Case Report

Successful Treatment of Retinoic Acid Syndrome with Dexamethasone: A Case Report

Apichai Leelasiri MD*,
Tontanai Numbenjapol MD*, Wichai Prayoonwiwat MD*,
Wichean Mongkolsritrakul MD*, Chantrapa Srisawat MD*

** Hematology Division, Department of Medicine, Phramongkutklao Hospital*

Retinoic acid syndrome (RAS) is the clinical syndrome that occurs after treatment of acute promyelocytic leukemia with all-trans-retinoic acid (ATRA). The patients experience fever, dyspnea, hypotension, respiratory distress, edema and weight gain. Chest x-ray will show pulmonary infiltrates and pleuropericardial effusion. The onset of this syndrome is usually 5-21 days after ATRA treatment when white blood cell counts are rising more than 10,000/cu.mm. The authors have reported a case of RAS. The patient was a 29-year-old man who had been working in a battery manufacturing factory for 7 years. He presented with easily bruising for one month. The initial blood test showed hematocrit of 36.2%, white blood cells count of 3,200/cu.mm with 28% neutrophils, 20% lymphocytes, 2% eosinophils and 50% promyelocytes and platelet of 20,000/cu.mm. Peripheral blood smear revealed numerous fragmented red blood cells. Bone marrow examination showed hypercellularity with abnormal promyelocytes of 95% and bone marrow cytogenetics was translocation of chromosome 15 and 17 [t (15;17)(q22;q12)]. The diagnosis was acute promyelocytic leukemia and the patient was treated with ATRA 45 mg/m^2/day per oral starting on day 1 and intravenous idarubicin 10 mg/m^2 on day 4, 5 and 6. On day 13, he had a body temperature of 39 ˚C and a dry cough. The white blood cells were rising to 7,400/cu.mm with 16% neutrophils. On day 18, he had oliguria, high grade fever, hypotension, cough with chest pain and white blood cells rose to 21,300/cu.mm with 65% neutrophils and rising of blood urea nitrogen and creatinine. Chest x-ray showed enlarged cardiac shadow with pleural effusion. Echocardiogram revealed moderate amount of pericardial effusion. The diagnosis of RAS was made and ATRA was withdrawn. Intravenous dexamethasone 4 mg every 6 hours and hemodialysis was started. The patient's symptoms improved dramatically and bone marrow examination was in complete remission. He was subsequently given cytarabine and idarubicin as consolidation. This patient had clinical manifestation consistent with RAS, which improved after prompt treatment.

Keywords: *Acute promyelocytic leukemia, All-trans-retinoic acid, Retinoic acid syndrome*

J Med Assoc Thai 2005; 88(Suppl 3): S302-10
Full text. e-Journal: *http://www.medassocthai.org/journal*

Correspondence to: Leelasiri A, Division of Hematology, Department of Medicine, Phramongkutklao Hospital, 315 Rajavithee Rd, Bangkok 10400, Thailand. Phone: 0-2354-7711 ext 93305, 93306, Fax: 0-2644-4408, E-mail address: leelasiri@thaimail.com

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) having specific characteristics and evolution of treatment. APL has been characterized by

life-threatening coagulopathy[1] since 1957 and is highly sensitive to anthracyclines compared with other subtypes of AML reported since 1973. The specific cytogenetics[2] in APL is reciprocal translocation of chromosome 15 and 17 [t (15;17)] which was discovered in 1976. In 1987 APL was shown to be sensitive to all-trans-retinoic acid (ATRA)[3] and since 1991 it has been known that t (15;17) causes chimeric PML-RARα fusion gene[4]. In 1988, APL was also discovered to show sensitivity to arsenic trioxide.

At present APL can be cured in more than 70% of patients. High sensitivity of APL to anthracyclines is the result of leukemic cells having lower P-glycoprotein, lung resistance-related protein (LRP) and multidrug resistance-associated protein (MRP). The mechanism of ATRA-induced remission is caused by the differentiation of leukemic cells. ATRA can also downregulate tissue factor causing decreased thrombin generation, disseminated intravascular coagulation (DIC) and fibrinolysis. The combination of ATRA and chemotherapy in remission induction can cause rapid resolution of life-threatening coagulopathy, decreased relapse rate compared with chemotherapy alone and prolonged disease free survival and overall survival[5].

