Acute renal failure in patient treated with ATRA and amphotericin B: case report

Insuficiência renal aguda em paciente tratada com ATRA e anfotericina B: relato de caso

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Abstract

This is a report of the case of a patient with acute promyelocytic leukemia treated with all trans-retinoic acid (ATRA), who had suspected all-trans retinoic acid syndrome (ATRA syndrome). The nonspecific febrile leukopenia observed justified the association with antimicrobial and antifungal therapy. Signs and symptoms contributed to the suspicion of ATRA syndrome, and renal function was impaired by the combination with antifungal agents. The decrease in renal function observed initially contributed to the suspicion of ATRA syndrome and was aggravated by antifungals. Thus, the use of ATRA was discontinued. Eight days after the pneumonia characterization, the possibility of ATRA syndrome was dismissed. In this context, ATRA's nephrotoxicity and the synergic adverse effect by the use of nephrotoxic antifungal agents were discussed, particularly amphotericin B, as well as the importance of differential diagnosis between ATRA syndrome and infectious diseases.

Keywords: tretinoin, amphotericin B. ATRA syndrome, acute renal failure.

Resumo

O presente relato apresenta o caso clínico de uma paciente com leucemia promielocítica aguda tratada com ácido todo-transretinoico (ATRA), que apresentou suspeita de síndrome do ácido transretinoico (síndrome de ATRA). Com a ocorrência de leucopenia febril inespecífica, foram associados ao tratamento antimicrobianos e antifúngicos. A diminuição da função renal, observada inicialmente, contribuiu para a suspeita de síndrome de ATRA, que foi agravada pelos antifúngicos. Assim, o uso de ATRA foi suspenso, mas somente 8 dias depois foi caracterizada pneumonia e descartada a hipótese de síndrome de ATRA. Nesse contexto, foi discutida a nefrotoxicidade do ATRA e a potencialização desse efeito adverso pelo uso de antifúngicos nefrotóxicos, em particular da anfotericina B, assim como a importância do diagnóstico diferencial entre síndrome de ATRA e doença infecciosa.

Palavras-chave: tretinoína, anfotericina B, insuficiência renal, insuficiência renal aguda.

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Introduction

Acute promyelocytic leukemia (APL) with translocation t(15;17) corresponds to approximately 20 to 25% of acute myeloid leukemia cases in Latin American countries.[1] APL is treated with a specific drug – all trans-retinoic acid (ATRA) –, which directly induces cell differentiation in the bone marrow, thus inhibiting the growth of leukemia cells and enabling pro-apoptosis.[1,2] Treatment with ATRA increases complete remission and disease-free survival rates in about 90 and 80% of the patients, respectively.[3,4]

Although ATRA is well tolerated, 5 to 20% of the patients have severe adverse effects such as the ones which form the known clinical picture, like retinoic acid syndrome (ATRA syndrome).[1] The diagnosis is mainly clinical and based on the presence of at least four of the following symptoms, described by Frankel et al.:[5] fever, respiratory failure, pulmonary infiltrates, hypotension, pleural effusion, unexplained weight gain, hepatomegaly and acute renal failure.[5,6] Because of these signs and symptoms, ATRA syndrome may be mistaken for

complications that are common to APL, especially sepsis and pneumonia.[7]

Besides, the occurrence of adverse effects isolated from ATRA, such as renal lesion, is also reported in literature, once its main clearance course is the kidney.[8,9] Such lesion may be aggravated when the patient has a history of renal disease,[10] or at the occurrence of pharmacotherapy toxicity associated with ATRA.[9,11]

Empiric antimicrobial therapy is a common practice among immunocompromised patients and those with febrile neutropenia because infections are more common in such cases.[12] Therefore, patients with APL on ATRA therapy may need antifungal therapy.[13-15]

