

## Original Article

# All-trans-retinoic acid-induced rhabdomyolysis: a case report

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**Abstract:** All-trans retinoic acid (ATRA) induced rhabdomyolysis in the induction treatment of acute promyelocytic leukemia (APL) is a very rare complication. However, rhabdomyolysis-related acute renal failure increases the risk of high morbidity and mortality. Here we describe a case of rhabdomyolysis associated with ATRA during the induction therapy in an adult with APL. Clinical implications are discussed with a critical review of existing literature and we expect to draw much more awareness among clinicians regarding such association.

**Keywords:** All-trans retinoic acid, acute promyelocytic leukemia, rhabdomyolysis

### Introduction

Acute promyelocytic leukaemia (APL) is characterised by t(15;17) translocation, and coagulopathy combining with disseminated intravascular coagulation (DIC) and fibrinolysis [1-3]. Therapy with All-trans-retinoic acid (ATRA) can rapidly improved coagulopathy without myelosuppression toxicity. Therefore ATRA has been widely used in the treatment of acute promyelocytic leukemia (APL) [4]. However, ATRA still have some adverse effects including retinoic acid syndrome, which showed is characterized by fever, dyspnea, weight gain, pleural, pericardial effusions, hypotension, and acute neutrophilic dermatosis (Sweet's syndrome), hyperleukocytosis [4-6]. ATRA induced elevated creatine kinase (CK) levels and rhabdomyolysis is rare. Here, we describe a patient with a significant elevation in CK and creatinine (Cr) after beginning therapy with ATRA. There is few published literature about the rhabdomyolysis caused by ATRA.

### Case report

A 44-year-old man presented to our clinic with fever, fatigue, headache and epistaxis. Physical examination revealed fever (37.6°C), tachycardia (HR 108 bpm), pallor, wide-spread petechia. Results of the laboratory investigation were as

follows: white blood cell count 1400/dl, hemoglobin 5.7 g/dl and platelets 15000/dl; Coagulation profile was prothrombin time 15.8 s, activated partial thromboplastin time 23.4 s, fibrinogen 75 mg/dL (200-590 mg/dL), 3P(+), D-dimer >0.8 mg/dl (<0.025 mg/dl); And stool occult blood test (+++), urine occult blood test (+++). Bone marrow aspirate showed a morphologic. Detection of translocation t(15;17) by cytogenetic using bone marrow showed PML-RARA fusion signal in 12 of 20 metaphases, and the characteristic fusion of PML and RARA was detected by PCR.

The patient was started on treatment with ATRA 45 mg/m<sup>2</sup> p.o. The ongoing coagulopathy was transfused with plasma, intravenous unfractionated heparin was either given to the patient until the coagulation disorder resolved. No complications were observed and coagulation parameters were improved until day-17 from the start of therapy. However the patient felt severe waist pain especially on sacrococcygeal and xiphoid and nausea, vomiting, oliguria without headache, dyspnea and visual disturbance. Severe ecchymosis was found on his extremities and trunk. Further blood test including blood routine test and a coagulation panel only showed normal anemia: WBC: 4400/dl, Hb 4.1 g/dl and platelets 12000/dl; prothrombin time 22.8 sec, activated partial thromboplastin time

## ATRA-induced rhabdomyolysis

44.4 sec, fibrinogen 205 mg/dL (200-590 mg/dL), 3P(+), D-dimer >0.8 mg/dl (<0.025 mg/dl); Urine occult blood test (+++); However the elevated CK and renal dysfunction attract our attention: CK 1043 U/L (1-195 U/L), CK-MB 284 U/L (1-25U/L), LDH 7984 U/L (50-240 U/L), Cr 458 µmol/L (1-106 µmol/L), BUN 18.4 mmol/L (1.70-8.30 mmol/L). No obvious abnormality is found in the ultrasonography of kidney and prostate either of electrocardiogram, and abdominal plain. A diagnosis of ATRA-related rhabdomyolysis, DIC and ARF was made. Then ATRA was discontinued, instead of Arsenic trioxide and daily treatment with intravenous dexamethasone (10 mg/day) was given to the patient. The patient also accepted supportive care including plasma/platelet transfusion, intravenous unfractionated heparin, and diuretics, alkalizing hydration, which could improve the coagulation and renal function. Therefore the patient's uncomfortable symptoms disappeared, and the laboratory values became to normalize. The bone marrow aspirate and biopsy obtained on day 40 confirmed a morphologic and cytogenetic complete remission.

### Discussion

Rhabdomyolysis is a condition in which damaged skeletal striated muscle breaks down rapidly. Breakdown products of damaged muscle cells are released into the bloodstream; some of these, such as the protein myoglobin, are harmful to the kidneys and may lead to kidney failure. The severity of the symptoms, which may include muscle pains, vomiting, and confusion, depends on the extent of muscle damage and whether kidney failure develops. It could result in the release of muscular cell constituents into the extracellular fluid and the circulation [7]. The elevated myoglobin and CPK, are the main characteristic of rhabdomyolysis, which lead the clinician to the final diagnosis of the syndrome [7]. Myoglobinuria occurs only in rhabdomyolysis, but rhabdomyolysis not necessarily includes visible myoglobinuria. Myoglobin is rapidly and unpredictably eliminated by hepatic metabolism. Therefore, tests for myoglobin in plasma or urine are not a sensitive diagnostic procedure [8]. During rhabdomyolysis, extreme quantities of CKMM are released and peak concentrations of 100,000 IU/ml or more are not unusual. Because overall degradation and removal are slow, the concentration

of CK remains elevated longer. Consequently, CK is more reliable than myoglobin in assessing the presence and intensity of damage to the muscles [8].

Many drugs can cause rhabdomyolysis, perhaps the most frequent reason of drug-induced rhabdomyolysis is the administration of HMG-CoA reductase inhibitors [7, 8]. There have been a few reports of elevated CK with ATRA [9-20]. It is unclear how ATRA causes elevated CK levels and rhabdomyolysis. One hypothesis suggests that environmental factors and abnormalities in leukocytes, surface integrins and their receptors maybe playing a role [9-13].

Although the reports of toxicities associated with ATRA is increasing, rhabdomyolysis as a complication of the treatment of APL with ATRA is rare. To our knowledge, there has been only 11 case reports involving the musculoskeletal system during treatment with ATRA [9-20]. And none of them developed DIC and ARF as our patient. All reported cases with ATRA-induced myositis involved lower extremities, frequently being bilateral (7/11 patients). The median time to onset of muscular symptoms from beginning of induction with ATRA was 18 days (9-24 days) in the current literature. As typically occurs in Sweet's syndrome, all patients rapidly responded to a short course of corticosteroids and discontinuation of ATRA therapy without recurrence of symptoms.

Our patient had no recent musculoskeletal injuries, myalgias, surgical procedures, excessive exercise, or intramuscular injections, presented on day 18 with muscle pain, oliguria. The elevated CK (exceed 5 times the normal values) and Cr level with abnormal coagulation parameters were found in our case. The clinical setting of muscle disease and the speedy improvement after ATRA discontinuation and a short course of corticosteroids, led us to the interpretation of rhabdomyolysis because of ATRA therapy.

In conclusion, although ATRA-induced rhabdomyolysis in the induction treatment of APL is a very rare complication, rhabdomyolysis-related ARF increases the risk of high morbidity and mortality. The author recommended CK monitoring in all patients undergoing ATRA therapy, and withdrawal of ATRA when CK levels exceed 5 times the normal values.

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## Disclosure of conflict of interest

None.

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