The standard treatment of APL consists of ATRA 45 mg/m^2/day per oral for 45-90 days combined with anthracyclines such as idarubicin. After complete remission is achieved, anthracycline-based chemotherapy for 2-3 cycles is used as consolidation. Subsequently, ATRA, along with low dose methotrexate and 6-mercaptopurine (6-MP) is administered as maintenance treatment[6].

Retinoic acid syndrome (RAS)[7] is the clinical syndrome developing after ATRA administration in APL patients. The incidence of RAS is 25% in the patients receiving ATRA as the sole agent in the induction period and the onset is usually 5-21 days after treatment. The syndrome consists of respiratory distress, pulmonary infiltrates and acute renal failure. Hypotension, pleuropericardial effusion and cardiovascular collapse are also the associated clinical findings. The differential diagnosis of RAS is septicemia which is treated differently. The clue for the diagnosis of RAS is leukocytosis more than 10,000/cu.mm. The treatment of RAS is discontinuation of ATRA and administration of high doses of corticosteroids. Hydroxyurea or cytosine arabinoside along with anthracycline can also be used. It is shown that the incidence of RAS is decreased if both ATRA and chemotherapy are given concomitantly in remission induction as shown in Table 1.

Case Report

A 29-year-old man, a worker in a battery manufacturing factory for 6 years, presented with spontaneous and bruising with epistaxis for 1 month. He denied any previous medical problem and never

Table 1. The incidence and outcome of RAS[5]

Study	N	Induction	Incidence	Mortality	
				Pts with RAS	All pts
MSKCC	78	ATRA	27%	29%	8%
NAI	167	ATRA	26%	5%	1%
APL	413	ATRA ± chemo	15%	8%	1%
JALSG	196	ATRA ± chemo	6%	9%	0.5%
GIMEMA	480	ATRA ± chemo	9%	4%	0.4%
PETHEMA	123	ATRA ± chemo	6%	17%	0.8%
ALSG	87	ATRA ± steroids	16%	21%	3%

MSKCC = Memorial Sloan-Kettering Cancer Center, NAI = North American Intergroup, APL = Acute promyelocytic leukemia study group, JALSG = Japan acute leukemia study group, GIMEMA = Gruppo Italina Malattie Ematologiche dell' Adulto, PETHEMA = Programma para el Estudio de la Terapeutica en Hemopatia Maligna, ALSG = Acute leukemia study group

used any medication. He did not drink or smoke. Physical examination revealed a body temperature of 37°C, pulse rate 80/minute, respiration 18/minute and blood pressure 120/80 mmHg. He was acutely ill, mildly pale and without jaundice. There were multiple hemorrhagic spots sized 0.5 cm. in the buccal mucosa. Liver, spleen and lymph nodes were impalpable. Numerous petechaie and ecchymoses were found along both forearms and legs.

The initial investigation revealed a hematocrit of 36.2%, hemoglobin 13 gm/dl, white blood cell count 3,200/cu.mm. with PMN 28%, lymphocytes 20%, eosinophils 2%, promyelocytes 50%, platelet count 20,000/cu.mm. MCV 83 fl, MCH 29.8 pg, MCHC 35.8 gm/dl, RDW 13.5%, MPV 6.8 fl, activated partial thromboplastin time 38.1 second (control 33.2), prothrombin time 18 second (control 12.6), INR 1.5 and thrombin time 6.4 second (control 5.7). Blood chemistries showed fasting plasma glucose of 91.8 mg/dl, blood urea nitrogen (BUN) 11.2 mg/dl, creatinine 0.97 mg/dl, uric acid 3.7 mg/dl, calcium 9.3 mg/dl, phosphorus 3.3 mg/dl, lactate dehydrogenase 247 U/L (135-225), albumin 45 gm/L, globulin 27 gm/L, AST 40 U/L (0-37), ALT 79 U/L (0-40), total bilirubin 1.1 mg/dl, direct bilirubin 0.2 mg/dl, alkaline phosphatase 59 U/L (39-117). Peripheral blood smear revealed numerous schistocytes as shown in Fig. 1.

