated with rituximab had a quicker recovery of ADAMTS13 activity and reduced 1-year relapse rate.¹⁷ Hepatitis B status should be noted prior to administration of rituximab and lamivudine should be administered if hepatitis B is diagnosed.

A more recent development is the humanised single-variable-domain immunoglobulin caplacizumab, which inhibits the interaction between vWF multimers and platelets thereby preventing platelet activation and microvascular thrombosis. Patients who received subcutaneous caplacizumab during PLEX and for 30 days afterwards had a faster resolution of the acute TTP episode. However, these patients also had a higher bleeding risk.¹⁸

Review of case reports for patients with ocular TTP yielded varied treatment strategies and responses. One 46-year-old woman with recurrent TTP presented with sudden vision loss due to unilateral exudative retinal detachment received treatment with PLEX and steroids resulting in improvement in her vision symptoms starting at day 2.¹⁰ Another 32-year-old woman with TTP-associated serous retinal detachment also achieved significant of visual acuity after 6 days of treatment with PLEX and steroids.¹⁹ Another case report noted a young female who developed bilateral serous retinal detachments from TTP that was treated with PLEX and rituximab, with improvement in vision from 20/400 to 20/50 in the span of 16 months.¹³ A paediatric patient who presented with orbital and nasal mucosal bleeding had improvement in the platelet count after three sessions of PLEX, but required 3 months for resolution of the ocular bleeding with long-term vision impairment.⁷ Lastly, a patient with bilateral vision loss due to occlusion of the central retinal artery and vein was monitored for 2 weeks after TTP treatment. Despite pan-retinal photocoagulation and transscleral cyclophotocoagulation, she did not regain meaningful visual function despite successful treatment of the underlying TTP.¹¹

To the best of our knowledge, this is the first case report of TTP with ocular manifestations managed with caplacizumab alongside PLEX, corticosteroids and rituximab. Compared with previous reports in which only PLEX, corticosteroids and rituximab were given, the degree of visual recovery appeared favourable, with improvement noted within 2 days of initiating treatment and resolution within 1 month. In this case, prompt treatment with caplacizumab alongside PLEX, corticosteroids and rituximab might associate with speedy vision recovery. Further review of literature demonstrated two double, blind controlled trials using this regimen that showed a statistically significant reduction in TTP-related death, recurrence of TTP, treatment refractoriness and normalisation of organ-damage markers.^{20 21}

Learning points

- ▶ While acquired thrombotic thrombocytopenic purpura (TTP) is idiopathic in approximately one-third of all cases, it can be associated with malignancy, autoimmune disease, pregnancy and drugs.
- ▶ Ocular TTP, including bilateral retinal detachment, is a rare but devastating manifestation of TTP. Therefore, TTP presenting with ocular manifestation can be overlooked in the absence of other systemic symptoms and supporting laboratory results.
- ▶ Management of TTP includes urgent plasma exchange, steroids and rituximab.
- ▶ The initiation of caplacizumab, in addition to the aforementioned therapies for TTP-associated ocular manifestation, might result in favourable outcomes with near-complete vision recovery.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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