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Case report

Granulomatous tubulointerstitial nephritis induced by all-*trans* retinoic acid

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We report the first case of granulomatous tubulointerstitial nephritis induced by all-*trans* retinoic acid (ATRA) in a patient with acute promyelocytic leukemia (APL). Acute renal failure during treatment with ATRA has been previously reported as a part of an ATRA syndrome or a thrombotic complication of a hypercoagulable state. This case indicates an alternative mechanism of acute renal failure occurring during ATRA therapy. [© 2001 Lippincott Williams & Wilkins.]

Key words: acute promyelocytic leukemia, all-*trans* retinoic acid, granulomatous tubulointerstitial nephritis, renal failure.

Introduction

Differentiation therapy with all-*trans* retinoic acid (ATRA) is currently the first-line treatment for acute promyelocytic leukemia (APL).[1] During ATRA therapy, patients with ATRA syndrome or with a hypercoagulable state often develop acute renal failure usually accompanied by dysfunction of other organ systems. We report a patient with APL who developed renal failure alone during ATRA treatment. Examination of a renal biopsy specimen revealed that the cause of the complication was granulomatous tubulointerstitial nephritis induced by ATRA.

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Case report

A 72-year-old Japanese man was referred for anemia and leukocytopenia during a hospitalization for treatment of prostatic cancer in June 2000.

He had undergone right partial nephrectomy for renal cell carcinoma at age 71 and had no evidence of relapse. He also had no subjective symptoms. The white blood cell count was 1.4×10^9/l, with a differential count of 1% myelocytes, 1% bands, 42% segmented neutrophils, 1% eosinophils, 1% monocytes and 54% lymphocytes. The hemoglobin level was 9.1 g/dl and the platelet count was 131×10^9/l. Bone marrow aspiration revealed a normocellular marrow with 2.8% myeloblasts and 60.3% hypergranular promyelocytes, some of which contained Auer rods. PML/RAR-α was detected in 97% of the cells by fluorescence *in situ* hybridization, confirming the diagnosis of APL. Cytogenetic studies showed t(15;17) with del(14) (q13–21q24) in 75% and 46,XY in 25% of the metaphases. The initial blood urea nitrogen and serum creatinine concentrations were 25 and 1.0 mg/dl, respectively. Although the fibrinogen level was decreased at 108 mg/dl, the prothrombin time and fibrin/fibrinogen degradation product concentration were normal. There was no clinical evidence of infection.

Induction therapy was administered in the following order: ATRA 40 mg/m^2 from day 1, then idarubicin 9 mg/m^2 from day 5 to 7 (Figure 1). Antifibrinolytic therapy was not given. For prophylaxis against hemorrhage, fresh frozen plasma was given from day 0 to 7. Intravenous nafamostat mesilate (Futhan) was administered from day 1 to 12, but it was changed to gabexate mesilate (FOY) on day 13 because of an elevated serum potassium concentration. On day 17,

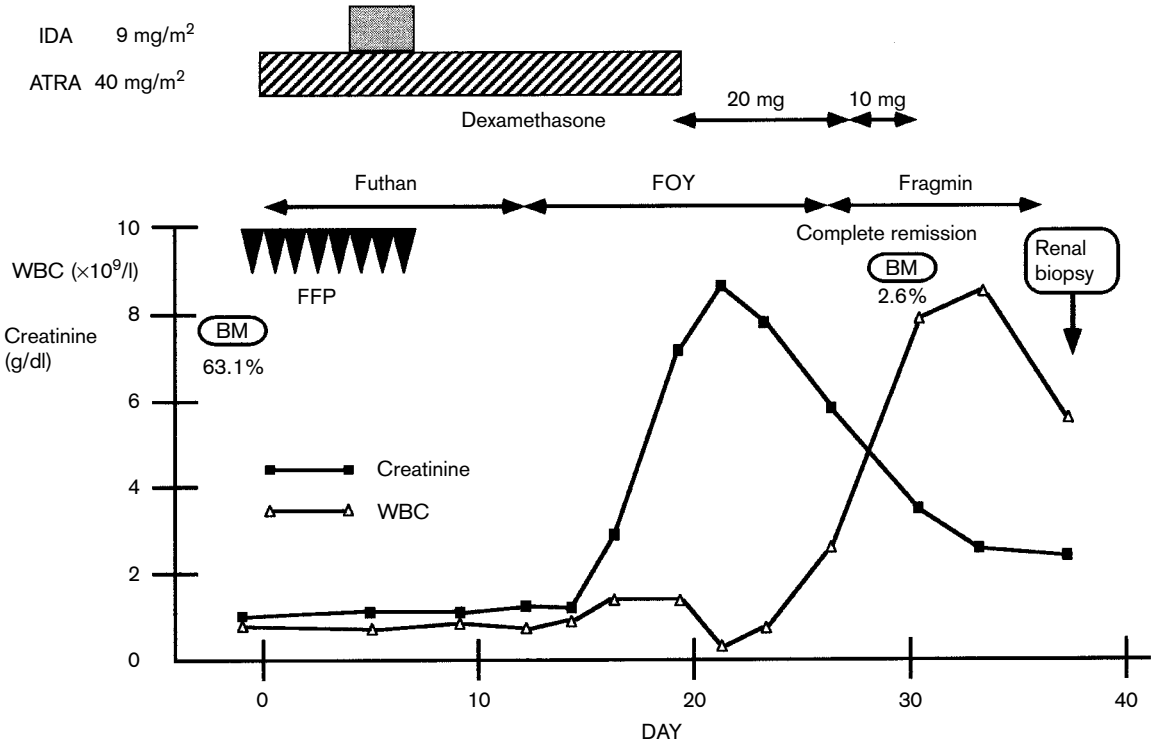

Figure 1. Clinical course of the case presented. BM, bone marrow aspiration and combined percentage of myeloblasts and promyelocytes. FFP, fresh frozen plasma administration.

