

Case Report

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# Severe Adult Still's Disease Complicated by Purtscher-Like Retinopathy Treated with Intravenous Pulse Methylprednisolone and Tocilizumab

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## Keywords

Purtscher-like retinopathy · Adult Still's disease · Intravenous pulse methylprednisolone · Tocilizumab · Nerve fiber layer defect

## Abstract

Adult Still's disease (ASD) is a rare systemic inflammatory disorder in which ocular manifestations have rarely been described. We report a 29-year-old Japanese woman with a rare case of refractory ASD complicated by Purtscher-like retinopathy. She was diagnosed with ASD and started on a high dose of oral prednisolone. Two days after the initiation of the treatment, she presented with blurred vision in the left eye, and the funduscopic examination revealed bilateral Purtscher-like retinopathy. Despite treatment with high-dose oral prednisolone for 2 weeks, she developed macrophage activation syndrome. Considering the severity of ASD, intravenous pulse methylprednisolone therapy and tocilizumab injection were administered. Although all the laboratory data and Purtscher-like retinopathy gradually improved, nerve fiber layer defect (NFLD) in both eyes appeared and visual field defect remained corresponding to the NFLD. In conclusion, Purtscher-like retinopathy might be useful as a poor prognostic factor of ASD, which needs appropriate systemic immunosuppressive treatment. Early detection and long-term follow-up of Purtscher-like retinopathy is important because it has the possibility of developing permanent visual field defect.

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## Introduction

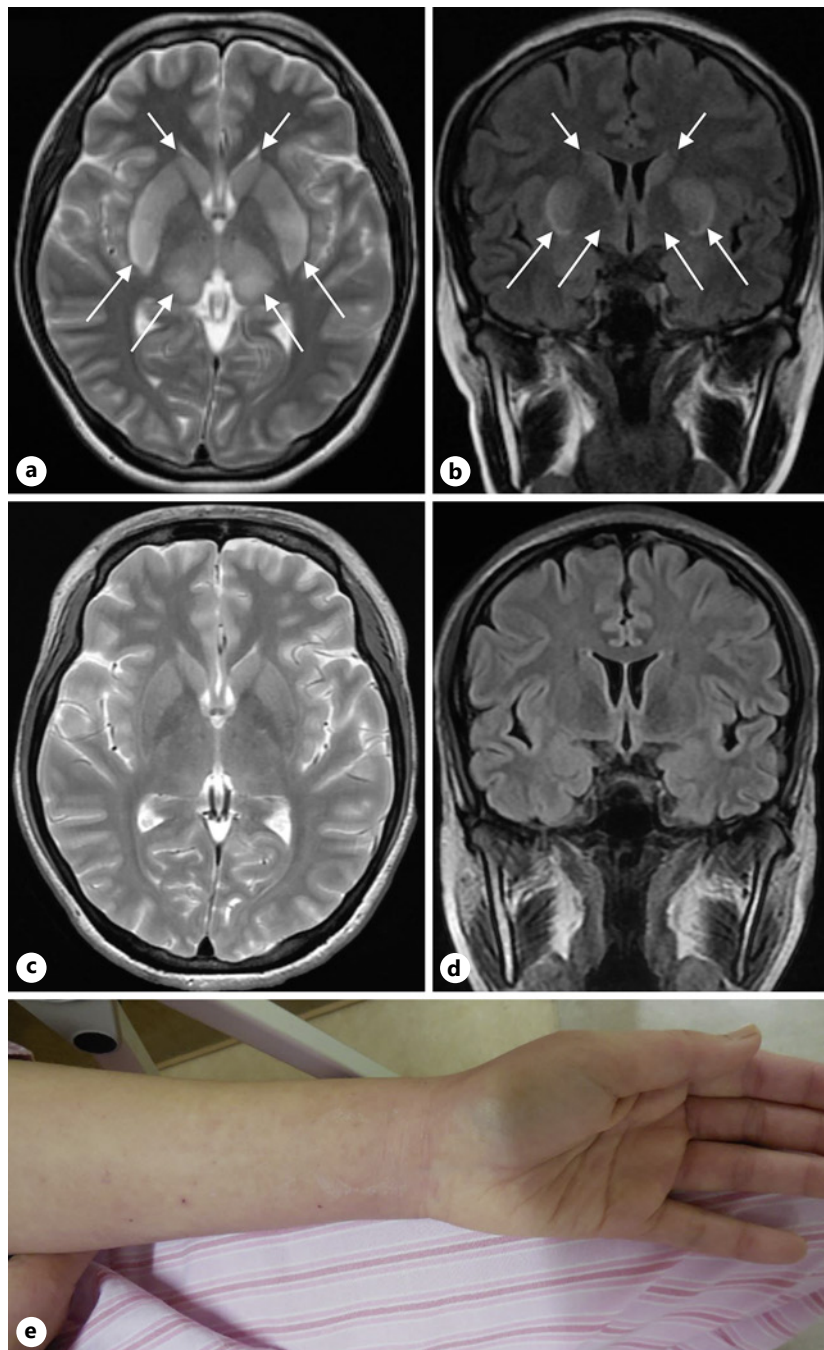
Adult Still's disease (ASD) is a rare systemic inflammatory disorder of unknown etiology typically characterized by spiking fever, arthritis, evanescent skin rash, sore throat, lymphadenopathy, splenomegaly, and the involvement of multiple organs [1, 2]. However, involvement of the central nervous system and ocular manifestations has rarely been described. Several reports have shown ocular involvement of ASD, including inflammatory orbital pseudotumor, ptosis, diplopia, nystagmus, uveitis, and scleritis. Some others have described Purtscher-like retinopathy in ASD patients [3, 4] that was mostly associated with thrombotic microangiopathy (TMA) [4].

