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CASE REPORT

Exudative Retinal Detachment During Induction Therapy for Acute Promyelocytic Leukemia: A Manifestation of Differentiation Syndrome

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Background/Aim: This report describes a case of exudative retinal detachment as an ocular manifestation of differentiation syndrome (DS) during induction therapy for acute promyelocytic leukemia (APL). A concise review of the literatures is also provided.

Case Presentation: A 25-year-old female with APL received induction therapy with all-trans retinoic acid (ATRA), arsenic trioxide (ATO), and daunorubicin. On day 15 of induction therapy, she developed dyspnea with pulmonary infiltrates, alongside bilateral epiphora and blurred vision in her right eye. Ophthalmic examination revealed a best-corrected visual acuity (BCVA) of 20/40 in the right eye and 20/20 in the left. Fundus examination demonstrated macular edema, mild optic disc edema, undulating exudative retinal detachment in the posterior pole and mid-peripheral retina, and scattered superficial hemorrhages bilaterally. Optical coherence tomography demonstrated corrugated retinal pigment epithelium elevation with subretinal fluid (SRF), choroidal thickening in both eyes, and neurosensory epithelium detachment in the right macula. Fundus fluorescein angiography confirmed diffuse vascular leakage bilaterally. A diagnosis of DS was established. Management with systemic corticosteroids, ATRA dose reduction, and ATO discontinuation led to the complete resolution of SRF and restoration of BCVA to 20/20 in both eyes within one month.

Conclusion: Exudative retinal detachment can be an ocular manifestation of DS during APL induction therapy, likely attributable to systemic capillary leakage. Prompt intervention with systemic corticosteroids is effective and generally associated with a favorable visual prognosis.

Keywords: exudative retinal detachment, differentiation syndrome, acute promyelocytic leukemia, all-trans retinoic acid, arsenic trioxide

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myelocytic leukemia, characterized by the chromosomal translocation t(15;17) coding a PML/RARα fusion protein, which arrests myeloid differentiation at the promyelocyte stage.[1]

Differentiating agents, specifically all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), have revolutionized APL treatment.[2–4] The ATRA-ATO combination is the standard of care across all risk strata, demonstrating superior efficacy and a more favorable toxicity profile compared to traditional ATRA plus chemotherapy regimens.[5–7] In patients with low-to-intermediate-risk APL, ATRA-ATO regimens achieve complete remission rates approaching 100% and a 50-month overall survival rate of 99.2%.[5]

However, the terminal differentiation of leukemic blasts may trigger differentiation syndrome (DS), a potentially life-threatening complication typically occurring within the first 1–2 weeks of therapy.[8] DS pathogenesis involves upregulated cytokines, chemokines, and adhesion molecules,[9] leading to systemic inflammatory states. Clinical manifestations

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include dyspnea, pulmonary infiltrates, pleural/pericardial effusions, fever, hypotension, edema, acute febrile neutrophilic dermatosis and renal dysfunction.[10,11]

In contrast to these well-characterized systemic manifestations, ocular manifestations of DS remain rare and under-recognized. Ocular manifestations, such as retinal hemorrhages, exudative retinal detachment and papilledema, may be overlooked amid life-threatening systemic manifestations, yet they can serve as critical early indicators of DS. This report describes a case of DS-associated exudative retinal detachment and reviews the literature to emphasize its potential as an early indicator of DS in APL patients undergoing induction therapy.

Case Description

A 25-year-old female presented to the hematology department with a three-day history of unexplained fever, spontaneous skin petechiae, and menorrhagia. Physical examination revealed a body temperature of 38.3°C and scattered ecchymoses on the upper extremities. Initial laboratory tests revealed a normal white blood cell (WBC) count (6.67×10^9/L), thrombocytopenia (14×10^9/L), and anemia (red blood cell count 3.38×10^{12}/L, hemoglobin 105 g/L). Coagulation studies were consistent with disseminated intravascular coagulation, revealing elevated D-dimer (>20,000 ng/mL), hypofibrinogenemia (0.77 g/L), prolonged prothrombin time [PT 19.4 seconds; international normalized ratio (INR) 1.64], and activated partial thromboplastin time (APTT 54 seconds). Serum biochemistry indicated hypokalemia (2.70 mmol/L), hyponatremia (134.0 mmol/L), and elevated lactate dehydrogenase (580 U/L) and α-hydroxybutyrate dehydrogenase (299 U/L) levels. Bone marrow aspirate confirmed hypercellularity with granulocytic hyperplasia (95% of nucleated cells), predominantly comprised of abnormal promyelocytes (91.5%), alongside erythroid hypoplasia. A concurrent peripheral blood smear showed that abnormal hypergranular promyelocytes accounted for 68% of the white blood cells. These findings confirmed the diagnosis of APL.

