



## Case report

## Two cases of differentiation syndrome with ocular manifestations in patients with acute promyelocytic leukaemia treated with all-trans retinoic acid and arsenic trioxide



A.R. Newman<sup>a,c,\*</sup>, B. Leung<sup>b,c</sup>, A. Richards<sup>a</sup>, T.G. Campbell<sup>a,d</sup>, J. Wellwood<sup>b</sup>, F.R. Imrie<sup>a</sup>

<sup>a</sup> Department of Ophthalmology, Gold Coast University Hospital, Queensland 4215, Australia

<sup>b</sup> Department of Haematology, Gold Coast University Hospital, Queensland 4215, Australia

<sup>c</sup> Griffith University School of Medicine, Griffith University, Southport, Queensland 4215, Australia

<sup>d</sup> University of Queensland School of Medicine, University of Queensland, St Lucia, Queensland 4072, Australia

## ARTICLE INFO

## Keywords:

Differentiation syndrome

Ophthalmic

Acute promyelocytic leukaemia

## ABSTRACT

**Purpose:** To describe two cases of differentiation syndrome presenting with ocular manifestations including bilateral chorioretinopathy in patients with acute promyelocytic leukaemia treated with all-trans retinoic acid and arsenic trioxide differentiation therapy.

**Observations:** This observational case series identifies two patients at a single tertiary institution diagnosed with differentiation syndrome with associated ophthalmic involvement. Both patients reported bilateral reduction in visual acuity at days fourteen and ten respectively following initiation of differentiation therapy in addition to developing other systemic manifestations of differentiation syndrome. Both patients received the same chemotherapeutic regimen including both all-trans retinoic acid and arsenic trioxide as well as ten days of routine differentiation syndrome prophylaxis with oral prednisolone. Case 1 presented with bilateral pale yellow sub-retinal lesions concentrated at the posterior poles with ocular coherence tomography (OCT) evidence of bilateral multifocal areas of focal RPE elevation and adhesion to the thickened outer retina with interspersed sub-retinal fluid. Fluorescein angiography revealed areas of early hyperfluorescence corresponding to the yellow chorioretinal lesions with late diffuse leakage of fluid into the subretinal space. Case 2 presented with a similar characteristic retinal findings on funduscopy and optical coherence tomography. Both patients experienced rapid improvement in the visual symptoms and marked resolution of the sub-retinal fluid within seven to fourteen days of onset with excellent long-term visual outcome. Both patients achieved molecular remission after induction and received standard consolidation and maintenance therapy without visual disturbance.

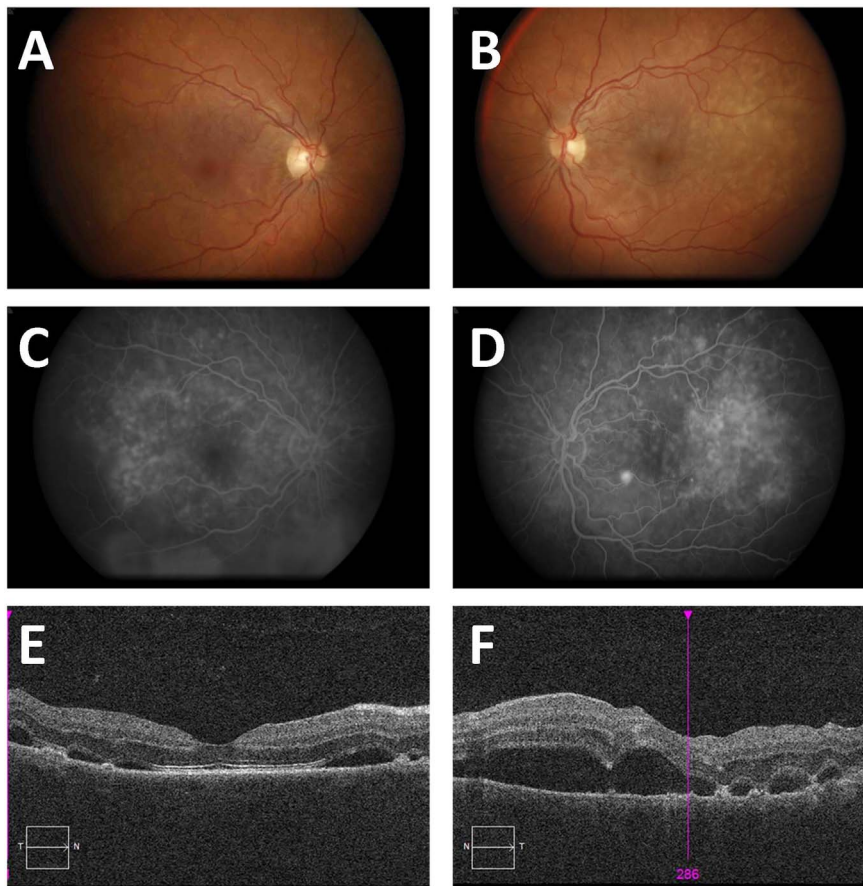
**Conclusion and importance:** Ocular manifestations of differentiation syndrome have been only recently recognised. We present a case series of two patients with differentiation syndrome with ocular involvement. Common to both presentations was the presence of bilateral reduction in visual acuity with multifocal serous retinal detachment secondary to chorioretinopathy. The visual outcome from both presentations was excellent with rapid normalisation of visual acuity and resolution of the sub-retinal fluid with only the first case having their differentiation therapy temporarily withheld during the acute phase of illness.