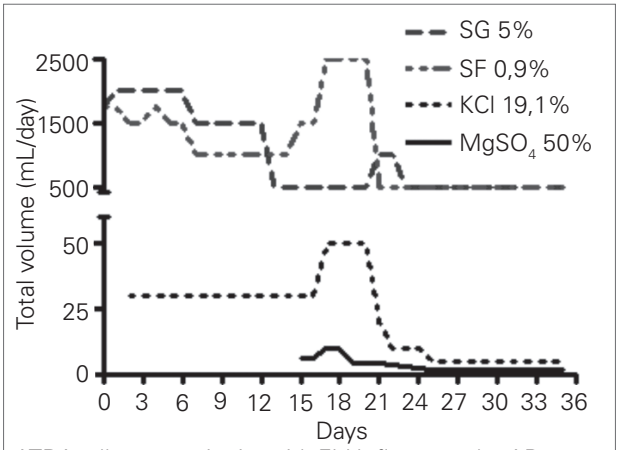
Since its discovery, in 1955, amphotericin B (AB)[16,17] remains as the antimicrobial of choice for this practice, as well as for the treatment of confirmed systemic fungal infections.[16,18] However, AB is associated with chronic and acute adverse effects, especially nephrotoxicity, which may cause renal damage and electrolytic disorder (hypokalemia and hypomagnesemia). Nephrotoxicity is common and severe, and is related to increased death risk, especially when the treatment with AB is associated with other nephrotoxic drugs.[18-20]

Case report

Case of a 47-year-old female patient, with body surface of 1.8 m^2 (68.8 kg, 1.71 m). She was admitted at *Hospital Universitário* of *Universidade Federal de Santa Catarina* (HU-UFSC) and diagnosed with APL with translocation t(15;17). The patient was pallor, and presented fever (38.6°C), asthenia, headache and rectal bleeding.

Peripheral blood analysis showed thrombocytopenia (63,000/mm^3), blast counts, neutropenia (94/mm^3) and erythrogram with decreased parameters (red blood cells count: 2.63 million/mm^3; hemoglobin: 7.6 g/dL; hematocrit: 22.8%), which leads to clinical pictures of febrile neutropenia and anemia. Hemoculture and uroculture were negative, and the focus of infection was not determined. For febrile neutropenia, oral dipyrone 500 mg and intravenous cefepime 2g were administered every eight hours as empiric therapy, for the infection agent had not been isolated. Concomitantly, cytostatic therapy with cytarabine 370 mg/m^2/day EV was administered for seven days, mitoxantrone 20mg/m^2/day EV for three days and ATRA 40 mg/m^2/day (continuous oral administration). On the third day, the patient presented febrile neutropenia and pancytopenia. On the seventh day, hemoculture and uroculture were performed again, and the results remained negative. On the same day, the patient presented mouth ulcer and white lesions in the oropharynx at clinical examination, both characteristics of candidiasis. For that, antifungal fluconazole 200 mg/day (oral route) was used.

The patient continued to have fever peaks (37.5 to 38.1°C), and fluconazole was replaced by AB 30 mg/day EV (6 hours of infusion) on the 13th day. On this same day, the urine test showed high red blood cell count (55,000/mL), with traces of hemoglobin and protein (approximately 30 and 50 mg/dL, respectively, by the semi-quantitative test), which characterized renal impairment. On the 14th day, the patient had intense asthenia and hepatomegaly. ATRA therapy was maintained until the 16th day, when the patient had dyspnea related to AB infusion. Besides, signs of pulmonary congestion (dyspnea, bronchospasm and respiratory failure), hepatomegaly and oliguria, added to the 4 kg weight gain, contributed to the suspicion of ATRA syndrome. At this point, ATRA administration was suspended, and the therapy with dexametasona 1 mg EV every 12 hours was administered to stop the evolution of the syndrome. Steroid treatment was maintained for 14 days. The patient presented dyspnea, bronchospasms and fever peaks (37.2 to 38.4°C). On the 17th day, cefepime (antibiotic) was replaced by meropenem 1 g EV every eight hours, as empiric therapy. Episodes of diarrhea were observed on the tenth day and between the 15th and 18th days, which might be a result of chemotherapy or cefepime. Despite the use of hydroelectrolytic replacement therapy from the beginning (Figure 1), potassium

