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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

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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 subretinal 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 hyperflouresence 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 fundoscopy 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).[1–3] In 95% of cases, the promyelocitic leukaemia (PML) gene on chromosome 15 is fused to the retinoic acid receptor-α (RARα) gene on chromosome 17 to form a chimeric PML-RARα 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.[4–8] The mainstay of induction therapy is all-trans retinoic acid (ATRA) typically in combination with anthracycline-based chemotherapy to reduce the incidence of relapse.[2,9–11] Administration of supra-physiologic doses of retinoic acid as occurs during

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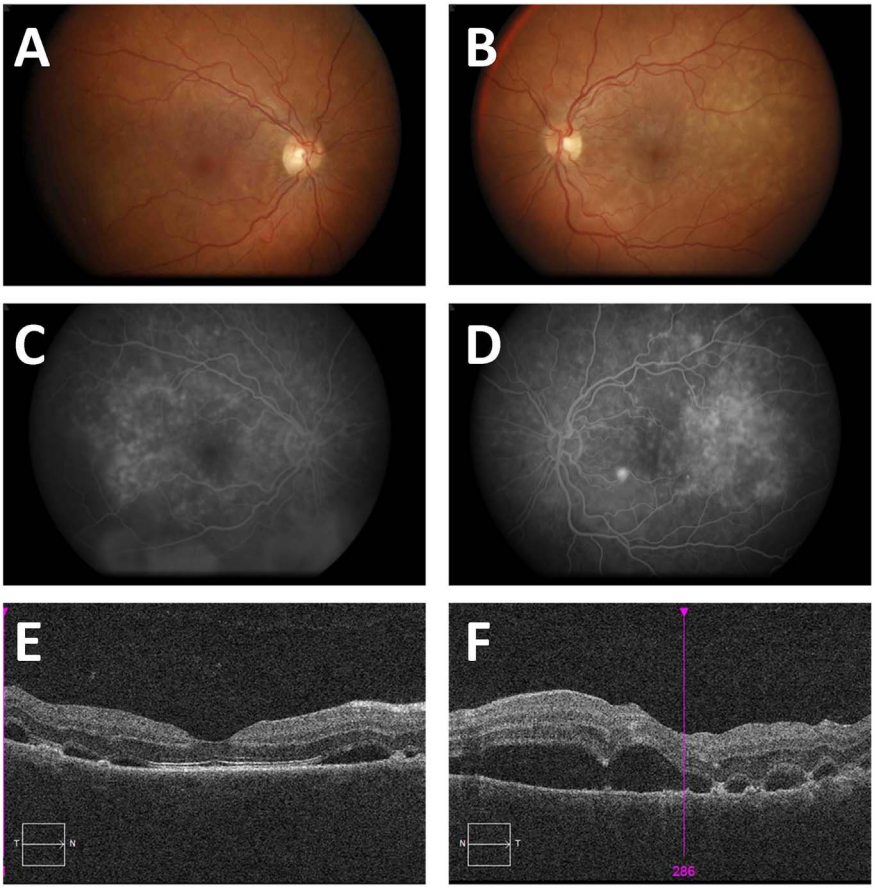

Fig. 1. Fundus photographs of Case 1 on day 15 of admission showing multifocal, pale yellow lesions concentrated at the posterior poles (A, B). Mid-phase fluorescein angiogram images show areas of early choroidal hyperfluoresence corresponding to the yellow retinal lesions with late leakage of fluid 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-RARα chimera.[6] 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.[6,9] 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.[2,9,10,12,13] ATO has been shown to promote cellular differentiation in APL and also induces apoptosis by non-PML-RARα dependent mechanisms, resulting in complete remission in 52–100% of cases.[6]

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.[4,13–15] 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%.[13,14,16] 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.[14,16–18] 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.[15,16] 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.[4,15] 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.[4,16,18] 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.[4,14,16,18–20] The management of DS involves prompt administration of corticosteroids as soon as it is suspected as either a primary or concomitant pathology.[15,16] Temporary cessation of differentiating agents is controversial however indicated in patients with profound organ dysfunction or in severe DS.[15,16] The use of cytoreductive agents may be considered for ATO based regimens in cases of leukocytosis.[15,16]

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.[21] 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 pancytopaenic and coagulopathic. Her peripheral blood films were consistent with APL demonstrating the presence of numerous blasts with reniform nuclei and Auer Rods. The PML/RARα chimera was detected by interphase fluorescence in-situ hybridisation consistent with a t(15:17)chromosomal translocation. The APML4[22] chemotherapy