## 1. Introduction

Acute promyelocytic leukaemia (APL) accounts for roughly 10% of *de novo* adult cases of acute myeloid leukaemia (AML-M3) and is characterised by leukaemic blast cell morphology, coagulopathy and the chromosomal translocation t(15:17).<sup>1–3</sup> In 95% of cases, the promyelocytic leukaemia (PML) gene on chromosome 15 is fused to the retinoic acid receptor- $\alpha$  (RAR $\alpha$ ) gene on chromosome 17 to form a chimeric PML-RAR $\alpha$  gene. Retinoic acid is a vitamin A-derived, non-

peptidic, small lipophilic molecule that acts as ligand for nuclear retinoic acid receptors, converting them from transcriptional repressors to activators. The chimeric retinoic acid receptor is less able to bind to retinoic acid, resulting in a differentiation block of terminal granulocytes in the promyelocytic stage due to repression of genes implicated in myeloid differentiation.<sup>4–8</sup> The mainstay of induction therapy is all-trans retinoic acid (ATRA) typically in combination with anthracycline-based chemotherapy to reduce the incidence of relapse.<sup>2,9–11</sup> Administration of supra-physiologic doses of retinoic acid as occurs during

\* Corresponding author. Department of Ophthalmology, Level 1, Gold Coast University Hospital, Southport, Queensland 4215, Australia.  
E-mail address: [alexander.newman@health.qld.gov.au](mailto:alexander.newman@health.qld.gov.au) (A.R. Newman).



**Fig. 1.** Fundus photographs of Case 1 on day 15 of admission showing multifocal, pale yellow lesions concentrated at the posterior poles (A, B). Mid-phase fluorescein angiogram images show areas of early choroidal hyperfluorescence corresponding to the yellow retinal lesions with late leakage of fluid into the sub-retinal space (C, D). Optical coherence tomography images (Cirrus Optical Coherence Tomographer, Carl Zeiss Meditec, Inc.) demonstrate multiple small discrete areas of retinal pigment epithelial elevation adherent to the thickened outer retina with widespread multifocal areas of sub-retinal fluid (E, F). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

ATRA induction therapy induces the terminal differentiation of the malignant blast progenitors by initiating re-activation of the repressed genes and additionally causing degradation of the PML-RAR $\alpha$  chimera.<sup>6</sup> These maturing granulocytes are released into the systemic circulation and are then able to undergo normal senescence and apoptosis. ATRA therapy is generally well tolerated and is highly efficacious in the management of APL and induces complete remission in 90–95% of cases.<sup>6,9</sup> There is also an emerging role of arsenic trioxide (ATO) during the induction phase not only in refractory or relapsing cases of APL, but also for new diagnoses.<sup>2,9,10,12,13</sup> ATO has been shown to promote cellular differentiation in APL and also induces apoptosis by non-PML-RAR $\alpha$  dependent mechanisms, resulting in complete remission in 52–100% of cases.<sup>6</sup>