Conventional ASD treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressive drugs [5]. Proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor, and interferon-gamma, were reported to be involved in ASD pathogenesis [6, 7]. The effectiveness of tocilizumab (TCZ), a monoclonal antibody against the IL-6 receptor, in the treatment of ASD has been demonstrated [6, 8]. TCZ was approved for ASD treatment in Japan in 2019. In this study, we report the case of an ASD patient who presented with Purtscher-like retinopathy treated with intravenous pulse methylprednisolone and TCZ without developing TMA. To the best of our knowledge, there are no published reports of treatment with both intravenous pulse methylprednisolone and TCZ for ASD that is complicated by Purtscher-like retinopathy.

## Case Report/Case Presentation

A 29-year-old Japanese woman was admitted with lowered consciousness and a high fever ( $>39^{\circ}\text{C}$ ), arthralgia, sore throat, and lymphadenopathy that had persisted for a week. She had a history of juvenile idiopathic arthritis and macrophage activation syndrome when she was 9 years old and was treated with oral prednisolone until she was 15 years old. Brain MRI showed bilateral swelling and high signal intensity in the basal ganglia and thalamus according to T2-weighted images and fluid-attenuated inversion recovery images (shown in Fig. 1a, b). Blood examinations revealed the following: leukocyte count,  $5,100/\mu\text{L}$  (88% neutrophils); hemoglobin, 14.3 g/dL; platelets,  $110,000/\mu\text{L}$ ; C-reactive protein, 5.36 mg/dL; erythrocyte sedimentation rate, 29 mm/h; slightly elevated liver enzymes (aspartate aminotransferase, 84 U/L, and alanine aminotransferase, 16 U/L), elevated soluble interleukin-2 receptor, 1,261 U/mL, and an elevated serum ferritin level of 4,088 ng/mL (reference range, 5–152 ng/mL). The kidney function test results were within normal limits, the antinuclear antigen was at the borderline level, and the rheumatoid factor and antineutrophil cytoplasmic antibody tests were negative. Her cerebrospinal fluid (CSF) on admission showed an opening pressure of 7 cm  $\text{H}_2\text{O}$ , 7 cells/ $\text{mm}^3$  (71% lymphocytes), increased protein levels (265 mg/dL; normal,  $<40$  mg/dL), and a slightly low glucose level (48 mg/dL; normal,  $>50$  mg/dL). Blood, urine, and CSF cultures were negative. Viral meningitis (human herpesvirus 1–6) was excluded using CSF in a polymerase chain reaction assay. An extensive infectious disease evaluation was negative. Her consciousness disorder improved without treatment, and her brain MRI also showed an improvement 3 weeks after admission (shown in Fig. 1c, d). Nevertheless, a high fever, arthritis, and salmon-colored rash on her trunk and limbs persisted (shown in Fig. 1e). Abdominal CT revealed splenomegaly.

