

# Retinoic Acid Syndrome: A Case Report and Review

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## Citation

C King, J Shermer. *Retinoic Acid Syndrome: A Case Report and Review*. The Internet Journal of Oncology. 2004 Volume 2 Number 2.

## Abstract

A 34-year-old white male with AML-M3 undergoing all-trans retinoic acid (ATRA) therapy was admitted to the hospital for suspected thrombophlebitis. The patient developed septic physiology with a temperature of 105 degrees Fahrenheit, tachycardia to 130's, and hypotension. An incision and drainage of a right upper extremity abscess was performed. Despite broad-spectrum antibiotic therapy and removal of the suspected source of infection, the patient's clinical status worsened and the patient suffered a cardiac arrest. The patient survived his cardiac arrest, but remained vasopressor and ventilator dependent. All cultures were negative. At this point, a diagnosis of retinoic acid syndrome was entertained. The patient's ATRA was discontinued and the patient was started on high-dose dexamethasone. After corticosteroid therapy and discontinuation of ATRA, the patient was rapidly weaned off his ventilator and vasopressors. Retinoic acid syndrome is reported to occur in up to 25% of patients treated with ATRA. The syndrome is characterized by development of fever, pulmonary infiltrates and effusions, pericardial effusions, hypotension, dyspnea, and renal dysfunction. The morbidity and mortality of retinoic acid syndrome is significant, with mortality rates as high as 9% reported; however, the majority of patients will make a rapid recovery if the syndrome is recognized early and ATRA therapy is discontinued.

## CASE REPORT

A 34-year-old white male with acute promyelocytic leukemia (AML-M3) was admitted to our hospital for presumed septic thrombophlebitis. The patient was an active duty soldier who was discovered to have pancytopenia on a routine physical. A bone marrow biopsy was done which confirmed the diagnosis of AML-M3. The patient was initially treated with idarubicin and all-trans retinoic acid (ATRA). His first cycle of chemotherapy was tolerated without incident, and the patient was discharged to home. While at home the patient started his second cycle of therapy with ATRA. On the day of admission, the patient noted subjective chills and reported to the hospital. He was noted to have fever of 101.7 degrees Fahrenheit. Erythema and edema were noted surrounding a peripherally inserted central catheter (PICC). This line was removed, and the patient was started on vancomycin and meropenem for presumed septic thrombophlebitis. The patient had overall improvement on IV antibiotics, but after seven days of therapy continued to have intermittent fevers. On hospital day 8, the patient developed tachycardia and hypotension. He was taken to the operating room and an incision and drainage of a small abscess at the site of the thrombophlebitis was performed. The patient's tachycardia and hypotension improved over the next 24 hours.

On hospital day 9, the patient again developed hypotension, tachycardia, and respiratory distress. Chest radiography revealed worsening bilateral interstitial infiltrates and pleural effusions. The patient suffered a pulseless-electrical activity (PEA) cardiac arrest. The patient was intubated and given epinephrine and atropine, with resultant return of circulation after approximately 3 minutes. The patient remained vasopressor dependent and intubated with increasing ventilator requirements. In addition, the patient developed acute renal failure requiring hemodialysis. A transthoracic echocardiogram revealed no pericardial effusion but did show a depressed left ventricular ejection fraction. The patient's antibiotic coverage was broadened to include ciprofloxacin and voriconazole in addition to the vancomycin and meropenem. Despite the broadened coverage and removal of the suspected nidus of infection, the patient continued to deteriorate clinically. Cultures of blood, urine, and sputum remained negative. At this point, a diagnosis of retinoic acid syndrome was entertained. ATRA therapy was discontinued and dexamethasone 10 mg every twelve hours was started. After these therapies were initiated the patient showed rapid clinical improvement. He was weaned off vasopressors and extubated three days after discontinuation of ATRA therapy. This patient developed features that were typical of retinoic acid syndrome to

include acute renal failure, pleural effusions, fever, cardiac failure, and respiratory distress, which developed after his infection had been appropriately treated. The patient recovered fully from this episode. He was re-challenged with ATRA without adverse effects.

### DISCUSSION

Acute promyelocytic leukemia (AML-M3) is a subtype of acute myeloid leukemia characterized by a balanced reciprocal translocation between chromosomes 15 and 17. The translocation results in a fusion of portions of the promyelocytic leukemia gene with the gene for retinoic acid receptor alpha. <sup>(1)</sup> All-trans-retinoic acid binds retinoic acid receptor alpha resulting in differentiation of leukemic promyelocytes into mature cells. <sup>(2,3)</sup> Through this mechanism, ATRA can produce complete remission in a large proportion of treated patients. The addition of ATRA to standard chemotherapeutic regimens has resulted in dramatic improvement in survival compared to conventional chemotherapy alone. <sup>(4,5,6,7)</sup> Given the demonstration in randomized clinical trials of improved survival in AML-M3 patients when treated with ATRA, this therapy has become the standard of care.

