

# Retinoic Acid Syndrome: A Case Report and Review

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## Abstract

**Background:** The treatment of acute promyelocytic leukemia with all-trans-retinoic acid (ATRA) sometimes results in a syndrome characterized by fever, respiratory distress, weight gain, pleural or pericardial effusion, and pulmonary infiltrates. We report the major clinical and radiologic features of ATRA syndrome.

**Materials and Methods:** In the past, occasional case reports and literature pertaining to ATRA syndrome. The purpose of our report and the literature review is to heighten physicians' awareness of this syndrome, which often manifests as nonspecific clinical and radiographic findings.

**Results:** The etiopathogenesis of the syndrome remain unclear. The Incidence of the syndrome has varied in reports from 5% to 27% and the mortality from 5%-29%. The time of time onset of ATRAS varies. The reported median time to the occurrence of ATRA syndrome is 7-12 days. Chest radiographs show increased cardiothoracic ratio in 64% of the patients, increased vascular pedicle width in 76%, increased pulmonary blood volume in 82%, ground-glass opacity in 57%, consolidation in 60%, nodules in 60% of the patients. Pleural effusion is noted in 75% of the patients either unilateral or bilateral effusions. Pulmonary hemorrhage is developed in about 20% of the patients during course of ATRAS.

**Conclusions:** Diagnosis of ATRAS manifestations and immediately starting corticosteroids after the diagnosis of ATRAS may be improve the patients' outcome. Because the radiologic features of ATRAS are nonspecific, it would be impossible to differentiate one from the other based solely on these features. . Prompt administration of steroids is critical, not only when the diagnosis is definitively established, but also at the first sign of unexplained dyspnea, fever, weight gain, or pulmonary infiltrates.

**Keywords:** Retinoic acid, Acute promyelocytic leukemia.

## Introduction

Acute promyelocytic leukemia (AML-M3) represents about 5% to 10% of childhood acute myeloid leukemia and is characterized by the clonal expansion of leukemic blasts blocked the promyelocytic stage of myeloid differentiation.<sup>1</sup> Nearly all cases of AML- M3 are characterized by the presence of t(15;17) chromosomal translocation, which involves the fusion of the PML gene on chromosome 15 to the retinoic acid receptor alpha (RARA) on chromosome 17.<sup>2</sup> AML-M3 can be distinguished from other subtypes of AML by virtue of extent of its response and overall outcome as a result of differentiation therapy with all-trans-retinoic acid (ATRA).<sup>3</sup> Many clinical trials convincingly demonstrated the benefits of ATRA in patients with AML-M3.<sup>4</sup> The outcome of AML-M3 has evolved during the last 40 years from one of the most fatal leukemia to one that is highly curable after entrance of ATRA.<sup>5</sup> ATRA, a naturally occurring derivative of vitamin A, exhibits profound anti-proliferative and pro-differentiating

effects on a variety of tumor cells in vivo and in vitro by modulating gene transcription.<sup>6-8</sup> Cellular retinoic acid-binding protein-II (CRABP-II) appears to function as a carrier of bound ATRA from the cytoplasm to the nuclear RARA.<sup>2,7</sup> Retinoic acid receptors (RARs) belong to the steroid/thyroid hormone receptor gene family, which encodes proteins that act as ligand-dependent regulators of gene transcription.<sup>2,7</sup> The PML/RARA chimeric protein has oncogenic properties both in vivo and in vitro.<sup>8,9</sup> Treatment with ATRA induces differentiation of the leukemic blasts and results in hematological remission.<sup>1,10-12</sup> However, although ATRA provides an important benefit to patients with AML-M3, there are significant side effects.<sup>8,13</sup> Retinoic acid syndrome is the most life-threatening complication associated with ATRA.<sup>1,2,5,12,14</sup> We present a case report of retinoic acid syndrome.

## Case Report

A 14-year-old female with a history of 10-15 days pallor, weakness, fever, bone pain, low appetite, and

prolonged vaginal bleeding following menstruation was admitted to Shafa hospital, Ahvaz. The patient was pancytopenic and her coagulation profile was also abnormal. The bone marrow aspiration study was compatible to diagnosis of acute promyelocytic leukemia (AML-M3). The patient initially received supportive care such as blood, platelet, and fresh frozen plasma transfusion. After stabilization, ATRA was started with dose of 45mg/m<sup>2</sup>/day. During the treatment course with ATRA, the patient's complete blood count, coagulation profile, renal function, liver function, and electrolytes were checked daily.