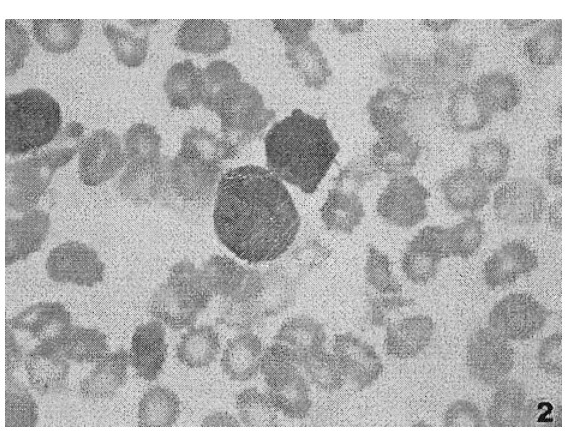


Fig. 1 Peripheral blood smear

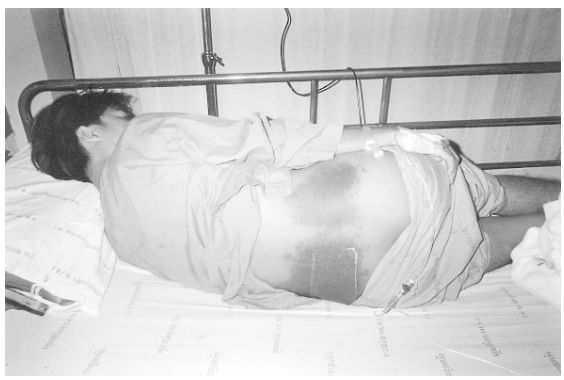
Special tests were D-dimer 2 μg/ml (< 0.5), fibrinogen 250 mg/dl (200-400), euglobulin clot lysis time-not lysed after 3 hours. Bone marrow smear revealed hypercellularity with 95% promyelocytes and cytogenetics by Q banding showed 46, XY with translocation of chromosome 15 and 17 [t (15;17)(q22;q12)].

The diagnosis of acute promyelocytic leukemia with DIC was made and the patient was given ATRA (Vesanoid®) 45 mg/m^2/day per oral on day 1 (7/2/03) along with idarubicin 10 mg/m^2/day intravenous for 3 days starting day 4 to day 6. He also received platelet transfusion for thrombocytopenic bleeding.

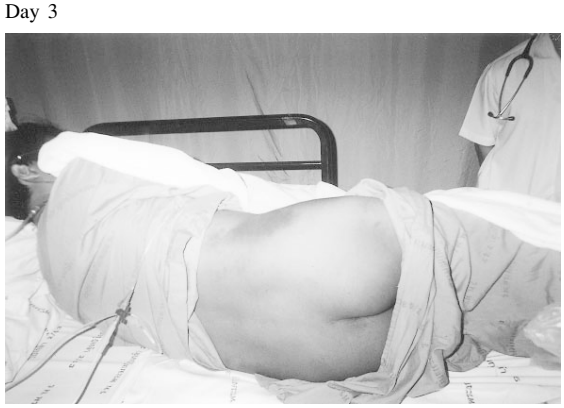
Clinical course

On day 2, the patient developed large ecchymoses at bone marrow aspiration sites. He also had nausea, vomiting and bloody expectoration. His hematocrit decreased from 32% to 22%. He received 2 units of packed red cells. On day 4, he received idarubicin 10 mg/m^2 intravenously for 3 days. He developed subconjunctival hemorrhage on day 7, but subsequently improved on day 10, and ecchymoses at bone marrow aspiration sites as shown in Fig. 2.

The patient experienced a non productive cough, and was afebrile without chest pain. Physical examination revealed no lung crepitation. On day 13, he developed a fever of 38°C and productive sputum. He still had a fever of 38.3°C and gross hematuria on day 14 when ceftazidime and amikacin were started as empirical antibiotics. He also received one unit of single donor platelet. On day 18, the patient developed oliguria with urine output of 70 ml/day, hypotension, tachycardia with heart rate 100-110/min, increased coughing and mid sternal chest pain, mild jaundice, pallor, hepatomegaly (liver span 15 cm.) and increased BUN and creatinine. His white blood cells rose to 21,300/cu.mm with 65% of polymorphonuclear