Though differentiating agents, including ATRA and ATO, are highly efficacious in the treatment of APL, induction may cause the development of the differentiation syndrome (DS). The DS occurs in approximately one quarter of patients, with reported incidences ranging between 2 and 48% after beginning induction therapy.<sup>4,13–15</sup> Formerly known as retinoic acid syndrome, DS represents a potentially life-threatening complication of differentiation therapy with reported mortality rates of between 1.0% and 1.4%.<sup>13,14,16</sup> A syndrome typically predominated by unexplained fever and respiratory distress, DS is also associated with peripheral oedema, pulmonary infiltrates, weight gain, pleuropericardial effusions, acute kidney injury and episodic hypotension.<sup>14,16–18</sup> This complication occurs during induction with differentiating agents when there are elevated leukaemic blasts, rather than during consolidation or maintenance therapy, or once the patient has attained complete remission.<sup>15,16</sup> The diagnosis of DS is mainly based on clinical and radiological features following induction with differentiating agents and after the exclusion of masquerading syndromes such as congestive cardiac failure, pneumonia, or sepsis.<sup>4,15</sup> The pathophysiology of DS remains unknown, however it is proposed that

there is a simultaneous differentiation of the large pool of promyelocytic blasts which display properties of both increased cellular adhesiveness and enhanced cytokine production.<sup>4,16,18</sup> These properties of the newly differentiated cells contribute to an inflammatory milieu characterised by massive tissue infiltration by differentiating APL cells and systemic capillary leak syndrome respectively.<sup>4,14,16,18–20</sup> The management of DS involves prompt administration of corticosteroids as soon as it is suspected as either a primary or concomitant pathology.<sup>15,16</sup> Temporary cessation of differentiating agents is controversial however indicated in patients with profound organ dysfunction or in severe DS.<sup>15,16</sup> The use of cytoreductive agents may be considered for ATO based regimens in cases of leukocytosis.<sup>15,16</sup>

Ophthalmic manifestations of the DS are rarely reported in the literature. In 2013, Levasseur and colleagues described the first case of bilateral chorioretinopathy with multifocal serous neurosensory retinal detachments and choroidal hyperpermeability following induction with ATRA.<sup>21</sup> Here we report two patients presenting to a tertiary institution which we believe is the first case series describing the ophthalmic manifestations of DS.

## 2. Findings

### 2.1. Case 1

A 35-year-old female patient presented in July 2016 with a two-month history of increasing lethargy, easy bruising, and bilateral lower limb lesions which were slow-healing. Blood analysis revealed that she was pancytopenic and coagulopathic. Her peripheral blood films were consistent with APL demonstrating the presence of numerous blasts with reniform nuclei and Auer Rods. The PML/RAR $\alpha$  chimera was detected by interphase fluorescence in-situ hybridisation consistent with a t(15:17) chromosomal translocation. The APLM4<sup>22</sup> chemotherapy

protocol was immediately commenced, consisting of ATRA (45mg/m<sup>2</sup>), idarubicin (12mg/m<sup>2</sup>) on day 2/4/6/8, and ATO (0.15mg/kg) from day 9 onwards. As per protocol, prednisolone (1mg/kg) was administered from days 1–10 as routine DS prophylaxis. On day 11 of therapy, the patient became febrile, hypotensive, and developed a mild headache. She was commenced on piperacillin-tazobactam and vancomycin for febrile neutropenia.

On day 14, she had continued hypotension, tachycardia and developed acute renal impairment, peripheral oedema and weight gain. There was no evidence of infection. She also complained of decreased vision, right worse than left. Urgent ophthalmic assessment revealed visual acuities of 6/36 in the right eye and 6/18 in the left and intraocular pressures of 36 mmHg and 27 mmHg in each eye respectively. Gonioscopy demonstrated bilaterally shallowed anterior chambers with closed angles confirming a diagnosis of bilateral angle closure. This was treated with bilateral peripheral iridotomy, topical pilocarpine and intraocular-pressure lowering medications. Posterior segment examination revealed bilateral, multifocal pale yellow chorioretinal lesions concentrated at the posterior poles, with superficial retinal haemorrhages (Fig. 1). Optical coherence tomography (OCT) showed multifocal areas of sub-retinal fluid with focal areas of retinal pigment epithelium (RPE) elevation and adhesion to the overlying thickened retina. OCT raster images with enhanced depth imaging show significant choroidal thickening with multifocal areas of sub-retinal fluid and multiple small nodular elevations of the RPE (Fig. 2). Fluorescein angiography showed multiple areas of early hyperfluorescence corresponding to the yellow retinal lesions with late leakage of fluid into the sub-retinal space. The ophthalmic signs combined with other clinical features were consistent with a diagnosis of DS with ocular involvement.