On hospital day 12, the patient developed fever, respiratory distress, hypertension, and tachycardia. Chest radiography revealed bilateral interstitial infiltrations and pleural effusions (figure1). The patient's arterial blood gas analysis showed respiratory acidosis with partial renal compensation. The patient's ATRA was hold and immediately high-dose intravenous dexamethasone (12mg/12hr) was started with suspicion of retinoic acid syndrome. With worsening of the patient's hypoxemia and pulmonary infiltrations, she needed to receive mechanical ventilation support. High blood pressure was treated with diuretics and fluid limitation. On physical examination, the patient had bilateral rales, and intercostal and supracostal retractions. The patient's antibiotic coverage included vancomycin and imipenem. All cultures were negative. Despite the efforts, the patient's condition worsened, and pulmonary hemorrhage, cardiac failure, and hypotension were developed. At this point, vassopressor and cardiac inotropic agents started. Because of cardiac dysfunction and severe pulmonary hemorrhage, the patient died after 24 hours.

## Discussion

Although ATRA is generally well tolerated, some patients develop the retinoic acid syndrome manifested by unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, episodic hypotension, and acute renal failure.<sup>3,11,15,16</sup> This syndrome is the most serious toxicity of ATRA and is often, but not always, associated with development of hyperleukocytosis.<sup>14</sup> It has been suggested that patients with a white blood cell (WBC) count exceeding 5000/ $\mu$ L on day 1, 6000/ $\mu$ L on day 5, 10000/ $\mu$ L on day 10, or 15000/ $\mu$ L on day 15 are at

high risk for development of the syndrome.<sup>5</sup> The diagnosis of retinoic acid syndrome is made on clinical grounds by the presence of at least three of the following signs in the absence of other causes: fever, weight gain, respiratory distress, lung infiltrates, pleural or pericardial effusion, hypotension, and renal failure.<sup>4,5,17-19</sup> There were no pretreatment predictors of the syndrome and there is no uniform agreement on its optimal treatment in randomized clinical trials that have evaluated therapy.<sup>3,4,12,20</sup> Based on anecdotal evidences when the diagnosis of retinoic acid syndrome is made, corticosteroids (prednisolone or dexamethasone) are given immediately, and administration of ATRA is discontinued.<sup>2-5,11,12,14</sup> Neither the pathogenesis nor the optimal way to prevent or treat the syndrome has been determined.<sup>4,7,18,21</sup> In newly diagnosed AML-M3 patients treated with ATRA, the incidence of retinoic acid syndrome varies from 5% to 27% based on recent studies. Also, the onset time onset of retinoic acid syndrome varies.<sup>12</sup> The reported median time to the occurrence of retinoic acid syndrome is 7-12 days after ATRA therapy.<sup>14</sup> This syndrome is usually, but not necessarily, associated with hyperleukocytosis and a rapid rise in the leukocyte count.<sup>4</sup> Retinoic acid syndrome is associated with a high mortality ranged from 5% to 29%.<sup>2</sup> However, the mortality rate of patients with the syndrome likely reflects the time of recognition and institution of corticosteroids (prednisolone or dexamethasone).<sup>12,14,22</sup>

Clinically, the symptom complex most closely resembles the capillary leak syndrome associated with the administration of various cytokines, particularly interleukins (IL).<sup>2,5,12</sup> The proposed mechanisms could involve changes in the cytokine secretion and adhesive qualities of acute promyelocytic cells (APL) cells during ATRA-induced differentiation.<sup>2,16,18</sup> Drug-induced release of vasoactive cytokines (IL-1 $\beta$ , IL-6, IL-8, and the tumor necrosis factor) from differentiating leukemic cells would explain certain manifestations such as fever, generalized weight gain, and episodic hypotension.<sup>11,18</sup> Organ infiltration by AML-M3 cells found in postmortem studies of the retinoic acid syndrome suggests that drug-induced maturation of previously undifferentiated leukemic cells, although still dysfunctional, could impair certain functions of mature neutrophils, including their migratory capabilities.<sup>15,18,20</sup> Migration of these cells into