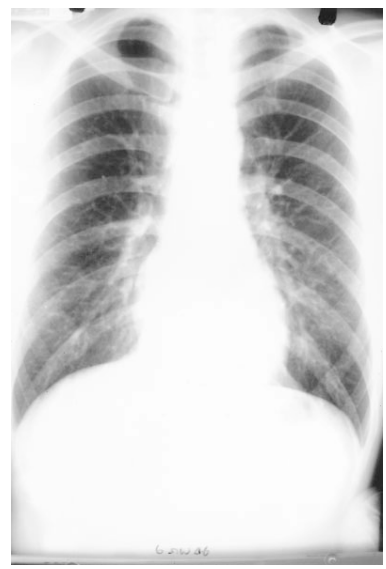


Day 3

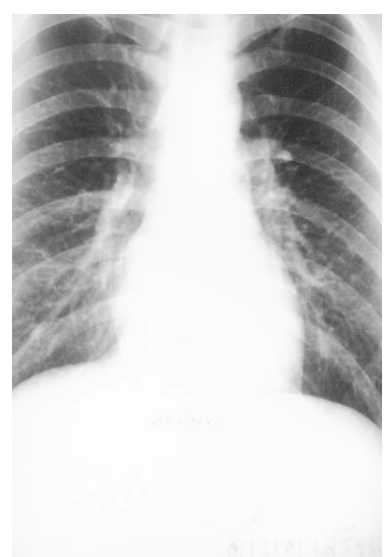


Day 10

Fig. 2 Ecchymoses at bone marrow aspiration sites



On admission



Day 14

Fig. 3 Serial chest x-ray

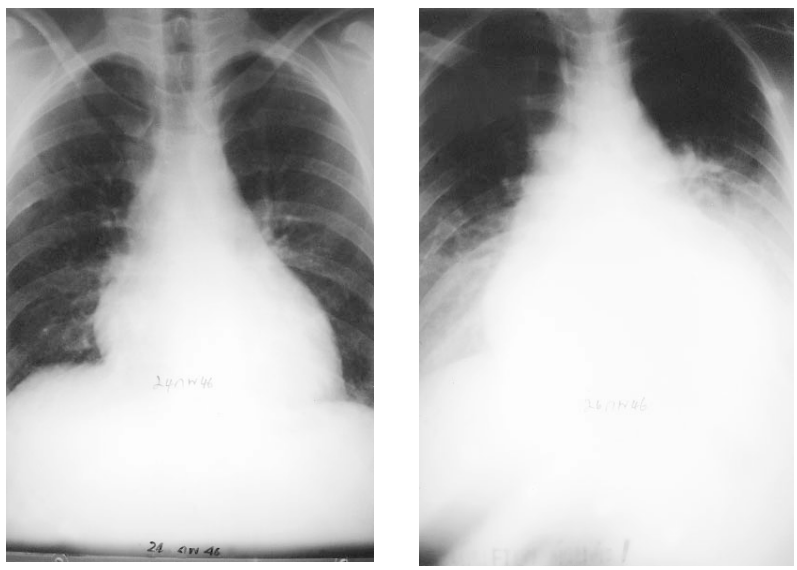
neutrophils and chest x-ray revealed enlarged cardiac shadow with pleural effusion as shown in Fig. 3.

The patient underwent hemodialysis on day 19 when chest examination revealed fine crepitation over both lungs and echocardiogram showed pericardial effusion as shown in Fig. 4. ATRA was discontinued and dexamethasone, 4 mg intravenously every 6 hours, was started.

Bone marrow examination was done on day 20 and revealed promyelocytes only 10-15% (partial remission). On day 21, the patient's condition improved. Physical examination revealed pericardial friction rub and blood chemistries showed increased BUN and creatinine. The serial white blood cells during are shown in Fig. 5 and BUN/creatinine in Fig. 6. On day 26, he felt more comfortable and dexamethasone was tapered and discontinued 4 days later. Bone marrow examination was repeated on day 49 and showed complete remission. He subsequently received consolidation with cytarabine and idarubicin.

Discussion

This is a young patient diagnosed as APL with DIC. He developed RAS after receiving induction treatment with ATRA and idarubicin. The clinical manifestation was typical of RAS. He experienced dyspnea, fever, cough and chest pain