A multidisciplinary decision was made to cease ATRA and ATO therapy and restart oral prednisone at 1mg/kg with topical ocular dexamethasone. Both differentiating agents were restarted after 6 days of cessation, prednisolone was tapered over the next twenty days and all topical eye drops were ceased due to improvement of vision, and stable deepening of the anterior chambers. Marked resolution in sub-retinal fluid was seen at day fourteen of diagnosis with DS. Following completion of induction therapy, repeat bone marrow aspirate and trephine were negative for PML-RAR $\alpha$  on bone marrow PCR confirming APL in remission. The patient went on to receive standard consolidation treatment courses with ATRA and ATO without steroid cover and without visual sequelae. At seven months post presentation, the patient remains in complete remission with final visual acuities of 6/5 in both

eyes.

## 2.2. Case 2

A 30-year-old female presented in November 2013 with a one-month history of lethargy, easy bruising, intermittent subjective fevers, and a dental infection requiring a prolonged course of antibiotics. Blood tests revealed a coagulopathy and pancytopenia with blasts on her peripheral blood smear. A bone marrow examination confirmed the diagnosis of APL by morphologic, cytogenetic, and molecular analysis. Chemotherapy was commenced with ATRA and ATO as part of the AMPL4 regimen as in Case 1.<sup>22</sup> On day 9 of treatment she complained of headache, nausea, and epigastric pain and was febrile, hypotensive and tachycardic. She was commenced on piperacillin-tazobactam, gentamicin and vancomycin but developed neutropenic septic shock with *Escherichia coli* bacteraemia. She required a three day admission to the intensive care unit for inotropic support and intensive antimicrobial therapy. During this admission her thrombocytopenia worsened with epistaxis, haematuria and bruising and she required platelet transfusions to maintain platelet counts above  $50 \times 10^9/L$ .

On day ten, she reported bilateral reduction in visual acuity with acuities of 6/120 in the right eye and 6/24 in the left. Examination of the anterior segments was unremarkable. Superficial and intra-retinal haemorrhages were evident at both posterior poles along with the presence of multifocal diffuse yellow chorioretinal lesions (Fig. 3). OCT imaging on day 14 demonstrated bilateral multifocal areas of serous retinal detachment with interspersed areas of adhesion between the RPE and thickened overlying neurosensory retina. Fluorescein angiography was not performed. No evidence of infective endocarditis was identified on transthoracic echocardiography.

In the context of the clinical scenario, the ocular findings were attributed to sepsis with hypoproteinaemia. In addition to anti-microbials, blood products and haemodynamic support, the AMPL4 chemotherapy protocol was continued without adjustment. Vision showed rapid improvement from day 16 onward, with complete resolution of the sub-retinal fluid seven days after the initial visual disturbance and final visual acuities were 6/6 in each eye. Bone marrow examination on day 36 showed complete molecular remission. Whilst not considered at the time, a review of her case (in light of case 1) suggested that the clinical features are consistent with DS with ophthalmic manifestations.

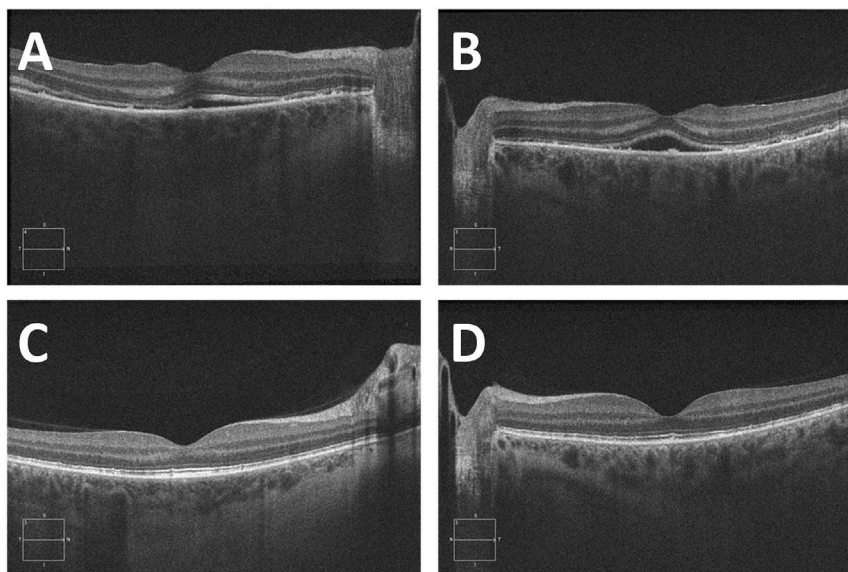


Fig. 2. Raster scans with enhanced depth imaging (Cirrus Optical Coherence Tomographer, Carl Zeiss Meditec, Inc.) on day 22 of admission, 8 days following the initial visual disturbance demonstrate significant choroidal thickening, and multifocal areas of sub-retinal fluid with multiple small nodular elevations of the retinal pigment epithelium (A, B). At day 73 of admission, there is marked reduction in choroidal thickness and total resolution of the sub-retinal fluid (C, D).