After excluding infections, malignancies, and other rheumatic diseases, ASD was diagnosed based on the presence of fever, arthritis, rash, lymphadenopathy, splenomegaly, and hepatic dysfunction, according to the Yamaguchi criteria [1]. Her schistocytosis and worsening of anemia (hemoglobin, 8.7 g/dL) became clinically evident, and oral prednisolone of

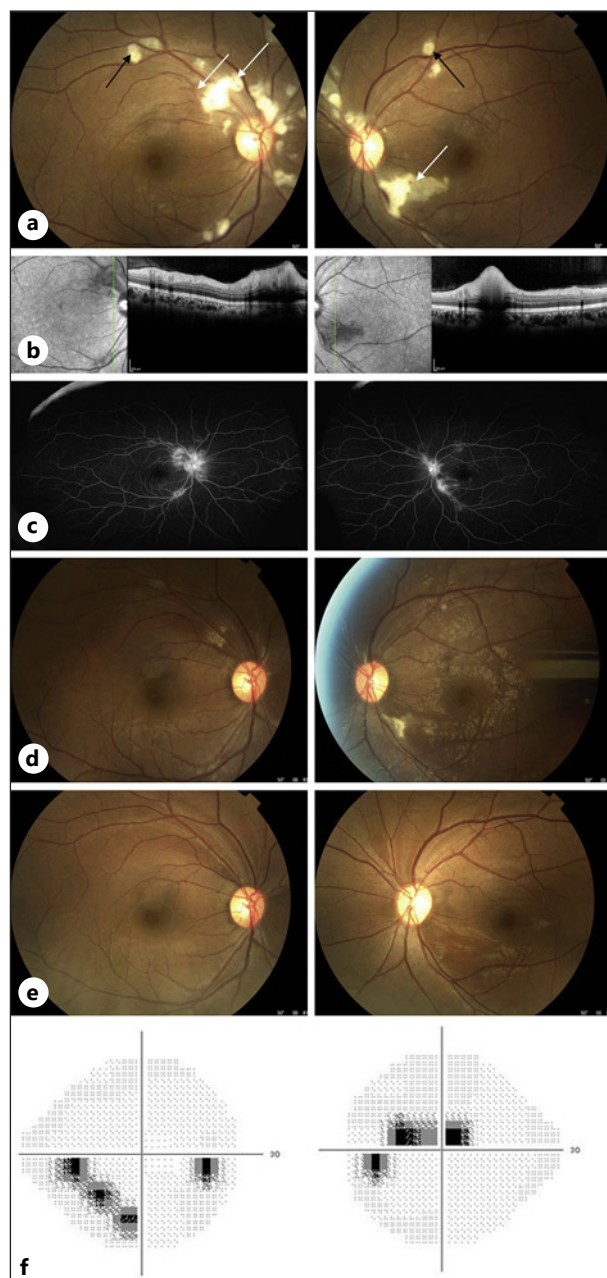


**Fig. 1.** MRI on admission shows bilateral swelling and high signal intensity in the basal ganglia and thalamus on the T2WI (a) and FLAIR image (b). MRI 3 weeks after admission shows improvement on the T2WI (c) and FLAIR image (d). e Salmon-colored rash on the forearm. T2WI, T2-weighted image; FLAIR, fluid-attenuated inversion recovery.

45 mg (1 mg/day/kg) was administered. TMA was ruled out because of her normal platelet count (162,000/ $\mu$ L), normal kidney function (creatinine, 0.60), and normalized fever without any neurological signs. After administering oral prednisone for 2 days, the patient presented with blurred vision in the left eye and was referred to the ophthalmology department. Her best-corrected visual acuity was 20/17 in each eye, and her intraocular pressure was normal

at the initial visit. A slit-lamp examination of the anterior segment of the eye was unremarkable. A funduscopic examination revealed bilateral cotton-wool spots, Purtscher flecken, and a small number of intraretinal hemorrhages around the optic nerve and in the posterior pole (shown in Fig. 2a), which were compatible with Purtscher-like retinopathy [9]. Optical coherence tomography showed inner retinal thickening consistent with cotton-wool spots in both eyes (shown in Fig. 2b). Fundus fluorescein angiography showed hypofluorescence in the early phase and increased permeability in the late phase, consistent with the lesions (shown in Fig. 2c). There was no apparent nonperfusion area in either eye.