Day 18 Day 20

Fig. 3 Serial chest x-ray

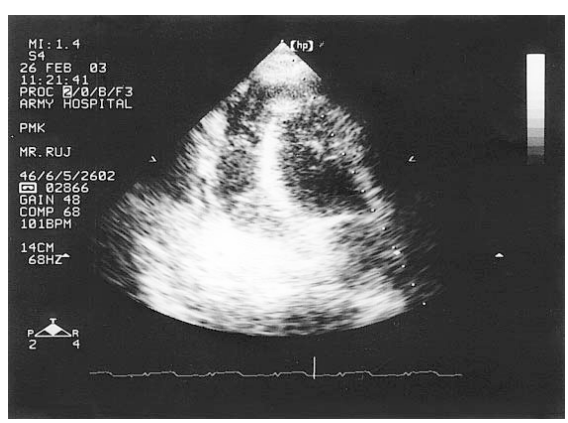


Fig. 4 Echocardiogram

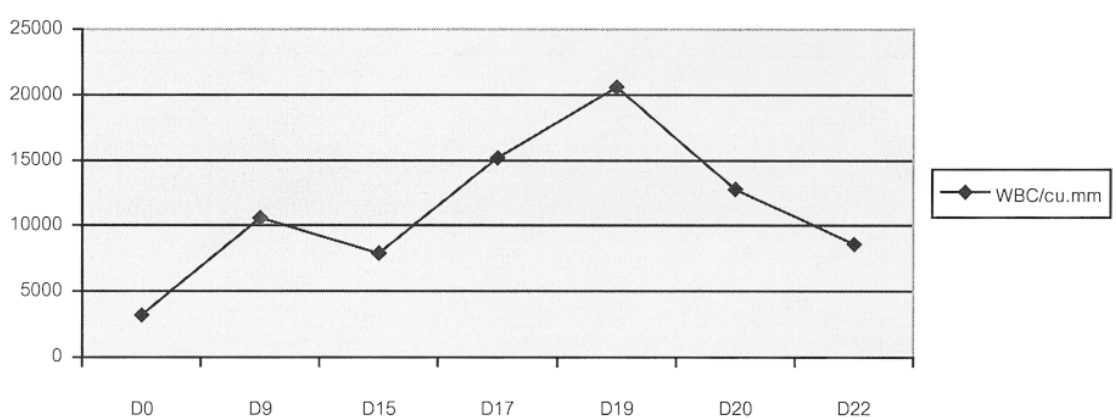


Fig. 5 Serial white blood cells during treatment (D0 = day of admission)

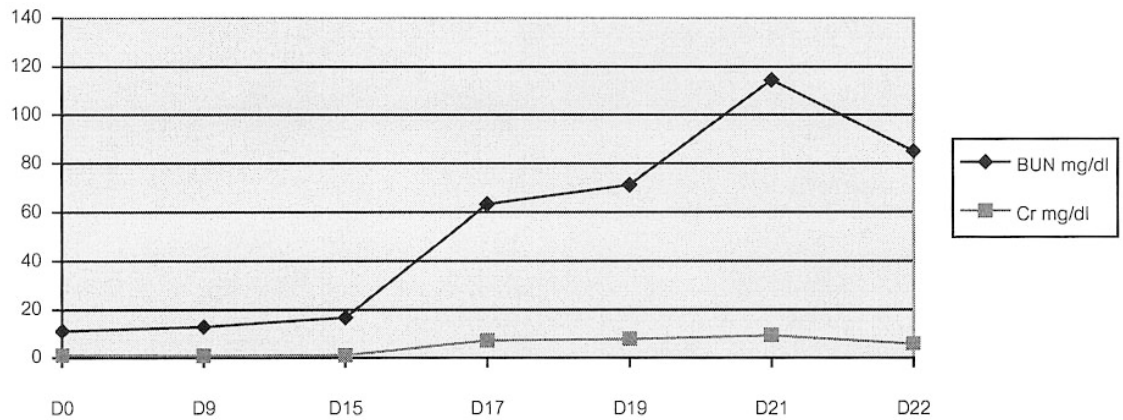


Fig. 6 Serial BUN/Cr during treatment (D0= day of admission)

