A Child Patient with Acute Promyelocytic Leukemia Presenting with White Lung: Differentiation Syndrome in the Differential Diagnosis: Case Report

Beyaz Akciğer ile Başvuran Akut Promiyelositik Lösemi Tanılı Çocuk Hasta: Ayırıcı Tanıda Diferansiasyon Sendromu

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Geliş Tarihi/*Received:* 21.12.2015
Kabul Tarihi/*Accepted:* 11.04.2016

This case report was presented as a poster in 7th World Congress on Pediatric Intensive and Critical Care, 4-7 May 2014, İstanbul, Turkey.

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ABSTRACT Acute promyelocytic leukemia (APL) is a rare malignancy in childhood. Treatment includes all-trans retinoic acid (ATRA) that can cause differentiation syndrome (DS). 1.5-year-old boy undergoing induction chemotherapy for APL developed fever and respiratory distress. He was started on antibiotics for presumed sepsis. He rapidly progressed into severe respiratory failure necessitating intubation and admission to the pediatric intensive care unit. Ventilation and oxygenation was difficult with extensive fluid overload complicated by his acute kidney injury. His cultures were negative for 48 hours. For presumed DS intravenous dexamethasone was administered. He was also started on continuous venovenous hemofiltration. With appropriate fluid removal his lung compliance improved, ventilator settings weaned, hemofiltration stopped, and he was finally extubated at the 9th day and discharged from the intensive care unit 6 days after. Clinicians must have a high index of suspicion for diagnosis of DS in patients receiving ATRA to prevent progression and lethal outcomes.

Key Words: Leukemia, promyelocytic, acute; tretinoin; child

ÖZET Akut promiyelositik lösemi (APL) çocukluk çağının nadir lösemilerindendir. Tedavisinde diferansiasyon sendromuna (DS) yol açabilen all-trans retinoik asit kullanılır (ATRA). APL tanılı indüksiyon tedavisi görmekte olan 1,5 yaşındaki erkek hasta ateş ve solunum sıkıntısı ile başvurdu. Sepsis şüphesi nedeniyle hastaya antibiyotik tedavisi başlandı. Ancak hastada solunum sıkıntısı hızla ilerledi ve entübe edilerek yoğun bakıma yatırıldı. Akut böbrek yetmezliği de gelişen hastada ventilasyon ve oksijenasyon sıvı yükü nedeniyle zor sağlanmaktaydı. Kültürleri 48 saat boyunca üremesiz kalan hastada DS düşünülerek parenteral deksametazon tedavisi başlandı. Bunun yanında devamlı venovenöz hemofiltrasyon uygulandı. Sıvı yükü uzaklaştırılan hastada akciğer kompliansı iyileşti, ventilatör ayarları düşürüldü ve dokuzuncu günde ekstübe edilerek, on beşinci günde yoğun bakımdan taburcu edildi. ATRA tedavisi alan hastalarda, ölümcül sonuçları engellemek için DS gelişimi açısından dikkatli olunmalıdır.

Anahtar Kelimeler: Lösemi, promiyelositik, akut; tretinoin; çocuk

Turkiye Klinikleri J Case Rep 2016;24(2):114-7

Acute promyelocytic leukemia (APL) is a rare malignancy in childhood. Induction therapy includes all-*trans* retinoic acid (ATRA), which can cause life-threatening differentiation syndrome (DS). It is characterized mainly by acute respiratory distress, unexplained fever and pulmonary infiltrates and may resemble a variety of other clinical conditions like sepsis and acute respiratory distress syndrome (ARDS). Unrecognized patients may quickly deteriorate leading to respiratory insufficiency

doi: 10.5336/caserep.2015-48895

and hemodynamic failure necessitating mechanical ventilation, hemodynamic support and dialysis. Awareness of the condition is crucial, because early initiation of dexamethasone is life-saving in the treatment. Besides, critically ill patients particularly with respiratory signs and pulmonary infiltrates benefit from intubation and early admission to intensive care unit (ICU) for management of DS. Delayed diagnosis may result in death of patients that could be cured with dexamethasone and vigorous treatment options like mechanical ventilation and hemodialysis. Here we report a severe case of DS, treated first as sepsis, but showed dramatic response to treatment with dexamethasone.

