## All–Trans-Retinoic Acid–induced Myositis in a Child with Acute Promyelocytic Leukemia

**Anthracyclin-based regimens and all-trans-retinoic acid (ATRA, tretinoin) as differentiating agent are commonly utilized for the treatment of acute promylelocytic leukemia (APL). There are many adverse effects that may be seen during the use of ATRA in patients with APL. Of these, ATRA-induced myositis is rarely described in adults and rare in the children with APL. Herein, we report an 11-year-old girl with APL who developed ATRA-induced myositis during induction treatment.**

**Haematologica 2006;** 91:(7)e97-e99

Acute promyelocytic leukemia (APL) (M3 by FAB classification) is characterized by typical morphologic findings, a balanced reciprocal translocation between the long arms of chromosome 17 and 15 t (15;17), and usually the presence of coagulopathy.[1-3] Acute promyelocytic leukemia with these distinctive features constitutes approximately 10% of acute myeloblastic leukemia in children likewise in adults.[4,5]

Anthracyclin-based regimens and all-trans-retinoic acid (ATRA, tretinoin) as differentiating agent are commonly utilized for the treatment of APL. However, the use of ATRA may have some adverse effects including retinoic acid syndrome that is characterized by fever, dyspnea, weight gain, pleural or pericardial effusions and hypotension, and acute neutrophilic dermatosis (Sweet's syndrome), hyperleukocytosis, and ATRA-induced myositis in rare cases of adults and children.[6-13] Herein, we describe an 11-year-old girl with APL who developed ATRA-induced myositis during induction chemotherapy.

An 11-year-old girl was admitted to our hospital because of fever, fatigue, headache, sore throat, nausea, vomiting, and abdominal and bone pain. Physical examination revealed fever (37.5°C), pallor, wide-spread petechia, dyspnea, tachycardia and paronychia of fifth finger on her right hand. Results of the laboratory investigation were as follows: white blood cell count 22900/μl (on peripheral blood smear: myeloblast 14%, abnormal promyelocytes without Auer rod 46%, myelocyte 16%, metamyelocyte 2%, lymphocytes 20%, monocytes 2%) hemoglobin 9.4 g/dl and platelets 15000/μl, the erythrocyte sedimentation rate 100 mm/h, normal liver and kidney function tests, LDH 490 IU/L (140-300 IU/L), prothrombin time 15.8 sec. (normal: 11-15 sec.), activated partial thromboplastin time 31.3 sec (normal: 25-36 sec), fibrinogen 337 mg/dL (200-400 mg/dL). Bone marrow aspirate displayed a morphologic and cytogenetic diagnosis of APL (FAB M3) in a hypercellular marrow. Cytogenetic studies confirmed the presence of the characteristic 15;17 translocation in 9 of 20 metaphases, and the characteristic fusion of PML and RARA was detected by PCR.

The chemotherapy protocol (APL-93 protocol) that consisted of ATRA (45/mg/m$^2$/d, days 1-28), cytosine arabinoside (200 mg/m$^2$/d, days 1-7), and daunorubicine (60 mg/m$^2$/d, days 1-3) was given. She experienced an episode of neutropenic fever while receiving chemotherapy no coagulopathy was observed. Despite the antibiotic treatment with third-generation cephalosporin, amikacin, vancomycin and clarithromycin, the body temperature did not decrease. No pathogenic organisms were isolated on repeated blood and urine cultures. On day 5, the patient complained of pain in lower extremities. Physical examination revealed tenderness and firmness in the affected muscles and analgesics were given to relieve the pain. On day 11, she complained of severe pain in both arms with similar findings as seen in the lower extremities. Myositis was suspected. Creatine kinase, aldolase and LDH values were 40 U/L (normal=25-192 U/L), 5.30 U/L (normal=2.30-13.50 U/L) and 321 U/L (normal=240-480 U/L), respectively.