Induction therapy was initiated with oral ATRA. The dosing was adjusted from 13.3 mg/m^2 once daily to 6.7 mg/m^2 twice daily (total daily dose: 20 mg) on the second day of APL diagnosis. Hydroxyurea (1 g three times daily) was added for leukocytosis control, and prophylactic oral dexamethasone (10 mg daily) was administered. Supportive care included antipyretics and transfusions to maintain platelet counts above 50×10^9/L, fibrinogen above 150 mg/dL, and hemoglobin above 80 g/L, per standard guidelines. Intravenous daunorubicin (43 mg/m^2 daily, total daily dose: 65 mg) was started on day 4 and last for 3 days, followed by intravenous ATO (5 mg/m^2 daily, total daily dose: 7.5 mg) on day 13.

On day 15 of APL treatment, the patient developed acute dyspnea and chest tightness. Laboratory tests showed a WBC count of 3.15×10^9/L, hemoglobin of 57 g/L, and a platelet count of 28×10^9/L. Coagulation profile indicated a D-dimer level >6600 ng/mL, a fibrinogen level of 4.20 g/L and a PT of 13 seconds. Chest computed tomography (CT) revealed bilateral diffuse pulmonary infiltrates, supporting a diagnosis of DS. Concurrently, she reported new-onset bilateral excessive tearing and blurred vision in the right eye. Ophthalmic examination revealed a best-corrected visual acuity (BCVA) of 20/40 in the right eye and 20/20 in the left. Intraocular pressures and anterior segment examination were unremarkable. Dilated fundus examination demonstrated bilateral macular edema, mild optic disc edema, undulating exudative retinal detachment in the posterior pole and mid-peripheral retina, and scattered superficial retinal hemorrhages (Figure 1). Optical coherence tomography (OCT) showed corrugated retinal pigment epithelium (RPE) elevation with subretinal fluid (SRF) accumulation, choroidal thickening bilaterally, and neurosensory epithelium detachment in the right macula (Figure 2). Given the coincidence of exudative retinal detachment and systemic manifestations of DS, we speculated that this was exudative retinal detachment secondary to DS.

In response to these complications, ATO was discontinued, and the ATRA dose was reduced by 50% on day 15. This regimen maintained for two weeks. The dexamethasone dose was increased to 10 mg intravenously twice daily, supplemented with topical prednisolone acetate eye drops every 8 hours. Fundus fluorescein angiography (FFA) performed on day 19 revealed diffuse late-phase leakage from retinal vessels at the posterior pole and around the optic disc, with intermittent hemorrhages obscuring fluorescence bilaterally (Figure 3).

The patient's respiratory symptoms improved with resolution of pulmonary infiltrates on repeat chest CT over the following week. On day 24, she reported mild bilateral blurred vision and blood-tinged sputum. Significant chest tightness or shortness of breath was absent. BCVA improved to 20/30 (right eye) and 20/20 (left eye) after 11 days of