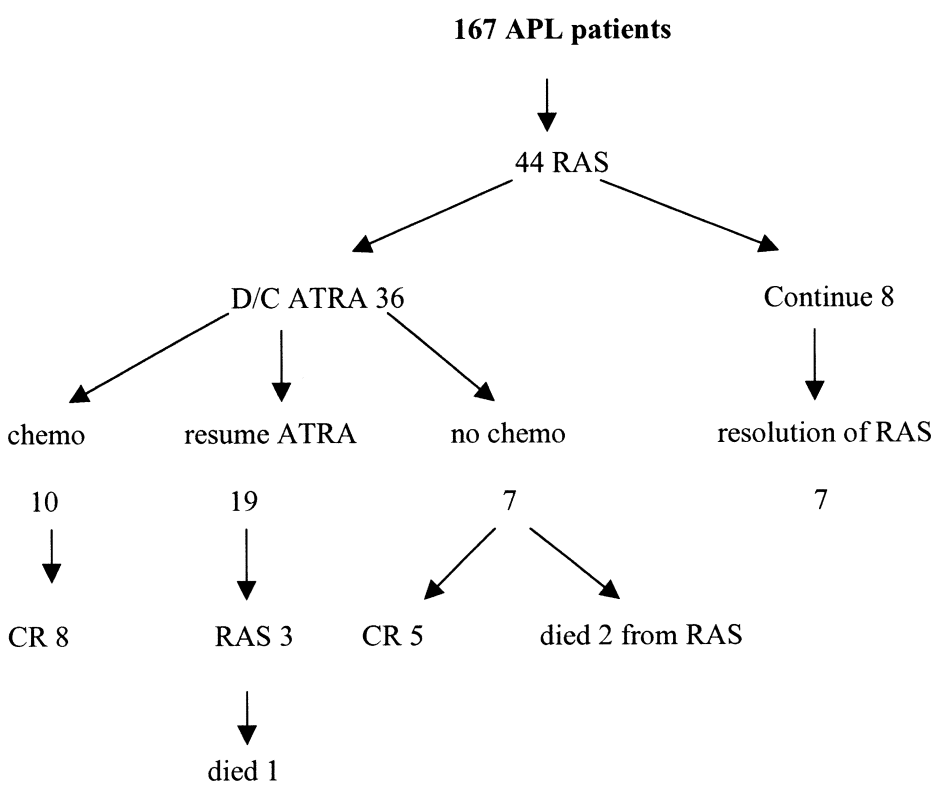


Fig. 7 RAS in APL patients[8]

on day 18. At that time his white blood cells increased to 21,000/cu.mm and BUN/creatinine was also increased with oliguria and pleuropericardial effusion. ATRA was discontinued and dexamethasone was started. He also received respiratory support and hemodialysis, which subsequently relieved the symptoms dramatically as shown by chest x-ray. Tallman et al[8] had reviewed 167 APL patients receiving induction with ATRA alone and discovered RAS in 44 patients (22%). The median white blood count at diagnosis of APL was 1,450/cu.mm. and median white blood

count at the onset of RAS was 31,000/cu.mm (6,800-72,000/cu.mm.). There were 36 patients (82%) who discontinued ATRA and 8 patients (18%) still received ATRA as shown in Fig. 7.

Among patients who discontinued ATRA, 10 patients received chemotherapy subsequently and 8 patients were in complete remission. Nineteen patients resumed ATRA and RAS reoccured in 3 patients (one died) and 7 patients did not receive any chemotherapy. The result was complete remission in 5 patients and 2 patients died of RAS. Seven of 8 patients who were still on ATRA experienced improvement of RAS. It is recommended that patients who develop RAS should discontinue ATRA and start consolidation with chemotherapy as soon as possible. Although this patient received idarubicin along with ATRA, RAS eventually developed.

In one study, de Botton et al[9] showed that early initiation of chemotherapy could decrease the incidence of RAS. They studied 306 patients with newly diagnosed APL aged 65 or less and with initial white blood count less than 5,000/cu.mm. They divided the patients into 2 groups. The first group of 122 patients were put on ATRA until complete remission and then received chemotherapy. The second group of 184 patients received ATRA along with chemotherapy. They discovered RAS in 22 patients (18%) in the first group and 17 patients (9.2%) in the second group ($p = 0.035$). There were 3 patients (2.5%) in the first group who died of RAS compared with only one patient (0.5%) in the second group. At present it is recommended to give chemotherapy with ATRA as induction of remission.

There are many reports proposing the mechanism of RAS from ATRA. After promyelocytes received ATRA, there is a change of adhesion receptor such as acquisition of the $\beta 2$ integrin function causing leucocyte extravasation from blood into the tissue[10]. Another study showed ATRA causing increased expression of IL-8, IL-1β, TNFα, ICAM-1, which can be amplified after G-CSF administration[11].

There are many reports supporting the efficacy of dexamethasone in RAS[12-19]. Mann G et al[20] studied 22 pediatric APL patients, all received ATRA with chemotherapy. Three patients developed RAS. After discontinuation of ATRA and initiation of dexamethasone, all patients were improved. Sentero D et al[21] reported the same result in RAS after treatment with dexamethasone. Flombaum et al[22] studied one patient with RAS and acute renal failure. This patient also showed good response after dexamethasone administration. Larrea L et al studied one RAS patient who had cardiac temponade and cardiogenic shock. They found the beneficial response with dexamethasone[23].

Conclusion

RAS can occur even in patients who receive anthracycline along with ATRA. The warning signs of RAS are chest manifestation such as cough, dyspnea and chest pain. The early detection of RAS is very important. Patients should discontinue ATRA immediately and dexamethasone should be started without delay. Pneumonia and sepsis should be differentiated from RAS because they have different treatments.