CASE REPORT:

1.5-year-old boy undergoing induction chemotherapy with cytarabine, idarubicine and all- *trans*-retinoic acid for APL developed fever and respiratory distress on the 4th day of treatment. Blood cultures were drawn and he was started on broad-spectrum antibiotics for presumed sepsis. Next day, he rapidly progressed into severe respiratory failure necessitating intubation and admission to the pediatric intensive care unit (PICU).

His physical examination revealed: a temperature of 36.1 C°, pulse rate of 183 beats/min, blood pressure equal to 86/52 mmHg, and oxygen saturation of 51% with a fraction of inspired oxygen 1.0 at admission. His skin appeared pale and cutis marmaratus was present. Capillary refill time was prolonged and lung examination revealed bilateral rales. Examination of heart and abdomen was normal. Extremities were cold and pulses on arteria dorsalis pedis and arteria radialis were hardly palpable.

Laboratory results show the following: White blood cell count, 16.900/μL, with 81.5% neutrophils, 18.2% lymphocytes, 0.2% monocytes, 0.1 % eosinophils, and 0.0% basophils; hemoglobin, 9.8 g/dL; platelets, 65×10^3/μL; C-reactive protein, 13.2 mg/L; BUN, 9 mg/dL; creatinine 0,45 mg/dL. Initial capillary blood gas analysis revealed respiratory acidosis with pH, 7.08; pCO_2, 87.5 mmHg; HCO_3, 25.2 mmol/L; base excess,-3.7 mmol/L; lactate, 5.4 mmol/L.

Bilateral diffuse pulmonary infiltrates was present on chest radiograph (Figure 1). He was in decompensated shock and ionotropic support with adrenalin and dobutamin was started. He was oliguric and ventilation and oxygenation was difficult with extensive fluid overload complicated by his acute kidney injury. He was also started on continuous venovenous hemofiltration (CVVHF). His cultures were negative for 48 hours, so sepsis didn't seem to be the cause of his clinical condition. Concerning the adverse effects of used drugs for treatment of APL, intravenous dexamethasone was administered for presumed differentiation syndrome caused by ATRA.

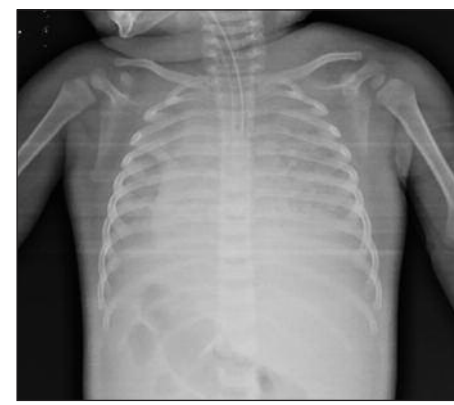

FIGURE 1: Bilateral diffuse pulmonary infiltrates are seen at presentation.

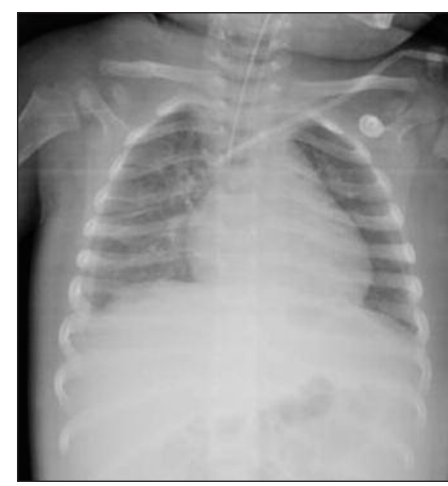

FIGURE 2 Pulmonary infiltrates regressed after fluid removal with continuous venovenous hemofiltration.