Despite treatment with high-dose oral prednisolone for 2 weeks, her laboratory data gradually worsened, showing elevated serum ferritin levels (5,663 ng/mL) and developed macrophage activation syndrome [10]. Therefore, intravenous pulse methylprednisolone



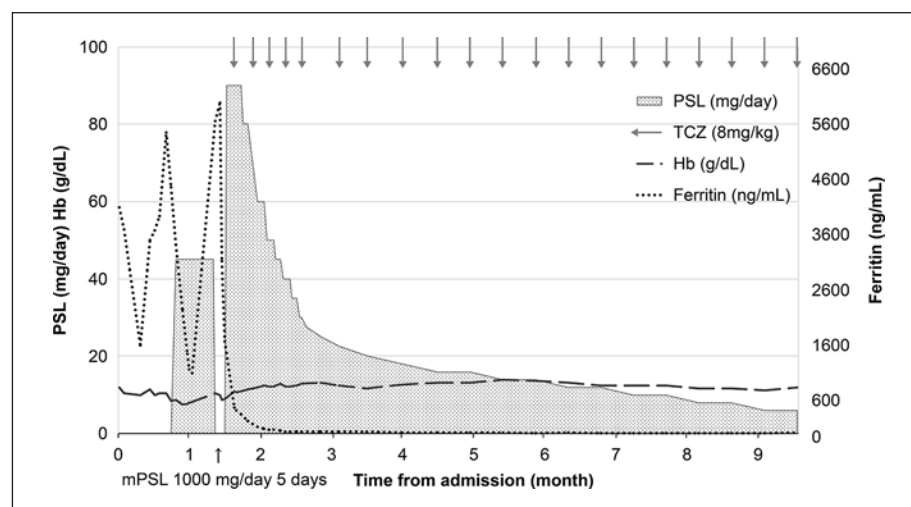
**Fig. 2.** **a** Fundus photographs show bilateral cotton-wool spots, Purtscher flecken (black arrow), and intraretinal hemorrhages (white arrow) around the optic nerve and in the posterior pole. **b** Optical coherence tomography shows inner retinal thickening consistent with the patches of retinal whitening. **c** Ultrawide-field fluorescein angiography shows increased permeability in the late phase, consistent with the lesions. There was no apparent nonperfusion area in either of the eyes. **d** Fundus photographs 15 days after initiating the administration of intravenous pulse methylprednisolone therapy show reduced cotton-wool spots and Purtscher flecken. **e** Fundus photographs 7 months after initiation of treatment show the improvement of Purtscher-like retinopathy and appearance of NFLD. **f** Humphrey visual field testing shows visual field defect corresponding to NFLD. NFLD, nerve fiber layer defect.

therapy was initiated at 1,000 mg/day for 5 days, followed by oral prednisolone of 90 mg (2 mg/kg/day). Nine days after the administration of intravenous pulse methylprednisolone therapy, the patient's serum ferritin levels dropped to 462 ng/mL, and aspartate aminotransferase levels and the platelet count fell within normal limits. TCZ (8 mg/kg every week during hospitalization and 8 mg/kg every 2 weeks after discharge) was administered considering the severity of ASD (shown in Fig. 3). The patient visited the ophthalmology department again 15 days after the administration of intravenous pulse methylprednisolone therapy, and her funduscopy examination revealed reduced bilateral cotton-wool spots and Purtscher flecken (shown in Fig. 2d). Her ASD was successfully treated, and the oral prednisolone treatment was tapered. Although her Purtscher-like retinopathy improved as her ASD activity decreased, nerve fiber layer defect (NFLD) in both eyes appeared 7 months after initial visit (shown in Fig. 2e). Humphrey visual field testing showed visual field defect corresponding to NFLD (shown in Fig. 2f). At her last visit, that was 1 year after the administration of intravenous pulse methylprednisolone therapy, the patient was taking prednisolone (5 mg/day) and continuing TCZ, and she remained in good health without a major ASD flare.