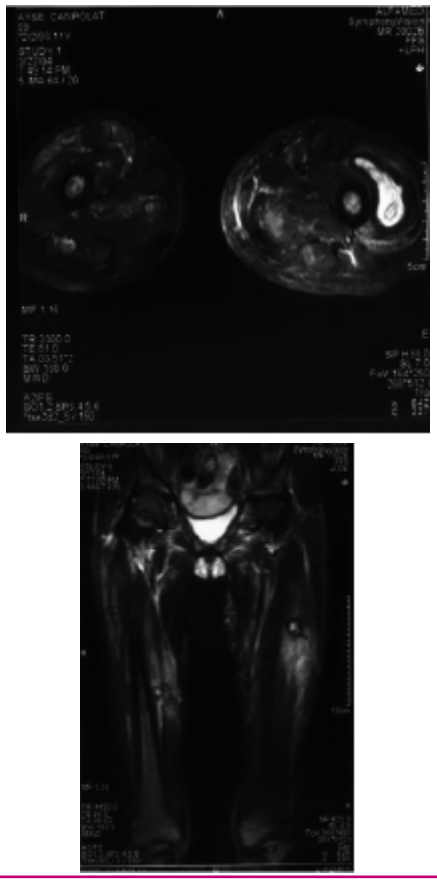

**Figure 1.** Axial (A) and coronal (B) T2-weighted MR images of the thighs show hyperintense hematoma containing low intensity peripheral rim in the left vastus lateralis and multiple areas of increased signal intensity in the anterior and posterior musculature on both thighs consistent with inflammation.

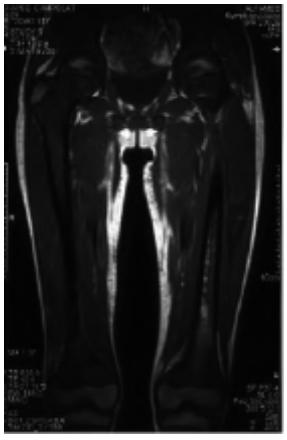

**Figure 2.** A coronal T1 weighted image of the thighs demonstrates diffuse infiltration of marrow in the femoral shafts epiphysis

**Table 1.** Reported cases of ATRA-induced myositis.

| References | Age (years) | Sex | Skin lesions | Fever | Time to ATRA induced myositis (days) | Affected muscles | Bilateral | Creatine kinase values |
|---|---|---|---|---|---|---|---|---|
| 7 | 28 | F | Yes | Yes | 9 | Calf | No | Unknown |
| 7 | 48 | F | Yes | Yes | 17 | Thigh | No | Unknown |
| 8 | 28 | F | No | No | 23 | Calf | Yes | Normal |
| 9 | 39 | M | Yes | Yes | 18 | Thigh-Calf | Yes | Normal |
| 9 | 35 | F | No | Yes | 20 | Calf | Yes | Increased |
| 10 | 33 | M | Yes | Yes | 18 | Unknown | Yes | Increased |
| 11 | 45 | M | No | Yes | 24 | Thigh-Cardiac | Yes | Increased |
| 12 | 27 | M | Yes | Yes | 20 | Calf | Yes | Increased |
| 13 | 6 | F | No | Yes | 10 | Thigh-Deltoid | No | Unknown |
| 14 | 18 | F | No | Yes | Not Avaliable | Thigh | No | Unknown |
| Current Case | 11 | F | No | Yes | 5 | Calf-Arms | Yes | Normal |

Ultrasonography of the affected region demonstrated that there was an echogenic lesion which contains necrotic areas and heterogeneous internal echogenity, located in the muscle just anterior to the femur. The lesion's diameter was approximately 2x2 cm which was located 1.5 cm below the skin surface. Also there was similar lesion at the right forearm.

Magnetic resonance (MR) imaging of the same region showed low signal intensity suggesting the diagnosis of hematoma in the left vastus lateralis, multiple areas of increased signal intensity in the anterior musculature on both thigh due to myositis (Figure 1), and diffuse infiltration of marrow in the femoral shafts (Figure 2).