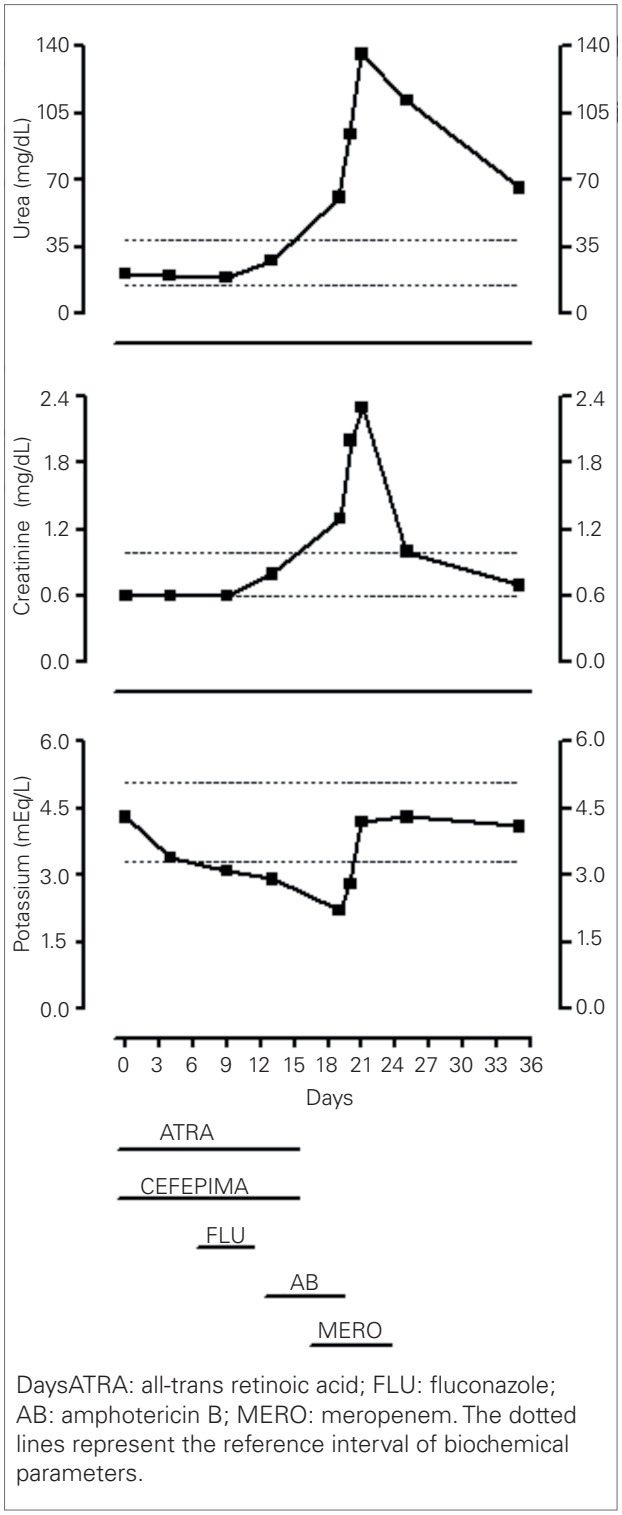


ATRA: all-trans retinoic acid; FLU: fluconazole; AB: amphotericin B; MERO: meropenem. The dotted lines represent the reference interval of biochemical parameters.

Figure 1. Hydroelectrolytic replacement therapy with physiological solution (0.9%), glucose physiological solution (5%), potassium chloride (19.1%, 10 mL vial), and magnesium sulphate (50%, 2 mL vial).

values were still decreasing (Figure 2). On the 19th day, the patient was referred to the Intensive Care Unit (ICU) with respiratory failure due to pulmonary hemorrhage, oliguria and intense hypokalemia. From the 17th to the 21st day, diuresis decreased (urinary output was not registered in the file), and urea and creatinine increased (Figure 2), which indicates severe renal damage, leading to the discontinuation of AB therapy on the 21st day. In this period, the patient remained with a fever (38 to 38.4°C), with oral and urethral bleeding and tachycardia.

Blood count showed leucopenia, thrombocytopenia and anemia (Figure 3). On the 22nd day, there was a suspicion of pneumonia and, since the fever did not present reduction (38.3°C), meropenem therapy was maintained. On the 24th day, hemoculture (from the



DaysATRA: all-trans retinoic acid; FLU: fluconazole; AB: amphotericin B; MERO: meropenem. The dotted lines represent the reference interval of biochemical parameters.

Figure 2. Evolution of biochemical laboratory parameters in a patient with suspicion of ATRA syndrome.

