# Differentiation syndrome induced by all-trans retinoic acid in acute promyelocytic leukemia

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**ABSTRACT**

Differentiation syndrome (DS) is a serious and potentially life-threatening complication associated with differentiation therapy such as all-trans retinoic acid (ATRA) in patients with acute promyelocytic leukemia (APL). This case report describes the clinical presentation, management, and outcome of ATRA-induced differentiation syndrome. ATRA promotes the maturation of malignant promyelocytes into functional granulocytes and is an essential component of APL treatment, particularly in patients with the characteristic t(15;17) chromosomal translocation. However, the therapeutic benefit may be accompanied by DS, which commonly presents with fever, dyspnea, rapid weight gain, pulmonary infiltrates, and features of capillary leak syndrome. Early recognition and prompt treatment, especially with corticosteroids such as dexamethasone, are crucial to prevent serious complications. This case highlights the importance of continuous monitoring during induction therapy and rapid intervention to reduce morbidity and mortality associated with differentiation syndrome.

**Key words:** Differentiation syndrome, All trans retinoic acid, Acute promyelocytic leukemia, RARα and PML genes, Adverse drug reaction.

## INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct kind of acute myeloid leukaemia characterized by a specific chromosomal translocation between chromosomes 15 and 17, resulting in the formation of PML-RARα fusion genes[1].The PML-RARA fusion protein produces a dominant negative mutation that suppresses differentiation, apoptosis, and promotes the development of leukemic progenitors, this protein has been the target of numerous in vitro studies that have enhanced our knowledge towards APL and its specific reactivity to retinoic acid[2,3]. ATRA is a type of retinoid that is produced from vitamin A by rapid oxidation process in extrahepatic cells, that helps in tissue development, neurological function, immunological function, reproduction, vision, cell proliferation and differentiation, tumour immunity, and apoptosis[4].The established strategy for treating patients with APL consists of four key elements: early diagnosis and timely ATRA administration; early mortality mitigation; identification and management of complications associated with treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (As2O3, ATO); and monitoring of measurable residual disease (MRD)[5].ATRA binds to the modified fusion protein and promotes the differentiation of malignant promyelocytes into mature granulocytes thereby restoring transcriptional activity[6]. Differentiation syndrome, which is a potential adverse reaction is caused by all-trans retinoic acid, arsenic trioxide, mutant isocitrate dehydrogenase inhibitors (such as enasidenib), and the FLT3 inhibitor gilteritinib[6,7]. This case report aims to emphasize the clinical presentation and management strategies for ATRA- induced differentiation syndrome.

## CASE REPORT

A 47-year-old female patient presented with complaints of fever and headache for 4-5 days. The headache was holocranial with no photophonophobia. The patient was previously diagnosed with acute promyelocytic leukemia with low fibrinogen and was now experiencing headache, increased visual blurring, and repeated episodes of bilious vomiting. Her Hb was 9.0, Plt was 82, Tc was 13.2, and peripheral smear revealed promyelocytes and faggots cells.CT brain was performed, which revealed no indication of bleeding, and a neurology consultation was scheduled, with the recommendation of an MRI brain headache procedure. She began taking ATRA on 7-7-25 and was periodically examined for CBC, TLS, and fibrinogen levels, with transfusions as needed. She received three doses of Inj.Daunorubicin 40mg IV over three days. She began running a persistent temperature on the evening of 11-05-25.Blood cultures, urine cultures, procalcitonin, and CRP were submitted, and the patient was started on IV antibiotics, Inj.Piperacillin Tazobactum 4.5gm TID and Inj.Clindamycin 600mg, but the fever persisted, so the antibiotics were escalated to Inj.Meropenem 1gm TID. Blood culture sent on 11-7-25 revealed pseudomonas aeruginosa, which is sensitive to meropenem, therefore the treatment was maintained. She suffered from cramping discomfort in both lower limbs and was treated with Tramadol.Because the patient had continuous discomfort, ATRA was briefly withheld on 16-7-25 due to differentiation syndrome and the patient was continued on Tab.Dexamathasone 8mg.BD. ATRA was reintroduced after 5 days, however she had bilateral lower limb pain the next day, which was not improved by Inj.Tramadol, therefore ATRA was withdrawn. She got blisters and soreness along the left angle of her lips and began taking therapeutic doses of Tab.Acyclovir 400mg TID.She continued to experience bilateral pain, therefore dexamethasone was raised from BD to TID and progressively tapered off. She was started on Inj.Arsenic Trioxide instead of ATRA and was constantly evaluated for serum electrolytes, while ATO was