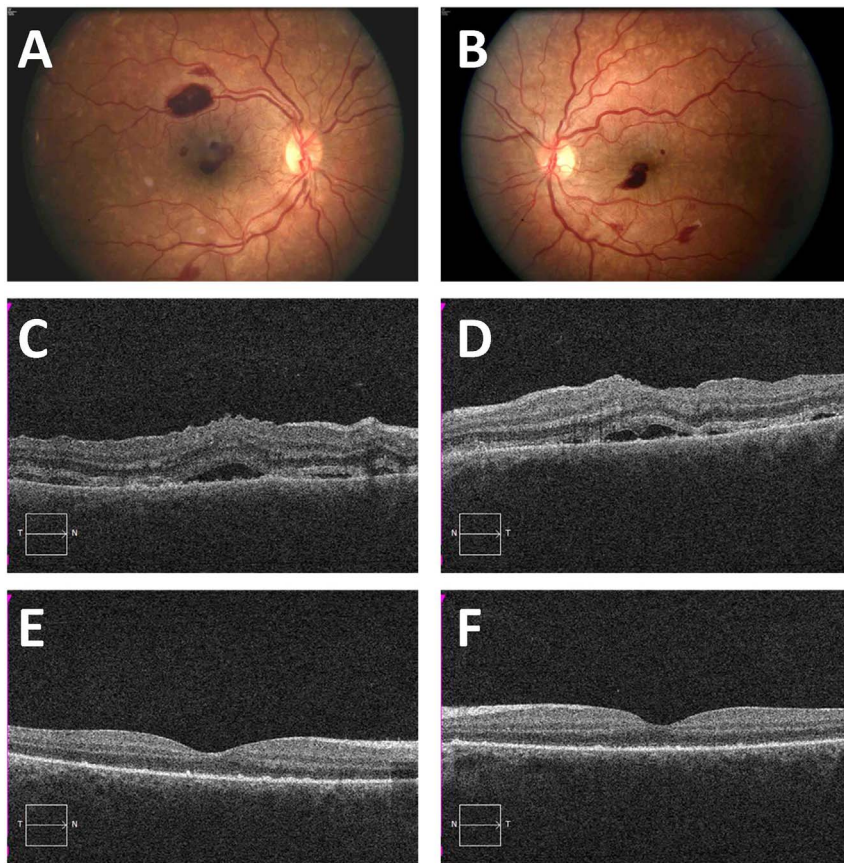


Fig. 3. Fundus photographs of Case 2 on day 14 showing the widespread multifocal yellow chorioretinal lesions, with superficial and intra-retinal haemorrhages (A, B). Optical coherence Tomography (Cirrus Optical Coherence Tomographer, Carl Zeiss Meditec, Inc.) images on day 14 of presentation demonstrate multifocal serous retinal detachment with interspersed areas of adhesion between the thickened neurosensory retina and focal retinal pigment epithelial elevations (C, D). There is complete resolution of the sub-retinal fluid after seven days, on day 21 of admission (E,F). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

### 3. Discussion

There are many similarities between each of the reported cases of DS with ocular manifestations. In each case the bilateral visual disturbance was coincident temporally with the onset of systemic symptoms of DS, with rapid resolution of the sub-retinal fluid and concurrent recovery of vision. The median time to DS onset in patients treated with ATRA is approximately 7–12 days, with the more severe phenotype presenting earlier than moderate disease.<sup>1,14,18,19</sup> This timing is consistent with the development of DS at days fourteen and ten respectively in this series and is similar to the other reported case onset at day eighteen, notably their patient was not receiving routine steroid DS prophylaxis.<sup>21</sup> In this series, both patients had an excellent visual prognosis and have remained in complete molecular remission. It remains unclear whether there is a benefit of temporarily stopping the differentiating therapy in individuals with DS with ocular involvement as both patients experienced prompt visual recovery despite only one patient temporarily ceasing differentiation therapy. The decision to withhold treatment should be determined based on the overall severity of DS in accord with current recommendations.