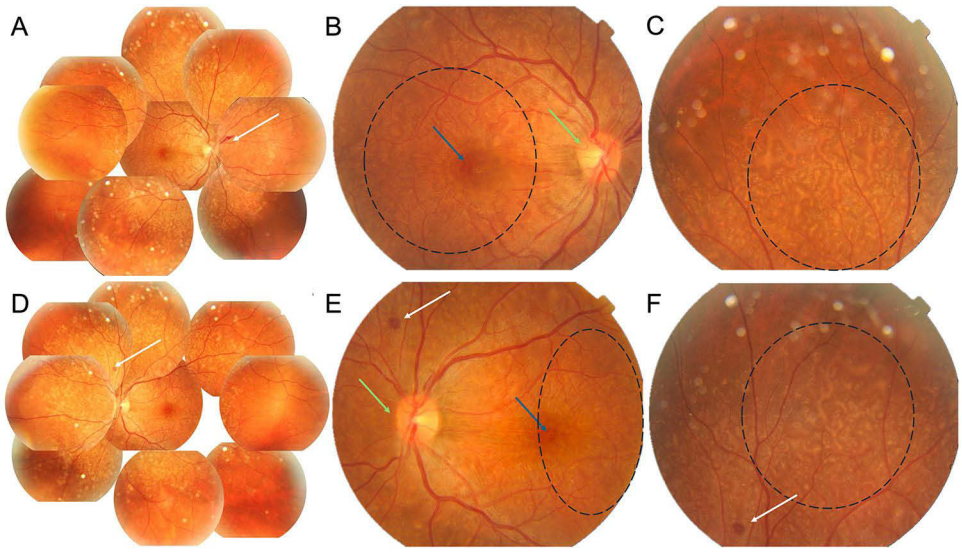

Figure 1 Fundus photographs on initial assessment revealed macular edema (blue arrows), mild optic disc edema (green arrows), undulating edematous detachment in the posterior pole and mid-peripheral retina (dashed circles) accompanied by scattered superficial retinal hemorrhages (white arrows) in the right eye (**A**–**C**) and the left eye (**D**–**F**).

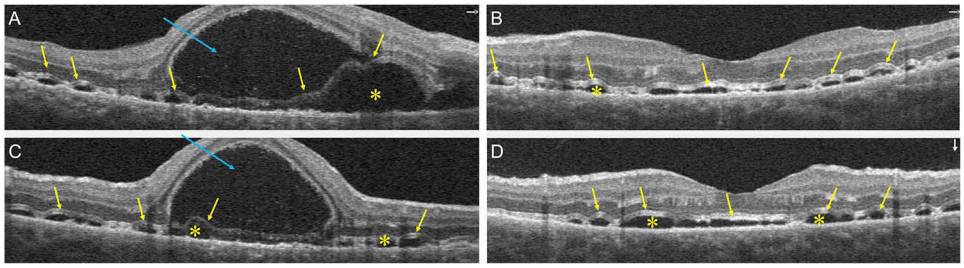

Figure 2 Optical coherence tomography on initial assessment demonstrated corrugated retinal pigment epithelium elevation (yellow arrows) with subretinal fluid accumulation (yellow asterisks) bilaterally (**A**–**D**) and neurosensory epithelium detachment (blue arrows) in the right macula (**A** and **C**).

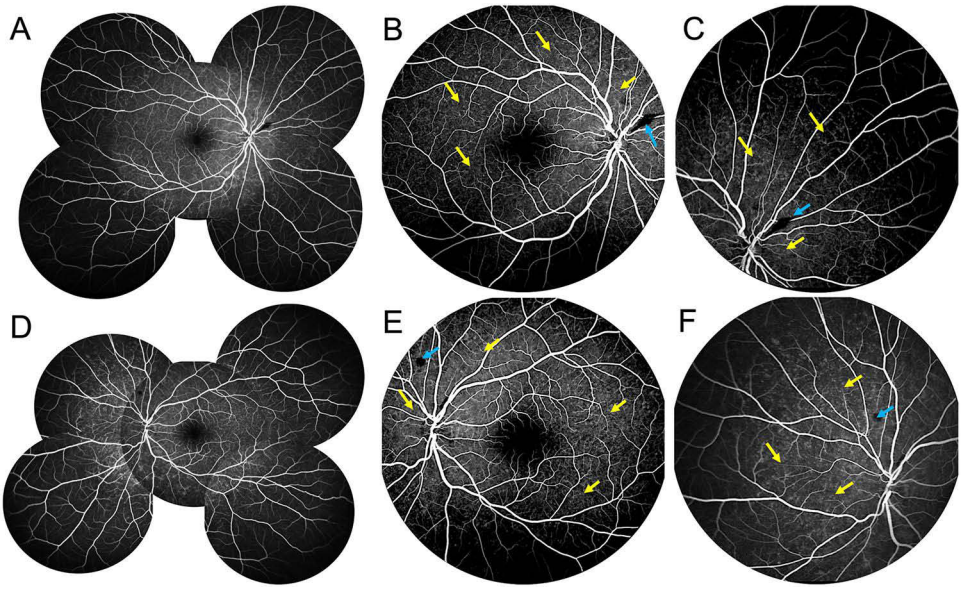

Figure 3 Fundus fluorescein angiography on day 19 revealed diffuse late-phase leakage from retinal vessels at the posterior pole and around optic disc (yellow arrows) with intermittent hemorrhages (blue arrows) obscuring the fluorescence in the right eye (**A**–**C**) and the left eye (**D**–**F**).