tissues, such as the lung and kidney, could explain the clinically observed respiratory distress and occasional renal impairment.<sup>5,18</sup> Finally, leukocyte adherence to capillary endothelial cells and to the extracellular matrix is mediated by integrins (leukocyte adhesion receptors). Genes encoding integrins were recently found to be up-regulated by retinoic acid.<sup>2,5,7,12,18</sup> Conceivably, ATRA increases integrin expression on the leukemic cell surface; this would enhance the cell's adherence to capillary endothelium and would promote focal endothelial leakage.<sup>2,5,7,12,18</sup> Methylprednisolone rapidly inhibits AML-M3 cell aggregation in a dose-dependent manner, consistent with its prompt clinical effectiveness *in vivo*.<sup>5,7</sup> Radiologic features may also be explained by the proposed hypothesis for ATRA syndrome pathophysiology.<sup>18</sup> Most of the patients with retinoic acid syndrome show cardiomegaly, widening of the vascular pedicle width, increased pulmonary blood volume, ground-glass opacity, and pleural or pericardial effusion.<sup>18</sup> Patients with microgranular variant promyelocytic leukemia appear to be protected from the syndrome, but the

reason(s) is not clear.<sup>5</sup> Based on recent reports, the initial WBC count as well as the rate of rise is not statistically correlated with the development of the syndrome.<sup>6</sup> Usual dose of ATRA in patients with AML-M3 is 45mg/m<sup>2</sup>/day.<sup>1</sup> Strategies to prevent the syndrome with administration of a lower dose of ATRA (25mg/m<sup>2</sup>/day) resulted in a similar cure rate and toxicity profile, including a similar incidence of retinoic acid syndrome as the standard dose.<sup>5,14,21</sup> Several observations suggest that ATRA need not necessarily be discontinued if the retinoic acid syndrome develops and corticosteroids instituted at the earliest sign or symptom. However, the success of the approach may depend on the severity of the syndrome and the rapidity of steroids administration.<sup>19</sup> Prophylactic corticosteroids could not be recommended for routine use currently.

Frankel et al first described this syndrome in nine (25%) of 35 patients who were newly diagnosed with APL and treated with ATRA.<sup>14</sup> Retinoic acid syndrome developed in patients at an average of 7 days (range, 1-22 days) after the start of ATRA.<sup>5,14,18</sup> The major clinical manifestations of ATRA syndrome

**Figure 1.** Chest radiograph of the patient on day 12 shows bilateral pleural effusion.



included respiratory distress (80%), fever(37%), and generalized edema(47%).<sup>1,14,15,17,18</sup> Leukocytosis is found in 46% of the patients.<sup>5</sup> All patients show chest radiographic abnormalities when clinical symptoms develop.<sup>18</sup> Chest radiographs show increased cardiothoracic ratio in 64% of the patients, increased vascular pedicle width in 76%, increased pulmonary blood volume in 82%, ground-glass opacity in 57%, consolidation in 60%, and nodules in 60% of the patients.<sup>18</sup> Pleural effusion is noted in 75% of the patients either unilaterally or bilaterally.<sup>18</sup> Pulmonary hemorrhage is developed in about 20% of the patients during the course of retinoic acid syndrome.<sup>18,5</sup> When pulmonary hemorrhage occurs, diffusely bilateral and poorly defined nodules, ground-glass opacity, and consolidation develop on chest radiography.<sup>16-18</sup>

In one study on 44 patients with APL who developed the retinoic acid syndrome, a median time of 11 days after start of ATRA (range, 2-47 days) was reported and the maximum WBC count ranged from 6800/ $\mu$ L to 72000/ $\mu$ L (median: 31000/ $\mu$ L). Mechanical ventilation is required in about 26% of patients with this syndrome.<sup>3-5,18</sup> Among 167 patients with newly diagnosed AML-M3 treated with ATRA alone for induction, retinoic acid syndrome developed in 26%.<sup>12,17</sup> The symptoms generally begin within the first thirty days of ATRA therapy, the median time to onset is 7 days.<sup>2</sup> An overall incidence of 15% was reported by the European APL group, with a mortality rate of 8% of patients with the syndrome. No difference in the incidence of the syndrome was observed among patients treated with concurrent versus sequential ATRA and chemotherapy.<sup>12</sup> Definite outcome of retinoic acid syndrome and efficacy of treatment with corticosteroids are not obvious but early diagnosis of the syndrome manifestations and immediate treatment with corticosteroids after the diagnosis of retinoic acid syndrome may improve the outcome.<sup>1-4,11,12,14,16</sup> Prednisolone is the treatment of choice in retinoic acid syndrome (20-40mg/kg, divided doses).<sup>2,3,5</sup> After treatment, the radiologic features and clinical symptoms gradually improve in 67% of the patients but 23% of the patients fall into acute respiratory distress.<sup>18</sup> All patients who had retinoic acid syndrome with acute respiratory distress died despite intensive care on a ventilator.<sup>5</sup> All patients with AML-M3 who developed the syndrome and pulmonary