The appearance of the chorioretinal lesions and OCT appearance of the subretinal fluid with focal RPE elevation and retinal adhesion in both Case 1 and Case 2, as well as the pattern of hyperfluorescence and leakage during fluorescein angiography described in Case 1 is consistent with the other published case report.<sup>21</sup> The bilateral multifocal areas of sub-retinal fluid due to chorioretinopathy implicate both choroidal and RPE hyperpermeability<sup>21</sup> and appears to be the consistent mechanism of visual acuity reduction in patients with DS. The yellow chorioretinal lesions are presumed to be due to localised leukaemic cellular infiltrate and exudate between the outer retina and sub-RPE space. These yellow lesions appear to correlate with the focal areas of RPE elevation and adhesion to the thickened outer retina identified on OCT, rather than the exudative material occupying the sub-retinal

space which is resultant from choroidal and RPE hyperpermeability. A proposed mechanism of choroidal and RPE hyperpermeability is related to the systemic capillary leak syndrome in addition to leukaemic infiltration and microvascular occlusion with secondary ischaemia and RPE dysfunction, incompetence of the blood-retinal barrier, and alterations in intercellular junctions.<sup>4,16,18,21,23–27</sup>

Of the cases of ophthalmic DS described so far, there has been a predilection for disease to affect the choroidal and retinal tissues as has been seen in patients with ocular leukaemia, with a pattern of chorioretinopathy which is clinically similar to Vogt-Koyanagi-Harada disease.<sup>21,23,24,28–31</sup> Notably absent in the three described cases of ophthalmic DS however have been the findings of vitritis, sterile hypopyon, keratic precipitates, retinal vasculitis, vascular sheathing, retinal vascular congestion, choroidals, or orbital involvement. In this series, the retinopathy has been limited to intra-retinal and superficial retinal haemorrhages, with one patient presenting with a unilateral Roth's spot, however both patients had concurrent thrombocytopenia. The differential diagnoses considered for the ocular appearances above include the differentiation syndrome, leukaemic infiltration, hypoproteinaemia, central serous chorioretinopathy secondary to steroid use, the multifocal inflammatory chorioretinopathies, choroiditis, choroidal ischaemia secondary to intravascular coagulation, autoimmune uveitis, and posterior scleritis.<sup>21,31–34</sup> Focal endogenous endophthalmitis secondary to the *Escherichia coli* septicaemia in Case 2 was considered to be less likely as *E. coli* endophthalmitis is typically associated with poor visual prognosis.<sup>35–40</sup> A case of bilateral exudative retinal detachment secondary to *E. coli* septicaemia has been recently reported, however the pattern of chorioretinopathy and other ophthalmic manifestations were not in keeping presentation of the two above reported cases.<sup>41</sup> The bilateral angle closure diagnosed in Case 1 was attributed to anterior rotation of the lens-iris diaphragm occurring due to presumed anterior choroidal thickening as significant posterior choroidal thickening was demonstrated on enhanced depth OCT. It is unclear whether this

patient had an anatomical conformation that predisposed them to developing angle closure compared with the two other described cases.

Timely ophthalmic assessment of patients presenting with visual symptoms in the context of induction therapy with differentiating agents is critical for diagnosis and to ensure optimal ophthalmic outcomes. Such assessment should include OCT and angiography if possible. The urgency of assessment is firstly due to the possible occurrence of angle closure as this may lead to the development of glaucomatous neuropathy if untreated. In addition, the characteristic ophthalmic examination findings appear to be highly specific to DS in contrast to the systemic features that can be vague in the early stages of disease. Therefore ocular assessment may play an important role in the early diagnosis of this life-threatening illness and subsequently direct prompt definitive management. Finally, broader recognition of this condition may identify other ophthalmic manifestations of DS in addition to the apparent predilection for retinal and choroidal tissues.

Levasseur and colleagues highlight that the ophthalmic involvement during DS may be under-appreciated as visual symptomatology in these patients may be unrecognised or deprioritised due to concomitant organ dysfunction.<sup>21</sup> It remains unclear whether severe DS shows more marked ocular involvement. Prospective data is required to investigate the incidence of ocular involvement in DS and ascertain whether a different phenotype of disease is appreciated in cases with ocular involvement. Once the incidence and nature of ophthalmic involvement in DS is more fully appreciated, the role and timing of ophthalmic examination in patients with DS or those receiving differentiation therapy can be evaluated. Given the sensitivity of OCT to vascular leakage it may even be possible to monitor patients for DS in the early, high risk phase of induction therapy. In addition, further recognition of the ophthalmic manifestations of DS may lead to the identification of biochemical or systemic features predictive of ocular involvement and the development of an optimised management approach.