A working diagnosis of ATRA-induced myositis was made, and intravenous dexamethasone therapy (0.3 mg/kg/d) was started on day 16. ATRA was not discontinued during steroid therapy. On day 17, the patient's fever resolved and in the ensuing days her pain decreased and the muscles felt softer and less tender. On day 19, use of dexamethasone was discontinued. On day 20, she experienced high body temperature (39.7°C) and abdominal pain. Examination showed abdominal tenderness. Therapy with intravenous dexamethasone (0.3 mg/kg/d) was reinstituted on day 21. Once again there was a prompt resolution of pain and fever. On day 25, therapy of dexamethasone was again discontinued. The patient's symptoms did not recur. A bone marrow aspirate obtained on day 28 confirmed a morphologic and cytogenetic remission.

All–trans-retinoic acid is an effective agent to induce remission in patients with a molecular diagnosis of acute promyelocytic leukemia.[15-17] The common adverse effects of ATRA therapy that are headaches, intracranial hypertension, skin reactions, cheilitis, nausea, vomiting, bone pain, nose and ear congestion, tonsillar and servical lymphadenopathy, thrombosis, weight gain, congestive heart failure, pericarditis, hepatic or renal biochemical abnormalities, the retinoic acid syndrome and Sweet's syndrome.[18-20]

Till today to our knowledge, ATRA induced myositis have been reported in nine adult patients, and only two pediatric patients including ours' (Table 1). All reported cases with ATRA-induced myositis involved lower extremities, frequently being bilateral (7/11 patients, including ours).[7-14] Interestingly, myositis in our patient involved bilateral upper and lower extremities. The median time to onset of muscular symptoms from beginning of induction with ATRA was 18 days (9-24 days) in the current literature. However, the symptoms began earlier (on day 5) in our case.

The mechanism of ATRA-induced retinoic acid syndrome and, Sweet's syndrome remains unclear. Several mechanisms that are play a role in the pathogenesis of ATRA-induced myositis including environmental factors and abnormalities in leukocytes, surface integrins and their receptors, and cytokines.[9]

As typically occurs in Sweet's syndrome and ATRA induced myositis, all patients rapidly responded to a short course of corticosteroids and discontinuation of ATRA therapy without recurrence of symptoms.[8-13] The same response was observed in our patient after the institution of dexamethasone treatment even without discontinuation of ATRA. Thus, corticosteroids seem to be the drug of choice in the treatment of ATRA-induced myositis without discontinuation of ATRA.

In conclusion, although ATRA-induced myositis has been an unusual adverse effect of ATRA therapy in APL, it has distinctive clinical features and MR findings that should allow its recognition in order to initiate prompt steroid therapy. If myalgia and fever of unknown origin develop during treatment with ATRA, ATRA-induced myositis should be considered and a diagnostic work-up should be performed.

*Funda Erkasar Citak,[1] Ustun Ezer,[1] Emel Akkaya,[1] Nilgun Ozbulbul,[1] Muhterem Bahce,[2] Ahmet Emin Kurekci[3]*
*[1]Losev-Losante, Ankara Foundation of Children with Leukemia, Hospital For the Children with Leukemia, Ankara, Turkey;*
*[2]Gulhane Military Medical Academy, Department of Genetics, Ankara, Turkey;*
*[3]Gulhane Military Medical Academy, Department of Pediatric Hematology, Ankara, Turkey*