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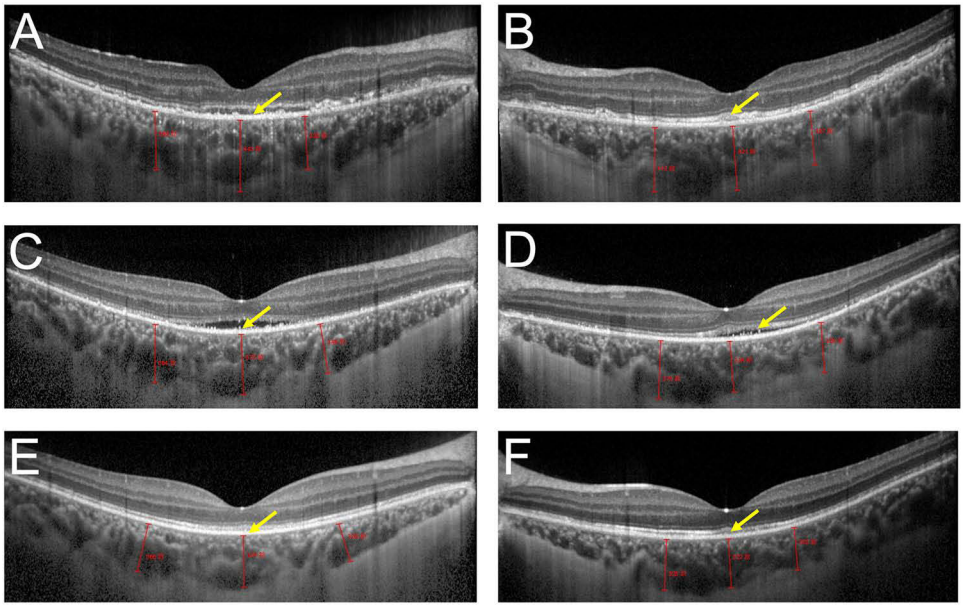

Figure 4 Optical coherence tomography demonstrated bilateral anatomical recovery during differentiation syndrome (DS) treatment. On day 4 of DS treatment, subretinal fluid (SRF) was significantly resorbed at the posterior pole, but choroidal thickness remained in the right eye (**A**) and the left eye (**B**). On day 13 of DS treatment, SRF was further resorbed at the posterior pole but remained in the fovea, choroidal thickness was reduced in the right eye (**C**) and the left eye (**D**). On day 35 of DS treatment, there was complete resolution of the SRF in the right eye (**E**) and the left eye (**F**). The red lines indicate choroidal thickness assessment while the yellow arrows indicate SRF.

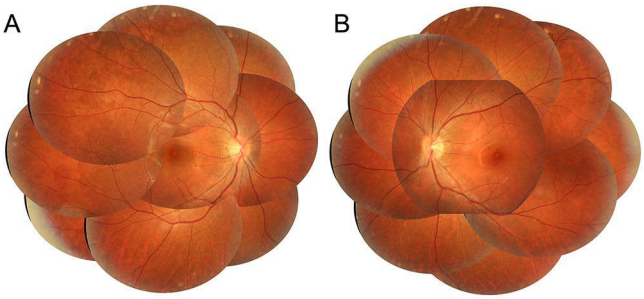

Figure 5 Fundus photographs at the 35-day follow-up revealed complete remission of retinal edema, retinal detachment, retinal hemorrhage, papilledema and macular edema in the right eye (**A**) and the left eye (**B**).

DS treatment and normalized to 20/20 bilaterally after one month. Serial OCT examinations demonstrated symmetrical choroidal thickness reduction and SRF resorption in both eyes with corticosteroid administration (Figure 4).