With appropriate fluid removal his lung compliance improved, pulmonary infiltrates regressed (Figure 2), ventilator settings weaned, CVVHF stopped, and he was finally extubated at the 9th day and discharged from the PICU 6 days after. He had a total 9 days of dexamethasone treatment that was started at 2-mg/ kg (in two divided doses) for 3 days and tapered to off. ATRA was discontinued when DS suspected.

Final diagnosis was differentiation syndrome concerning his clinical picture characterized with respiratory distress, pulmonary infiltrates, hypotension and renal failure and dramatic response to treatment with dexamethasone.

DISCUSSION

APL is a rare malignant disorder in childhood, affecting 8-12% of children with acute myeloblastic leukemia.[1,2] Treatment protocols include anthracyclines, cytarabine and additionally ATRA. As in adults, the outcome of children diagnosed with APL is improved with the addition of ATRA to chemotherapy regimens.[3,4]

Although usually well tolerated, ATRA can cause a clinical syndrome, named as differentiation syndrome (DS), which is characterized by respiratory distress, pulmonary infiltrates, fever, weight gain, pleural effusion, pericardial effusion, renal failure, cardiac failure and hypotension. [5] Incidence in children varies between 7.5-20% in different trials. [3,4,5-7] It is not a rare condition but it may be difficult to recognize the DS due to the fact that it may resemble a variety of other clinical conditions such as sepsis, acute respiratory distress syndrome (ARDS) and pulmonary hemorrhage. Besides that the syndrome is diagnosed clinically and there are no definitive diagnostic criteria. When our patient developed fever, which was actually the earliest sign of DS in our patient, he was also treated like sepsis, which causes a one-day delay both in diagnosis and treatment of DS.

Signs of DS develop between 1-35th days of treatment with ATRA.[5] It is reported that severe DS is more common at first week.[8] Our patient was at the 4th day of treatment when he shows signs of DS. Concerning his need for mechanical ventilation, ionotropic support for hypotension and CVVHD for fluid removal, he was considered as developing severe DS. Assuming the prevalence and timing of DS, it must be suspected in any patient treated with ATRA, when unexplained fever, weight gain or respiratory distress develops.

As mentioned earlier, there are no definitive clinical or radiological diagnostic criteria for DS. Chest X-Rays of patients may demonstrate increased cardiothoracic ratio, pleural effusion, ground glass opacity, interstitial edema, septal lines, peribronchial cuff and widening of vascular pedicle width.[9] None of these features are specific for DS. In severe cases ARDS may develop.[9] Chest X-Ray of our patient at presentation shows bilateral diffuse pulmonary infiltrates as in ARDS.

Mortality of DS in adult population varies between 8- 28% in different trials.[5,10] Dexamethasone is the mainstay of treatment. Concerning the high mortality rates of DS it is recommended to add dexamethasone to chemotherapy as soon as signs of DS develop.[5,8] Another approach for preventing ATRA toxicity is prophylactic use of dexamethasone concomitant with ATRA in high-risk patients presenting with high WBC counts (more than 15,000 /μL).[5] Benefit of prophylactic steroid use is unclear both in adults and children. In one study among children no statistical difference in the incidence of DS was shown in children receiving prophylactic prednisolone with ATRA compared with the group receiving only ATRA. [7] Concerning another report prophylactic steroid use reduces the incidence of severe DS but doesn't affect mortality rate.[8] Nevertheless there is a consensus over the prompt initiation of dexamethasone at the first sign of DS.

The most severe cases as our patient may require mechanical ventilation, hemodynamic support and dialysis. ATRA should be temporarily discontinued in such patients and dexamethasone should be continued until complete resolution of symptoms.[8] As most patients treated with dexam-

ethasone our patient showed also dramatic response to treatment with initiation of dexamethasone.

In conclusion DS is not a rare entity in a patient receiving ATRA for APL. Clinicians must have a high index of suspicion for diagnosis of DS in patients receiving ATRA therapy to prevent progression and lethal outcomes. Even severe cases requiring PICU admission as our patient show dramatic response to dexamethasone and supportive treatment.

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