References

1. Baker W, Bang Nu, Nachman RL, Raafat RT, Hortwitz HI. Hypofibrinogenemic hemorrhage in acute myelogenous leukemia treated with heparin. Ann Intern Med 1964; 61: 116.
2. Larson RA, Kondo K, Vardiman JW, Butler AE, Golomb HM, Rowley JD. Evidence for a 15;17 translocation in every patient with acute promyelocytic leukemia. Am J Med 1984; 76: 827-41.

3. Huang ME, Ye YC, Chen SR. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988; 72: 567-72.
4. Kakizuka A, Miller WH Jr, Umesono K. Chromosome translocation at t (15;17) in human acute promyelocytic leukemia fuses RAR alpha with a novel putative transcription factor, PML. Cell 1991; 66: 663-74.
5. Tallman MS, Nabhan C. Management of acute promyelocytic leukemia. Curr Oncol Rep 2002; 4: 381-9.
6. Fenaux P, Chastang C, Chevert S. 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: 1192-200.
7. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The retinoic acid syndrome in acute promyelocytic leukemia. Ann Intern Med 1992; 117: 292-6.
8. Tallman MS, Andersen JW, Schiffer CA. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. Blood 2000; 95: 90-5.
9. de Botton S, Chevret S, Coiteux V. Early onset of chemotherapy can reduce the incidence of ATRA syndrome in newly diagnosed acute promyelocytic leukemia (APL) with low white blood cell counts: results from APL93 trial. Leukemia 2003; 17: 339-42.
10. Brown DC, Tsuji H, Larson RS. All-trans retinoic acid regulates adhesion mechanism and transmigration of the acute promyelocytic leukaemia cell line NB-4 under physiologic flow. Br J Haematol 1999; 107: 86-98.
11. Hsu HC, Tsai WH, Chen PG. In vitro effect of granulocyte-colony stimulating factor and all-trans retinoic acid on the expression of inflammatory cytokines and adhesion molecules in acute promyelocytic leukemic cells. Eur J Haematol 1999; 63: 11-8.
12. Fenaux P, Chomienne C, Degos L. All-trans retinoic acid and chemotherapy in the treatment of acute promyelocytic leukemia. Semin Hematol 2001; 38: 13-25.
13. Cupitt JM. A case for steroids in acute lung injury associated with the retinoic acid syndrome. Anaesth Intensive care 2000; 28: 202-4.
14. Avvisati G, Tallman MS. All-trans retinoic acid in acute promyelocytic leukaemia. Best Pract Res Clin Haematol 2003; 16: 419-32.
15. Fenaux P, de Botton S. Retinoic acid syndrome. Recognition, prevention and management. Drug Saf 1998; 18: 273-9.
16. Fenaux P, Degos L. Treatment of acute promyelocytic leukemia. Baillieres Clin Haematol 1996; 9: 107-28.
17. Asami K, Sasazaki Y, Utsumi L. Successful treatment of retinoic acid syndrome with high-dose dexamethasone pulse therapy in a child with acute promyelocytic leukemia treated with ATRA. Acta Paediatr Jpn 1995; 37: 384-7.
18. Mahendra P, Harman K, Phillips M, Gunning K, Marcus RE. Rapid progression of 'retinoic acid syndrome' in the hypogranular variant of acute promyelocytic leukaemia, despite treatment with dexamethasone and conventional chemotherapy. Clin Lab Haematol 1994; 16: 371-4.
19. Marinakis T, Papadimitriou CA, Koufos C, Fertakis A. A recently recognized entity associated with the treatment of acute promyelocytic leukemia: the retinoic acid syndrome. Haematologica 1993; 78: 192-4.
20. Mann G, Reinhardt D, Ritter J, Hermann J, Schmitt K, Gadner H, Creutzig U. Treatment with all-trans retinoic acid in acute

promyelocytic leukemia reduces early deaths in children. Ann Hematol 2001; 80: 417-22.
21. Sentero D, Hosenpud J. Retinoic acid syndrome in acute promyelocytic leukemia. Wis Med J 1997; 96: 35-8.
22. Flombaum CD, Isaacs M, Reich L, Berman E, Warrell RP. Acute renal failure associated with the retinoic acid syndrome in acute promyelocytic leukemia. Am J Kidney Dis 1996; 27: 134-7.
23. Larrea L, de la Rubia J, Jimenez C, Martin G, Sanz MA. Cardiac temponade and cardiogenic shock as a manifestation of all-trans retinoic acid syndrome: an association not previously reported. Haematologica 1997; 82: 463-4.