continued and tolerated well with no side effects. On 16-8-25, she complained of mild breathlessness and orthopnea, so a 2D echocardiogram was performed, which revealed normal chamber dimensions, no RWMA, TR-mild to moderate, minimal pericardial effusion, borderline PA pressures, normal RV and LV functions, LVEF-55 to 60%, bilateral pleural effusion, and a cardiology opinion was obtained and advised with Tab.Losartan 25 mg OD, Cardivas 3.125 mg OD, and hydration restriction.Her blood culture was negative, and antibiotics were de-escalated to Inj.Cefepime 2gm BD. She improved symptomatically and was discharged with stable hemodynamics.

## DISCUSSION

Differentiation syndrome is a well-recognized complication associated with the use of differentiation agents such as ATRA and ATO in APL treatment. Although the exact pathophysiology remains incompletely understood, it is believed to involve an exaggerated inflammatory response triggered by cytokine release and endothelial activation[8]. Clinically, DS presents with a constellation of symptoms including fever, respiratory distress, hypotension, weight gain and fluid accumulation in serous cavity. The incidence of DS varies widely across studies, ranging from 2% to 27%, depending on diagnostic criteria and treatment protocols[9]. Due to the extravasation of mature myeloid cells in lungs, skin, and other soft tissues, the patient may experience edema, effusions and inflammation that clinically show as DS[10].The proinflammatory cytokines interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor that were released following the administration of ATRA could be the origin of this systemic inflammatory reaction[11]. Following APL induction therapy, around 25% of patients experience sudden renal failure[12].Post-mortem examination of patients with APL and DS revealed diffuse neutrophilic infiltration with corresponding diffuse alveolar hemorrhage in the lungs and diffuse leukemic infiltration in various other organs, supporting the theory of chemokine production and infiltration of alveolar and other organ tissues[13]. Given the severe morbidity and mortality rates associated with DS, it is crucial to identify the condition and provide treatment as soon as possible[14]. In the present case, the patient developed classical features of DS during ATRA therapy, early recognition and prompt administration of corticosteroids played a crucial role in preventing disease progression. Temporary discontinuation of ATRA and switching to arsenic trioxide further contributed to clinical improvement. Corticosteroids such as dexamethasone remain the cornerstone of DS management that aids in suppressing the inflammatory response and reduced capillary leakage[10].Furthermore, the DS mortality rate is now exceptionally low (1%), due to early corticosteroid treatment paired with concomitant ATRA-related chemotherapy[15,16]. This case also highlights the importance of differentiating DS from infectious complications, as both conditions may present with similar clinical features. Based on several studies, BMI also can serve as a predictor of DS, which could be explained by APL cells overexpressing leptin receptors, which can boost cytokine release after ATRA treatment[17,18].

## CONCLUSION

Differentiation syndrome remains an significant complication in patients with acute promyelocytic leukemia undergoing treatment with ATRA. Although advances in therapy have significantly improved survival rates, delayed recognition of DS can result in serious morbidity or mortality. This case emphasizes the importance of early identification, close clinical monitoring, and prompt corticosteroid therapy in patients receiving differentiation therapy. Increased awareness among healthcare professionals

and timely management strategies can significantly improve patient outcomes and reduce complications during APL treatment.

**DECLARATIONS**

Ethical approval: Ethical approval was obtained from the Institutional Ethics Committee of Erode Cancer Centre. The study was conducted in accordance with the Declaration of Helsinki.

Consent to Participate: Written informed consent was obtained from the patient for publication of this case report.

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