## References

1. 1.Larson RA, Kondo K, Vardiman JW, Butler Ar, Golomb HB, Rowley JD: Evidence for a 15;17 transloction in every patient in acute promyelocytic leukemia. Am J Med 1984;76:827-841
2. De The H, Lavau C, Marchio A, Chomienne C, Degos L, Dejean A. The PML-RAR alpha fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR. Cell 1991;66:675-684
3. Tallman MS, Kwaan HC: Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. Blood 1992; 79:543-553
4. Stone RM, Mayer RJ. The unique aspects of acute promyelocytic leukemia. J Clin Oncol 1990;8:1913-21
5. Mayer RJ, Schiffer CA, Peterson BA, Bumdan DR, Silver RT, Rai KR, Cornwell GG, Ellison RR, Maguire M, Berg DT, Davis RB, Mclntyre OR, Frei E III. Intensive postremission therapy in adults with acute nonlymhocytic leukemia using various dose schedules of ara-C: A progress report from the CALGB. Cancer and leukemia Group B. Semin Oncol 1987;14(Suppl 1):25-31
6. Frankel S, Weiss M, Warrell RP Jr. A "retinoic acid syndrome" in acute promyelocytic leukemia: Reversal by coticosteroids. Blood 1991;78(Suppl):380a
7. Christ E, Linka A, Jacky E, Speich R, Marincek B, Schaffner A. Sweet's syndrome involving the musculoskeletal system during tretment of promyelocytic leukemia with all-trans retinoic acid. Leukemia 1996;10:731-734

8. Martinez-Chamorro C, Martinez E, Gil-Fernandez JJ, Alonso A, Escudero A, Fernandez-Ranada JM. ATRA-induced myositis in induction therapy of acute promyelocytic leukemia. Haematologica 2002;87:ECR08
9. van Der Vliet HJ, Roberson AE, Hogan MC, Morales CE, Crader SC, letendre L, Prutri RK. All trans retinoic induced myositis: a description of two patients. Am J Hematol. 2000;63:94-98
10. Miranda N, Oliveira P, Frade MJ, Melo J, Marques MS, Parreire A. Myositis with tretinoin. Lancet 1994;344:1096
11. Fabbiano F, Magrin S, Cangialosi C, Felice R, Mirto S, Pitrolo F. All-trans retinoic acid induced cardiac and skeletal myositis in induction therapy of acute promyelocytic leukemia. Br J Haematol 2005;129:444-445
12. Chan KH, Yuen SLS, Joshua D. A case of all-trans retinoic acid induced myositis in the treatment of acute promyelocytic leukemia. Clin Lab Haem 2005;27:399-401
13. Melinkeri SR, Gupta RK, Dabadghao S. A swee-like syndrome manifesting as gingival hyperplasia and myositis without cutaneous involvement. Ann Hematol 2002;81:397-398
14. Kannan K, Khan HA, Jain R, Hussein SS, Dennison D. All-trans retinoic acid induced myositis. Br J Haematol 2005;131:560
15. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A, Shepherd L, Willman C, Bloomfield CD, Rowe JM, Wiernik PH. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med. 1997;337:1021-1028
16. Castaigne S, Chomienne C, Daniel MT, Berger R, Fenaux P, Dagos L. All trans retinoic acid as a differentiating therapy for acute promyelocytic leukemias. Clinical results. Blood 1990;76:1704-1709
17. Degos L, Chomienne C, Daniel MT, Berger L, Dombret H, Fenaux P, Castaigne S. Tretment of first relapse in acute promyelocytic leukemia with all trans retinoic acid. Lancet 1990;2:1440-1441
18. Kanamaru BA, Takemoto Y, Tanimato M, Murakami H, Asou N, Kobayashi T, Kuriyama K, Ohmoto E, Sakamaki H, Tsubaki K, Hiraoka A, Yamada O, Oh H, Saito K, Matsuda S, Minato K, Ueda T, Ohno R. All-trans retinoic acid for the tretment of newly diagnosed acute promyelocytic leukemia. Blood 1995;85:1202-1206
19. Warrell RP Jr, de The H, Wang ZY, Degos L. Acute promyelocytic leukemia. N Engl J Med. 1993;329:177-189
20. Tomas JF, Escudero A, Fernandez-Ranada JM. All-trans retinoic acid treatment and Sweet Syndrome. Leukemia 1994;8:1596