### Discussion/Conclusions

In the present study, we present a case of severe ASD complicated by Purtscher-like retinopathy and treated with intravenous pulse methylprednisolone and TCZ. Before the onset of vision problems, she presented encephalitis. Central nervous system involvement has been reported in several ASD cases, most of which were aseptic meningitis. Denault et al. [11] reported development of encephalitis in an ASD patient whose condition improved before corticosteroid treatment [11]. Similarly, infectious encephalitis was excluded in our patient, and she also improved before corticosteroid treatment. Thus, her encephalitis was possibly autoimmune encephalitis associated with ASD.

Purtscher-like retinopathy is observed in patients with systemic disease, including acute pancreatitis, renal failure, hemolytic uremic syndrome, and connective tissue disorders, and considered the result of retinal vasculitis that leads to thrombosis and vascular occlusion [9,



**Fig. 3.** Time course of laboratory values and treatment. PSL, prednisolone; TCZ, tocilizumab; Hb, hemoglobin; mPSL, methylprednisolone.

12–14]. Purtscher-like retinopathy has been reported in ASD patients mostly complicated with TMA, with eye presentations before TMA onset [4]. In our case, the patient's laboratory data and physical examinations did not fulfill the TMA criteria at the onset of visual symptoms. Buyukavsar et al. [3] also reported Purtscher-like retinopathy without TMA in a patient with ASD successfully treated with a high dose of oral prednisolone. Therefore, Purtscher-like retinopathy may be an early subclinical presentation of TMA, and systemic immunosuppressive therapy may have prevented the onset of TMA in our case.

Although NSAIDs and glucocorticoids are first-line ASD treatments, Franchini et al. [15] reported that >80% of ASD patients did not achieve remission with NSAIDs. Most patients receive glucocorticoid treatment and show an initially good response despite severe systemic inflammation [6, 8]. However, glucocorticoids are sometimes insufficient, and relapses are often observed with dose tapering. Thus, immunosuppressants, such as methotrexate and cyclosporin, have been used as steroid-sparing drugs [8]. Several reports have described TCZ efficacy in refractory ASD [16]. Nishina et al. [8] reported that TCZ effectively prevented ASD relapses and resolved disease activity. Our patient showed insufficient response to 2 weeks of oral prednisolone. She dramatically improved after intravenous pulse methylprednisolone. She continued TCZ treatment, and prednisolone was tapered to 5 mg without relapse or serious adverse effects. TCZ seems to be useful in suppressing relapses and sparing the dose of prednisolone in our case.

Although our patient's Purtscher-like retinopathy gradually improved as her ASD activity decreased, she developed a visual field defect. To the best of our knowledge, there is only one published report which mentioned Purtscher-like retinopathy showing visual field defect [17]. Our patient showed NFLD corresponding to the lesions of Purtscher-like retinopathy; thus, it is assumed that retinal infarction caused damage to the retinal fiber layer which led to the visual field defect. Our case suggests the importance of early detection of Purtscher-like retinopathy and early treatment of its underlying disease.

In conclusion, we report a rare case of severe ASD complicated by Purtscher-like retinopathy which showed improvement with decreasing severity of ASD after administration of intravenous pulse methylprednisolone and TCZ. Although Purtscher-like retinopathy is a rare presentation of ASD, it might reflect TMA-like pathophysiology and be an indicator for early administration of intensive immunosuppressive treatments. In addition, early detection and long-term follow-up of Purtscher-like retinopathy is important because it has the possibility of developing permanent visual field defect.

### Statement of Ethics

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at The University of Tokyo, Approval No. 10906. Written informed consent for publication was obtained from the patient.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Kaho Akiyama: conceptualization, visualization, and writing – original draft. Yukiko Iwasaki: investigation and writing – review and editing. Rie Tanaka: conceptualization, investigation, resources, visualization, writing (review and editing), and supervision.

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