hemorrhage during ATRA treatment died.<sup>18</sup>

## Conclusion

Early recognition of retinoic acid syndrome is important because early intervention with high doses of corticosteroid appear to abort the progression of this syndrome.<sup>3,4,5,7,18</sup> Although the imaging features are not characteristic, in combination with the clinical history, they may aid in early recognition of the retinoic acid syndrome and thus to its prompt resolution.<sup>18</sup> In a patient with AML-M3 receiving ATRA therapy, this syndrome should be considered when chest radiographs show cardiomegaly, vascular distention, ground-glass opacity, and pleural or pericardial effusion in the presence of a clinical history including respiratory distress, unexplained fever, hypotension, and generalized edema.<sup>5,12,18</sup> If moderate or severe retinoic acid syndrome develops, it is prudent to discontinue ATRA.<sup>12</sup> When the syndrome resolves, ATRA can safely be restarted in most patients; however, close observation is warranted.<sup>5,8,13</sup>

## References

1. Todd R. Golub, Robert J. Arceci. Acute Myelogenous Leukemia. Principles and Practice of Pediatric Oncology 2005; 20: 591-644. 1
2. Tara L. Lin and William Matsui. Differentiation Therapy in AML. Contemporary Hematology 2007; 14: 293-312.
3. Tallman MS, Anderson JW, Schiffer CA, et al: All-trans retinoic acid in acute promyelocytic leukemia. New Engl J Med 1997;337:1021-1028.
4. 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.
5. Martin S. Tallman et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. Blood 2000; 95: 90-95.
6. Cox N, O'Brien HA. Sweet's syndrome associated with Trans-retinoic acid treatment in acute promyelocytic leukaemia. Clin Exp Derm 1994;19:51-52.
7. Blomhoff A, Green MH, Green JB. Vitamin A metabolism: new perspective on absorption, transport, and storage. Physiol Rev 1991; 71: 951-990.
8. Kelaidi C, Chevret S, De Botton S, et al.

Improved outcome of acute promyelocytic leukemia with high WBC counts over the last 15 years: the European APL Group experience. *J Clin Oncol* 2009; 27: 2668-2672.

9. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. *Blood* 2009; 114: 5126-5137.

10. Elliott S, Talyor K, White S, et al. Proof of differentiative mode of action of all-trans retinoic acid in acute promyelocytic leukemia using X-linked clonal analysis. *Blood* 1992;79:1916-9.

11. Avvisati G, Lo Coco F, Diverio D, et al. AIDA (all-trans retinoic acid and idarubicin) in newly diagnosed acute promyelocytic leukemia: A Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. *Blood* 1996;88:1390-1398.

12. DeBotton S, Dombert 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. *Blood* 1998;92:2712.

13. Frankfurt O, Tallman MS. Strategies for treatment of acute promyelocytic leukemia. *J Natl Canc Newt* 2006; 4: 37-45.

14. Frankel SR, Eardley A, Lauwers G, et al. The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992;117:292.

15. Chomienne C, Ballerini P, Balitrand N, et al. All-trans retinoic acid in acute promyelocytic leukemia. II. In vitro studies:structure-function relationship. *Blood* 1990;76:1710-7.

16. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all-trans retinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999;94:1192-1200.

17. Kanamaru A, Takemoto Y, Tanimoto M, et al: All-trans retinoic acid for the treatment of newly diagnosed acute promyelocytic leukemia. *Blood* 1995;85:1202-1206.

18. Jung, JI, Choi JE, Hahn ST, Min CK. Radiologic Features of all-trans-retinoic acid syndrome. *AJR* 2002;178:475.

19. Nicolls M, Terada L, Tuder R, Prindiville S, Schwarz M. Diffuse Alveolar Hemorrhage with underlying capillaritis in the Retinoic Acid Syndrome. *Am J Respir Crit Care Med* 1998;158:1302-1305.

20. Yokukara M, Hatake K, Komatsu N, et al. Toxicity of tretinoin in acute promyelocytic

leukemia. *Lancet* 1994;343:361.

21. Christopher S.King, John Sherner.Retinoic Acid Syndrome:A case Report and Review.*J Oncolog.*2005.vol 2 Number 2.

22. Vahdat L, Maslak P, Miller WH Jr, et al Early mortality and the retinoic acid syndrome in acute promyelocytic leukemia: impact of leukocytosis, low-dose chemotherapy, PML-RAR? isoform, and CD13 expression in patients with all-trans retinoic acid. *Blood* 1994;84:3843-3849.