#### 4. Conclusions

We report the first case series of two patients presenting to our institution with ocular manifestations of the differentiation syndrome. Both patients receiving treatment of their APL presented with acute visual disturbance in the setting of the DS during induction chemotherapy with ATRA and ATO. Both presentations showed bilateral chorioretinopathy with bilateral multifocal poorly-circumscribed yellow lesions concentrated at the posterior poles. OCT images demonstrate multifocal shallow areas of sub-retinal fluid with interspersed areas of RPE elevation with adhesion to the overlying thickened retina. Fluorescein angiography demonstrates early choroidal hyperfluorescence corresponding to the yellow spots with late leakage of fluid into the sub-retinal space. OCT is sensitive to detecting sub-retinal fluid and may be useful to support the diagnosis of DS. Both patients experienced rapid recovery of vision and resolution of the sub-retinal fluid.

#### Patient consent

Both patients consented to publication of the case in writing.

#### Funding

No funding or grant support.

#### Conflicts of interest

The following authors have no financial disclosures: AN, BL, AR, TC, JW, FI.

#### Authorship

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

#### Acknowledgments

None.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ajoc.2018.01.026>.

#### References

1. Fenaux P, De Botton S. Retinoic acid syndrome. Recognition, prevention and management. *Drug Saf.* 1998;18:273–279.
2. Degos L, Wang ZY. All trans retinoic acid in acute promyelocytic leukemia. *Oncogene.* 2001;20:7140–7145.
3. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood.* 1999;94:1192–1200.
4. Luesink M, Pennings JLA, Wissink WM, et al. Chemokine induction by all-trans retinoic acid and arsenic trioxide in acute promyelocytic leukemia: triggering the differentiation syndrome. *Blood.* 2009;114:5512–5521.
5. Lin RJ, Egan DA, Evans RM. Molecular genetics of acute promyelocytic leukemia. *Trends Genet.* 1999;15:179–184.
6. Mistry AR, Pedersen EW, Solomon E, Grimwade D. The molecular pathogenesis of acute promyelocytic leukaemia: implications for the clinical management of the disease. *Blood Rev.* 2003;17:71–97.
7. Grignani F, Fagioli M, Ferrucci PF, Alcalay M, Pelicci PG. The molecular genetics of acute promyelocytic leukemia. *Blood Rev.* 1993;7:87–93.
8. Zhang JW, Wang JY, Chen SJ, Chen Z. Mechanisms of all-trans retinoic acid-induced differentiation of acute promyelocytic leukemia cells. *J Biosci.* 2000;25:275–284.
9. Altman JK, Rademaker A, Cull E, et al. Administration of ATRA to newly diagnosed patients with acute promyelocytic leukemia is delayed contributing to early hemorrhagic death. *Leuk Res.* 2013;37:1004–1009.
10. Lou Y, Qian W, Meng H, et al. High efficacy of arsenic trioxide plus all-trans retinoic acid based induction and maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Leuk Res.* 2013;37:37–42.
11. Douer D, Zickl LN, Schiffer CA, et al. All-trans retinoic acid and late relapses in acute promyelocytic leukemia: very long-term follow-up of the North American Intergroup Study 10129. *Leuk Res.* 2013;37:795–801.
12. Mi JQ, Li JM, Shen ZX, Chen SJ, Chen Z. How to manage acute promyelocytic leukemia. *Leukemia.* 2012;26:1743–1751.
13. Leblebjian H, DeAngelo DJ, Skirvin JA, et al. Predictive factors for all-trans retinoic acid-related differentiation syndrome in patients with acute promyelocytic leukemia. *Leuk Res.* 2013;37:747–751.
14. Montesinos P, Bergua JM, Vellenga E, et al. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood.* 2009;113:775–783.
15. Montesinos P, Sanz MA. The differentiation syndrome in patients with acute promyelocytic leukemia: experience of the pethema group and review of the literature. *Medierr J Hematol Infect Dis.* 2011;3:e2011059 e2011059.
16. Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood.* 2014;123:2777–2782.
17. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell Jr RP. The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med.* 1992;117:292–296.
18. Tallman MS, Andersen JW, Schiffer CA, et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. *Blood.* 2000;95:90–95.
19. De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood.* 1998;92:2712–2718.
20. Bi KH, Jiang GS. Relationship between cytokines and leukocytosis in patients with APL induced by all-trans retinoic acid or arsenic trioxide. *Cell Mol Immunol.* 2006;3:421–427.
21. Levasseur SD, Tantiworawik A, Lambert Maberley DA. All-trans retinoic Acid differentiation syndrome chorioretinopathy: a case of multifocal serous neurosensory detachments in a patient with acute promyelocytic leukemia treated with all-trans retinoic Acid. *Retin Cases Brief Rep.* 2013;7:46–49.
22. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). *Blood.* 2012;120:1570–1580.
23. Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. *Eye.* 2004;18:663–672.
24. Sharma H, Majumder PD, Rao C, Biswas J. A case of Acute Myeloid Leukemia masquerading as unilateral exudative detachment. *Am J Ophthalmol Case Rep.*