After one month of DS treatment, her systemic condition had significantly improved, with only a minor cough and expectoration remaining. Laboratory tests showed marked improvement in coagulation and hematological parameters (INR 1.05, PT 13.50 seconds, APTT 30.3 seconds, fibrinogen 2.00 g/L, hemoglobin 83 g/L, platelets 380×10^9/L, WBC 3.57×10^9/L). She was discharged on a tapering course of oral dexamethasone (2.25 mg once daily for 7 days) and ongoing topical prednisolone acetate. At the 35-day follow-up, fundus examination and OCT confirmed complete resolution of SRF, retinal hemorrhages, retinal detachment and edema, with restoration of normal retinal architecture in both eyes (Figure 5).

Discussion

DS is a well-established complication of induction therapy for APL. While systemic manifestations of DS like fever and respiratory distress are common, ocular involvement remains rare but increasingly recognized. This case underscores exudative retinal detachment as a potential early indicator of DS.

A review of the literature reveals 9 reported cases of DS-associated retinal manifestations, involving 5 females and 4 males, with ages ranging from 25 to 66 years. All cases showed bilateral eye involvement. Ocular symptoms occurred 5 to 20 days after induction therapy initiation (median: 14 days), coinciding with the typical onset of systemic DS. 5 cases received DS prophylaxis through corticosteroids while others did not. Ocular manifestations included blurred vision (9/9), epiphora (1/9), phosphenes (1/9), yellowing of vision (1/9), visual dimness (1/9), increased intraocular pressure (1/9), and anterior chamber angle closure (1/9). Visual acuity ranged from mild impairment (20/25) to severe loss (finger count/3 ft). Fundus manifestations included retinal hemorrhages (7/9), exudative retinal detachment (3/9), macular edema (3/9) and optic disc edema (2/9). Typical signs of leukemic retinopathy, such as Roth spots (1/9), cotton wool spots (1/9), and chorioretinal lesions (3/9), may occur before or alongside ophthalmic DS. OCT demonstrated SRF accumulation (7/9), RPE elevation (5/9) and choroidal thickening (3/9), while FFA predominantly showed vascular leakage (6/9). The anterior segment was universally unaffected. Ocular manifestations typically coincided with systemic manifestations but could also follow 1–3 days later. In one case, ocular symptom was the first manifestations of DS.[1]

Management primarily involved systemic corticosteroids (8/9), induction therapy adjustment (6/9) and topical corticosteroids (2/9). All patients exhibited significant visual improvement and anatomical recovery within one month. Most patients (7/9) achieved favorable visual outcomes. A summary of these cases is provided in Table 1.

The pathogenesis of DS is driven by a hyperinflammatory state from differentiating leukemic cells and enhanced cytokine production, leading to endothelial injury and systemic capillary leakage.[10] This hyperinflammatory state typically manifests as fever, tachycardia, tachypnea, and hypotension, potentially progressing to shock if untreated.[16] The ocular manifestations including papilledema, retinal edema, and exudative retinal detachment, are the direct consequence of ocular microvasculature disturbance.[17] Blood-retinal barrier (BRB) is crucial for maintaining retinal homeostasis by controlling fluid and molecular movement.[18] Hypoxia–ischemia secondary to leukemic infiltration and microvascular occlusion may disrupt the integrity of the BRB, which leads to SRF accumulation and exudative retinal detachment.[18] Moreover, circulating inflammatory cytokines may interact with vascular receptors, increasing choroidal capillary permeability.[19–22] Similarly, other conditions that compromise the integrity of BRB would also cause exudative retinal detachment such as Vogt-Koyanagi-Harada syndrome, autoimmune uveitis, and posterior scleritis.[18,23]

Ophthalmic DS must be differentiated from other conditions causing exudative retinal detachment in leukemia, including extramedullary relapse,[19,21] leukemic retinopathy,[24,25] systemic hypertension and drug toxicity. Leukemic retinopathy is characterized by venous dilation, tortuosity, Roth spots and cotton wool spots,[24,25] which is managed with systemic chemotherapy or ocular radiotherapy,[26,27] whereas ocular DS responds to corticosteroids. Pseudotumor cerebri, a complication of ATRA therapy, may also cause vision loss but typically presents with headache, nausea, vomiting and papilledema without SRF.[28]