The retinoic acid syndrome is a constellation of signs and symptoms that has been reported in patients receiving ATRA therapy. Estimates of the frequency of the retinoic acid syndrome range from 6 to 26%. <sup>(8,9,10)</sup> No pretreatment variable predictive of the syndrome has been found except presence of the microgranular variant of acute promyelocytic leukemia, AML-M3v. <sup>(13)</sup> The form constitutes approximately 15-20% of acute promyelocytic leukemia cases and appears to be protective against development of the retinoic acid syndrome for unclear reasons. The syndrome consists of respiratory distress, fever, pulmonary infiltrates, weight gain, pleural effusion, renal failure, pericardial effusion, cardiac failure, and hypotension. There are also reports of pulmonary hemorrhage and Sweet's syndrome (acute febrile neutrophilic dermatosis) related to the syndrome. <sup>(11,12)</sup> The symptoms generally begin within the first thirty days of ATRA therapy. The largest series of patients described found that the median time to onset was 7 days. <sup>(8)</sup> In this same series of 64 patients, 13 (20%) required mechanical ventilation and 2 (3%) required hemodialysis. Mortality rates reported range from 5 to 29%. In more recent reports mortality is on the lower end of this spectrum, likely reflecting increased recognition of the syndrome and earlier institution of therapy. <sup>(13)</sup>

### ETIOLOGY

The etiology of the retinoic acid syndrome is poorly understood; however, there are several proposed mechanisms. One theory is that ATRA results in increased levels of cytokines, which can cause a capillary leak syndrome. The fever, weight gain, and episodic hypotension that are seen in the retinoic acid syndrome are also seen with the administration of certain cytokines. <sup>(9)</sup> Another theory is that ATRA leads to increased migration of leukemic cells due to maturation resulting in extensive organ infiltration. This has been documented in post-mortem studies of patients who died from complications of the retinoic acid syndrome. <sup>(9)</sup> It has also been proposed that ATRA increases the production of various adherence ligands on the surface of leukemic myeloid cells resulting in increased attachment of leukemic cells to endothelial cells. This leads to upregulation of production of intercellular adhesion molecule-1, which in turn facilitates neutrophil attachment and activation. <sup>(11)</sup>

### TREATMENT

There is not uniform agreement on the optimal treatment of retinoic acid syndrome as there are no randomized clinical trials that have evaluated therapy. Anecdotal evidence suggests that high dose corticosteroid treatment (dexamethasone 10 mg every 12 hours) may be effective. In a report of 44 patients with retinoic acid syndrome, all were treated with high dose dexamethasone as soon as the syndrome was recognized. Only two of the 44 patients died as a complication of the retinoic acid syndrome, compared to 29% in an earlier cohort study. The authors of the trial attributed the decrease in mortality to the heightened awareness of the syndrome and the early institution of corticosteroid therapy. <sup>(13,14)</sup> It is unclear whether discontinuation of ATRA confers any benefit when patients develop retinoic acid syndrome. In the above-mentioned cohort of 44 patients, 8 patients were continued on ATRA despite development of retinoic acid syndrome. Of these seven went on to achieve complete remission, while the other died from intracranial hemorrhage due to his underlying disease. This led the authors to conclude that "ATRA need not be discontinued if retinoic acid syndrome develops, provided that dexamethasone is instituted at the earliest sign or symptom." <sup>(13)</sup> The authors do caution that the success of this approach may depend on the severity of the retinoic acid syndrome and the rapidity of institution of corticosteroid therapy. Therapy with leukopheresis and low dose chemotherapy has also been attempted although the benefit is unclear. <sup>(8, 14)</sup> Diuresis has also been effective

anecdotally, with patients reportedly recovering from retinoic acid syndrome without use of corticosteroids. (15) It seems that it is safe to re-challenge patients with ATRA after retinoic acid syndrome. In a study of 64 patients with retinoic acid syndrome, 17 were re-challenged with ATRA. None of these patients developed recurrence of the syndrome. (8)

### CONCLUSION

Our patient presented with symptoms consistent with the retinoic acid syndrome to include fever, pulmonary infiltrates, pleural effusions, renal failure, and cardiac dysfunction. While he had a clear source of infection, he worsened despite appropriate antibiotic therapy and source control. In addition the patient responded to therapy for the retinoic acid syndrome. While one cannot say definitely that his decompensation was not a delayed inflammatory response to infection, we feel this case is illustrative of the difficulty in making the diagnosis of retinoic acid syndrome. Patients are often critically ill with multiple confounding factors, including infectious issues and other drug toxicities.

The diagnosis of retinoic acid syndrome is difficult to make. It requires a high clinical suspicion in a patient developing the symptoms mentioned above. As illustrated in the case, a thorough evaluation for infection should be undertaken prior to arrival at this diagnosis. We felt that this case was relevant as the retinoic acid syndrome is not widely recognized in the general medical literature. Retinoic acid syndrome occurs frequently in patients receiving ATRA therapy and is associated with a high morbidity and mortality that can be significantly reduced by prompt recognition of the syndrome and institution of appropriate therapy.

### ACKNOWLEDGEMENTS

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