- 2016;4:47–49.
25. Kim J, Chang W, Sagong M. Bilateral serous retinal detachment as a presenting sign of acute lymphoblastic leukemia. *Kor J Ophthalmol*. 2010;24:245–248.
26. Liang MC, Bauml C. Bilateral serous retinal detachment as a presenting sign of acute lymphoblastic leukemia in an adult. *J Clin Stud Med Case Rep*. 2015;2:1–2.
27. Wu L, Calderón M, Hernández G, Marbis J, Ramírez V. Bilateral exudative retinal detachment as the first sign of relapsing acute myelogenous leukaemia. *Clin Exp Ophthalmol*. 2006;34:623–625.
28. Chinta S, Rani PK, Manusani U. Bilateral exudative retinal detachment as a presenting sign of acute lymphoblastic leukemia. *Middle East Afr J Ophthalmol*. 2012;19:410–412.
29. AlZamil WM. Lymphocytic leukemia presenting as acute Vogt-Koyanagi-Harada disease. *Saudi J Ophthalmol*. 2014;28:319–321.
30. Yang HK, Yu HG. Acute lymphoblastic leukemia manifesting as acute Vogt-Koyanagi-Harada disease. *Kor J Ophthalmol*. 2009;23:325–328.
31. Vieira L, Silva NA, Medeiros MD, Flores R, Maduro V. Acute lymphoblastic leukemia presenting with bilateral serous macular detachment. *Arq Bras Oftalmol*. 2015;78:382–384.
32. Gass JD, Slamovits TL, Fuller DG, Gieser RG, Lean JS. Posterior chorioretinopathy and retinal detachment after organ transplantation. *Arch Ophthalmol*. 1992;110:1717–1722.
33. Crawford CM, Igboeli O. A review of the inflammatory chorioretinopathies: the white dot syndromes. *ICA Inf*. 2013;2013 783190–783190.
34. Mansour SE. *Multifocal choroidopathy syndromes: medscape*. 2015; 2015<http://emedicine.medscape.com/article/1190935-overview#a1>, Accessed date: 24 September 2017.
35. Cheng NM, Chandra A, Roufail E, et al. Chorioretinal biopsy for the diagnosis of endogenous endophthalmitis due to escherichia coli. *Retin Cases Brief Rep*. 2017;11:30–33.
36. Park SB, Searl SS, Aquavella JV, Erdey RA. Endogenous endophthalmitis caused by Escherichia coli. *Ann Ophthalmol*. 1993;25:95–99.
37. Shammam HF. Endogenous E. coli endophthalmitis. *Surv Ophthalmol*. 1977;21:429–435.
38. Anand N, Brogden PE. Coli endophthalmitis. *Eye*. 1996;10(Pt 1):142–143.
39. Tseng CY, Liu PY, Shi ZY, et al. Endogenous endophthalmitis due to Escherichia coli: case report and review. *Clin Infect Dis: An Official Publication Of The Infectious Diseases Society Of America*. 1996;22:1107–1108.
40. Arévalo JF. *Retinal and Choroidal Manifestations of Selected Systemic Diseases*. New York: Springer; 2013.
41. Rani PK, Ambiya V, Senthil S, Jalali S. Bilateral choroidal detachment with exudative retinal detachment in a patient with septicemia. *BMJ Case Rep*. 2016;2016.