In conclusion, ophthalmic evaluation provides a critical window for early DS detection. Since ocular symptoms can precede or coincide with systemic deterioration, comprehensive assessment including OCT is recommended for any APL patient reporting visual disturbances during induction therapy. Ocular manifestations may be unrecognized in DS patients with compromised systemic status. Although the temporary cessation of differentiation therapy is controversial, it may be warranted in cases of severe DS with profound organ dysfunction.[11,16] Timely recognition of ophthalmic DS enables prompt corticosteroid administration, which is pivotal for mitigating life-threatening complications. Further investigation of ocular manifestations in DS may offer a non-invasive window into systemic inflammation and improve DS management strategies.

Conclusions

This case underscores that exudative retinal detachment can serve as an early indicator of DS in patients undergoing induction therapy for APL. The pathophysiology is attributed to inflammatory capillary leakage, which is highly responsive to systemic corticosteroids. Early recognition of ocular manifestations and prompt corticosteroid therapy can prevent both visual and life-threatening systemic complications.

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Table 1 Summary of Reported Cases with Retinal Manifestations in Differentiation Syndrome

Case Report	Age (Years)	Gender	Laterality	DS Prophylaxis	Systemic Manifestations	Time from Induction Therapy Initiation to Ocular Symptom Onset	Ocular Signs and Symptoms	Fundus Manifestations	OCT Manifestations	FFA Manifestations	Time Sequence of Ocular Manifestations and Systemic Manifestations	DS Management	Initial Visual Acuity	Post-Treatment Visual Acuity	Anatomical Recovery
This case	25	Female	Bilateral	Oral dexamethasone	Acute dyspnea, chest tightness, fever	15 days	Epiphora, blurred vision in the right eye	Macular edema, mild optic disc edema, undulating edematous detachment in the posterior pole and mid-peripheral retina, scattered superficial retinal hemorrhages	Corrugated RPE elevation with SRF accumulation and choroidal thickening bilaterally, neurosensory epithelium detachment in the right macula	Focal blockage from peripapillary hemorrhages, diffuse late-phase leakage from retinal vessels at the posterior pole and around optic disc	Co-occurrence	ATO discontinuation, ATRA reduction, IV dexamethasone, topical prednisolone	20/40 (BCVA OD), 20/20 (BCVA OS)	20/20 (BCVA OU)	Complete remission of retinal edema, detachment, hemorrhage, papilledema and macular edema
Boscaro E, et al[12]	39	Male	Bilateral	Steroid	N/A	10 days	Blurred vision and phosphenes	Retinal hemorrhages in the peripapillary region and multifocal areas of SRD in the macular region	Pockets of SRF and focal RPE changes with nodular elevations	Focal blockage from peripapillary hemorrhages, early and late hyperfluorescence from pinpoints in the macular region	No systemic manifestations	Dexamethasone	20/25 (BCVA OD), 20/20 (BCVA OS)	Completely restored	Persistent choroidal thickening, incomplete SRF reabsorption, and residual flat retinal detachment after 7 days of steroid therapy
Oh SE, et al[13]	27	Female	Bilateral	N/A	Fever	20 days	Yellowing of vision and decreased visual acuity	Multiple drusen-like lesions at the posterior pole with preretinal hemorrhage	Multiple areas of SRF and RPE elevations, choroidal thickening	Late-phase venous hyperfluorescence and diffuse late leakage	Co-occurrence	Dexamethasone administration and ATRA discontinuation	0.5 (BCVA OD), 0.4 (BCVA OS)	1.0 (BCVA OU)	Complete resolution of pale yellow subretinal lesions, preretinal hemorrhage, SRF and RPE elevations
Tam EK, et al[14]	25	Male	Bilateral	Steroid	Hypoxia, tachycardia, fever	10 days	Blurred vision	Scattered subretinal, intraretinal, and preretinal hemorrhages, optic nerve swelling and macular edema	Macular edema	Intact retinal perfusion and diffuse leakage from the optic nerves and retinal vessels	Co-occurrence	IV corticosteroids	20/60 (BCVA OD), 20/200 (BCVA OS)	20/40 (BCVA OU)	Decreased macular edema
Gim Y, et al[1]	66	Female	Bilateral	N/A	Fever, weight gain, and dyspnea	5 days	Visual dimness and peripheral blurred vision	Retinal hemorrhages, Roth spot in the left eye, macular edema and mild vitreous hemorrhage in the right eye	SRF in the right macula and progressed to bilateral SRD	A previous branch retinal vein occlusion lesion in left eye	Systemic manifestations appeared 2 days after the onset of ocular manifestations	IV dexamethasone, ATRA discontinuation	20/40 (BCVA OD), 20/32 (BCVA OS)	20/20 (BCVA OD), 20/25 (BCVA OS)	Complete remission of SRD
Hua HU, et al[15]	51	Male	Bilateral	N/A	Fever, tachycardia, odynophagia, productive cough, wheezing, and marked peripheral edema in upper extremities	2 weeks	Sudden vision loss	Choroidal effusions with diffuse SRD involving the macula, white centered intraretinal hemorrhages	Irregular inner retinal surface, SRF, loss of the ellipsoid zone	N/A	Co-occurrence	IV dexamethasone, ATRA discontinuation	Finger count at 3 ft (OU)	20/40 (OU)	Complete resolution of the choroidal effusions, intraretinal fluid and SRF with persistent disruptions of the ellipsoid zone