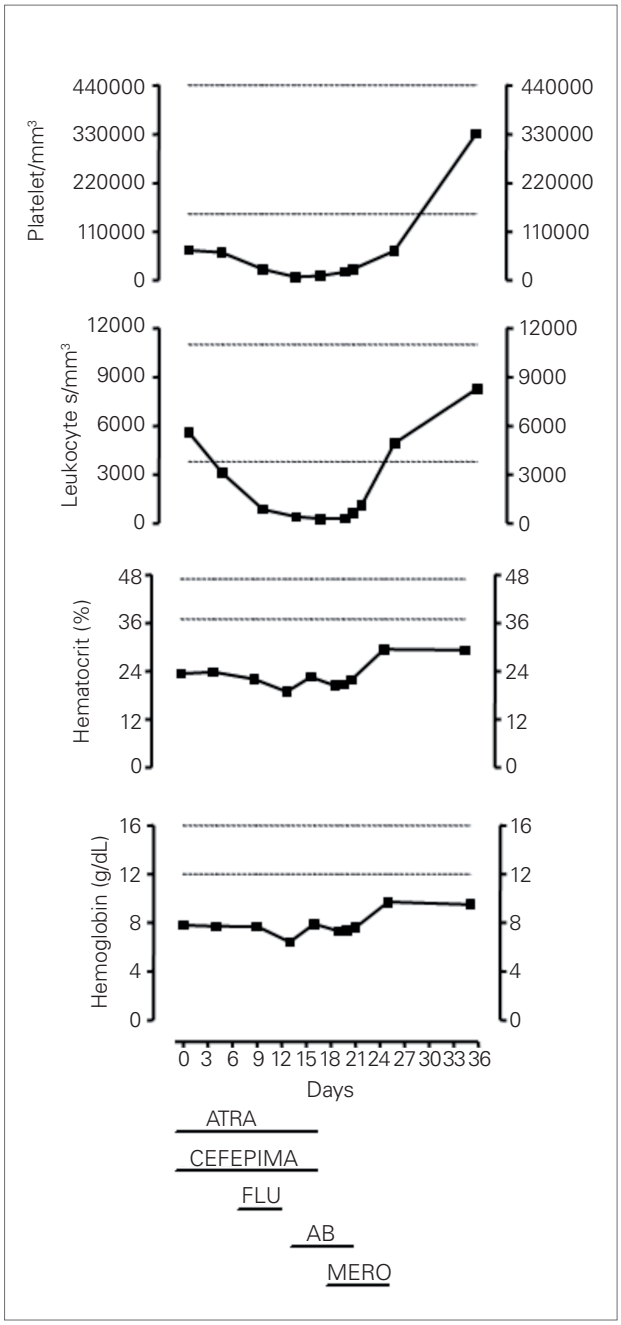


Figure 3. Evolution of hematologic laboratory parameters in a patient with suspicion of ATRA syndrome.

16th day) was positive for *Klebsiella pneumoniae*. The patient was hospitalized for more 14 days to recover, and was responsive to treatment, presenting clinical improvement as to the lung function, renal function and mouth ulcer. She had no fever after the 28th day, and was discharged from the ICU on the 32nd day. A new cycle of cytostatic therapy started on the 37th day, with methotrexate 7.5 mg/m^2/day EV and ATRA 20 mg/m^2/day (oral route). At blood count, leucogram presented cell remission, the anemia improved and the number of platelets was normal. The patient was discharged from the hospital on the 39th day, and was told to continue with oral ATRA 20 mg/m^2/day.

The publication of this case was approved by the Human Research Ethics Committee of the institution.

Discussion

ATRA syndrome is related to a mortality rate higher than 2% among patients who use it.[21] The ATRA dose prescribed for the patient is unusually indicated for those with APL.[9-11,13] However, the patient's symptoms together with the negative culture tests in the urine and the hemoglobinuria caused the suspicion of ATRA syndrome. ATRA was immediately suspended and replaced by corticosteroid therapy. This procedure is in accordance with Jácomo et al.,[1] who reported the need of early detection of symptoms and initiation of treatment, since ATRA syndrome decreases survival rates. According to these authors, besides the temporary interruption of ATRA, dexametasone must be administered at the dose of 10 mg every 12 hours for at least three to four days, or until the resolution of symptoms.