ผลการรักษา retinoic acid syndrome ด้วย dexamethasone: รายงานผู้ป่วย 1 ราย

อภิชัย ลีละสิริ, ต้นตนัย นำเบญจพล, วิชัย ประยูรวิวัฒน์, วิเชียร มงคลศรีตระกูล, จันทราภา ศรีสวัสดิ์

RAS (retinoic acid syndrome) เป็นอาการที่เกิดหลังการรักษา acute promyelocytic leukemia ด้วย all-trans retinoic acid (ATRA) ประกอบด้วย pleuropericardial effusion น้ำหนักเพิ่ม บวม ความดันโลหิตต่ำ และไตวาย ผู้ป่วยจะมีไข้ หอบเหนื่อย การตรวจเอกซเรย์ปอดจะพบ pulmonary infiltrates และ pleuropericardial effusion อาการดังกล่าวมักเกิดหลังจากรักษาด้วย ATRA ประมาณ 5-21 วัน และมักเกิดขณะที่เม็ดเลือดขาวเพิ่มขึ้นสูงกว่า 10,000 ต่อลบ.มม. ผู้รายงานและคณะได้รายงานผู้ป่วย 1 ราย เป็นชายอายุ 29 ปีอาชีพช่างซ่อมบำรุงโรงงานแบตเตอรี่มา 7 ปี มาโรงพยาบาลด้วยอาการจ้ำเลือดออกง่ายตามร่างกาย 1 เดือน ผลเลือดแรกรับ ฮีมาโตคริท 36.2%, เม็ดเลือดขาว 3,200 ต่อลบ.มม.นิวโทรฟิล 28% ลิมโฟซัยท์ 20% อีโอซิโนฟิล 2% และโปรมัยโลซัยท์ 50% เกล็ดเลือด 20,000 ต่อลบ.มม. การตรวจสเมียร์เลือดพบ fragmented red blood cells เป็นจำนวนมาก การตรวจพิเศษอื่นๆได้แก่ INR 1.50, D-dimer 2 mcg/ml, fibrinogen 250 mg/ml การตรวจไขกระดูกพบมีเซลล์ในไขกระดูกมากขึ้น โดยเซลล์ส่วนใหญ่ประมาณ 95% เป็นโปรมัยโลซัยท์ที่ผิดปกติ การตรวจ cytogenetics พบ translocation ของโครโมโซม 15 และ 17 [t(15;17)(q22;q12)] ได้ให้การวินิจฉัย acute promyelocytic leukemia และได้เริ่มการรักษาด้วย ATRA 45 มก/ม^2/วัน รับประทานเริ่มวันที่ 1 และ idarubicin 10 มก/ม^2/วัน วันที่ 4, 5 และ 6 ประมาณวันที่ 13 ผู้ป่วยเริ่มมีไข้ 39 ° ซ ไอแห้งๆ เม็ดเลือดขาวเพิ่มขึ้นเป็น 7,400/ลบ.มม นิวโทรฟิล 16% ต่อมาวันที่ 18 ผู้ป่วยปัสสาวะออกน้อยลง ไข้สูง ความดันโลหิตลดลง ไอและเจ็บหน้าอกมากขึ้นโดยเฉพาะเวลานอนราบ เม็ดเลือดขาวเพิ่มขึ้นเป็น 21,000/ลบ.มม นิวโทรฟิล 65% มีการเพิ่มขึ้นของ BUN และ creatinine ได้ตรวจเอกซเรย์ปอดพบเงาหัวใจโตและมีน้ำในช่องปอด ตรวจ echocardiogram พบน้ำในช่องหัวใจปริมาณมาก จึงได้วินิจฉัย retinoic acid syndrome ได้หยุด ATRA แล้วให้ dexamethasone 4 มก.เข้าหลอดเลือดดำทุก 6 ชั่วโมง และทำ hemodialysis ผู้ป่วยอาการดีขึ้น จึงได้ลดขนาดของ dexamethasone ลง และได้ตรวจไขกระดูกพบว่าได้ complete remission และได้ให้ consolidation ด้วย cytarabine และ idarubicin ผู้ป่วยรายนี้มีอาการและอาการแสดงเข้าได้กับ RAS ซึ่งจำเป็นต้องได้รับการวินิจฉัยและการรักษาให้เร็วที่สุด เพื่อป้องกันไม่ให้เกิดภาวะแทรกซ้อนที่รุนแรงซึ่งอาจถึงแก่ชีวิต