Newman AR, et al[16]	35	Female	Bilateral	Oral prednisolone	Fever, hypotension, tachycardia, acute renal impairment, peripheral edema and weight gain	14 days	Decreased vision, increased IOP, angle closure	Multifocal pale yellow chorioretinal lesions concentrated at the posterior poles, superficial retinal hemorrhages	Multifocal areas of focal RPE elevation and adhesion to the thickened outer retina with interspersed SRF, choroidal thickening	Early choroidal hyperfluorescence corresponding to the yellow retinal lesions, late leakage of fluid into the subretinal space	Ocular manifestations appeared 3 days after the onset of systemic manifestations	ATRA and ATO discontinuation, oral prednisone, topical dexamethasone	6/36 (OD), 6/18 (OS)	6/5 (OD), 6/5 (OS)	Significant reduction in choroidal thickness and complete SRF resolution
Newman AR, et al[16]	30	Female	Bilateral	Oral prednisolone	Fever, hypotension and headache	10 days	Decreased visual acuity	Widespread multifocal yellow chorioretinal lesions, superficial and intraretinal hemorrhages	Multifocal SRD with interspersed areas of adhesion between the thickened neurosensory retina and focal RPE elevations	N/A	Ocular manifestations appeared 1 day after the onset of systemic manifestations	Anti-microbials, transfusion, hemodynamic support	6/120 (OD) 6/24 (OS)	6/6 (OU)	Complete SRF resolution
Levasseur SD, et al[17]	39	Male	Bilateral	N/A	Fever, hypoxia, pulmonary infiltrates, pleural effusion, pitting edema, weight gain	18 days	Decreased visual acuity	Multifocal areas of macular SRF, peripapillary cotton wool spot	Multiple focal neurosensory detachment	Multiple areas of early hyperfluorescence with late leakage	Ocular manifestations appeared 10 days after the onset of systemic manifestations	Dexamethasone administration, ATRA discontinuation	20/30 (OD) 20/60 (OS)	20/20 (UCVA OD) 20/25 (UCVA OS)	Complete SRF resolution

Abbreviations: DS, differentiation syndrome; IV, intravenous; SRD, serous retinal detachment; SRF, subretinal fluid; OCT, optical coherence tomography; FFA, fundus fluorescein angiography; RPE, retinal pigment epithelium; BCVA, best-corrected visual acuity; UCVA, uncorrected visual acuity; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; IOP, intraocular pressure; ATRA, all-trans retinoic acid; ATO, arsenic trioxide

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Abbreviations

APL, acute promyelocytic leukemia; WBC, white blood cell; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; DS, differentiation syndrome; OCT, Optical coherence tomography; RPE, retinal pigment epithelium; SRF, subretinal fluid; SRD, serous retinal detachment; FFA, fundus fluorescein angiography; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; BCVA, best-corrected visual acuity; UCVA, uncorrected visual acuity; IOP, intraocular pressure; CT, computed tomography; BRB, Blood-retinal barrier.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Disclosure

The authors declare no conflicts of interest in this work.

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