ATRA therapy or its association with fluconazole (cumulative dose of 1,200 mg) impaired renal function (hypokalemia, oliguria, proteinuria and hemoglobinuria). Sastre et al.[9] observed that, among the 14 patients treated with ATRA who developed ATRA syndrome, six had acute renal failure and needed hydroeletrolytic replacement therapy. They also observed that renal involvement in patients with ATRA syndrome is not widely reported in literature. Another study performed with 732 patients with APL, all of them treated with ATRA, reported death of ten patients due to ATRA syndrome, and renal damage was involved in all of these cases.[6]

The patient's renal function was aggravated by the administration of 240 mg of AB (cumulative dose), which can be observed by the fast increase of creatinine and urea, besides the decrease in serum potassium, despite steroid and hydroeletrolytic therapy. Among the drugs that are famous for causing renal damage, antibiotics and non steroidal anti-inflammatories may be cited, and among the most important agents of acute tubular necrosis are aminoglycosides, radiologic contrast agents, cyclosporine and AB.[22] It is important to report that monotherapy with cefepime and meropenem is as effective as combined therapy to treat a patient with febrile neutropenia, with the advantage of enabling the association with other nephrotoxic drugs.[23,24] Thus, at that time, the possibility of nephrotoxicity was not taken into account by the association of ATRA and cefepime (cumulative dose of 32 g). Actually, no reports were found in literature regarding the interaction between cefepime and ATRA, and this does not exclude the possibility of strengthening nephrotoxicity as a result of this interaction. Therefore, the aggravation of renal function was attributed to AB.

ATRA derives from vitamin A, and is metabolized through the liver, via cytochrome P450 enzymes in 4-oxo ATRA, 13-cis-retinoic acid and other isomers that are excreted, such as bile glucuronide and, mainly, through the kidney.[25] Triazole derivatives, such as fluconazole, inhibit ATRA catabolism via cytochrome P450, which may increase the plasma concentration of ATRA.[11,25,26] Such association might only have favored renal alterations, which were aggravated by the administration of AB.

As in the case of ATRA, the kidney is the main course of AB excretion.[27] Nephrotoxicity is the most common adverse effect of AB, and it is aggravated when there is already some degree of renal impairment. The main nephrotoxic mechanism is the increase of afferent arteriole resistance and/or tubular permeability. The increase of afferent arteriole resistance decreases renal blood flow and glomerular filtration, and it is a probable explanation for the increase in the plasma creatinine concentration. The high permeability of the luminal tubular membrane to K^+ and H^+ cations is a result of the formation of intramembranous pores after AB is connected to the cholesterol of the membrane, enabling K^+ loss through urine and plasma K^+ decrease.[16,18,28,29] The patient had a decrease in renal blood flow, which led to oliguria, elevation of creatinine and decrease of serum potassium during the administration of ATRA and AB. Even though AB therapy causes hyponatremia and hypomagnesemia, sodium and magnesium serum values were within the reference limits from hospital admission to discharge, probably due to hydroelectrolytic therapy. Another mechanism of renal damage related to ATRA and AB is hypotension-induced endothelial lesion.[7,9]

It is believed that the renal damage induced directly by ATRA was also present during the treatment, regardless of the ATRA syndrome occurrence and despite being little reported in literature.It is supported by other authors that reported tubular or acute cortical necrosis as a consequence of ATRA use;[7,11] therefore, its administration is not recommended for patients with hepatic and renal dysfunction.[10]

In this manner, renal toxicity was not only a consequence of AB therapy. It is likely that ATRA and/or ATRA associated with cefepime or fluconazole have impaired the renal function, making it prone to AB damage. They might have been responsible for the development of renal toxicity, maintained by AB.

When suspecting ATRA syndrome, ATRA therapy was suspended (16th day), but microbiological investigation was maintained. Eight days after the interruption of ATRA therapy, clinical picture of ATRA syndrome presented no improvement, and hemoculture was positive for *Klebsiella pneumoniae*; ATRA syndrome was ruled out on the 24th day.

Such identification justified the fever without apparent focus and the pulmonary impairment, confirming the diagnosis of pneumonia

This result weakened the initial diagnosis of ATRA syndrome. Clinical presentation of ATRA syndrome and pneumonia is similar,[8] hence the importance of broad antibiotic coverage. Serna et al.[6] suggested it is essential to rule out the possibility of infection processes in order to confirm ATRA syndrome.

However, the suspicion of ATRA syndrome was maintained, since the infection agent was not isolated. Besides, imaging exams could have helped the differential diagnosis of pneumonia, but these were not performed.

Renal function of patients treated with ATRA must be monitored by clinical and laboratory parameters, especially when the treatment is associated with other nephrotoxic drugs, like antifungals, especially AB. This is due to the fact that, like the renal damage observed in the reported case, Sastre et al.[9] also reported renal failure in patients who had no ATRA syndrome and were treated with ATRA.

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