oliguria was observed and ATRA was subsequently discontinued on day 20 when the serum creatinine concentration was elevated to 7.0 mg/dl. Despite the presence of renal failure, he had no signs or symptoms indicating ATRA syndrome. In addition, there was no increase in the peripheral blood leukocyte count although this is a frequent finding accompanying the syndrome. Although it was not a typical case of ATRA syndrome, treatment with dexamethasone (10 mg/12 h i.v.) was begun on day 20. The serum creatinine concentration peaked at 8.7 mg/dl on day 22 and then gradually decreased. During the period of most severe renal failure, the fibrinogen and α_2-antiplasmin concentrations were not elevated. From day 27, dalteparin sodium (Fragmin) was administered in place of FOY. On day 30, a bone marrow examination revealed complete remission with 0.2% myeloblasts and 2.4% promyelocytes. The chromosomal abnormality had disappeared and PML/RAR-α was found in only 2.8% of the cells by fluorescence *in situ* hybridization. PML/RAR-α chimeric mRNA was not detected by polymerase chain reaction. To determine the cause of the acute renal failure, needle biopsy of the left kidney was performed on day 38 when the serum creatinine concentration was 2.4 mg/dl. Microscopic examination was compatible with granulomatous tubulointerstitial nephritis (Figure 2). The glomeruli were mostly intact and no evidence of fiblin thrombi or leukemic cell infiltration was seen. After one course of consolidation therapy, he was discharged with a normal serum creatinine concentration. He has remained in complete remission for 8 months.

Discussion

Acute renal failure is occasionally observed in patients with APL during ATRA therapy. Most develop it as part of ATRA syndrome, which is diagnosed based on the presence of at least three of the following: respiratory distress, fever, pulmonary infiltrates, weight gain, pleural effusion, acute renal failure, pericardial effusion, cardiac failure and hypotension. Renal failure is reported to be observed in 39% of patients with ATRA syndrome.[2] Although there are few post-mortem studies of patients with this syndrome, at least two cases of extensive organ infiltration, including the kidney in one case, by leukemic cells[3] have been found. This infiltration may be the cause of renal failure in ATRA syndrome, but no scientific proof has been established. Interstitial nephritis diagnosed by ultrasound was reported in one case of renal failure

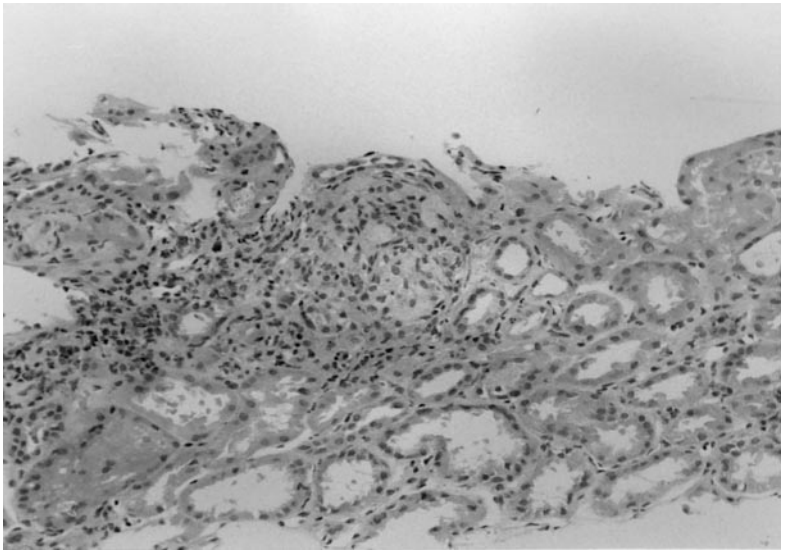

Figure 2. Photomicrograph of renal biopsy tissue showing interstitial granuloma formation (original magnification ×500).

during ATRA;[4] however, renal biopsy was not performed. On the other hand, the use of ATRA also induces a hypercoagulable state resulting from a rapid, ATRA-induced normalization of a state of hyperfibrinolysis.[5,6] Thrombotic complications including renal failure of a microangiopathic nature occur not only during the administration of ATRA together with antifibrinolytics such as tranexamic acid[7] or aprotonin,[8] but also during treatment with ATRA alone.[9] These events are always life-threatening.

In the case presented here, the cause of renal failure was neither of the two mechanisms discussed above. Examination of the renal biopsy specimen revealed an image of granulomatous tubulointerstitial nephritis without fibrin thrombi or leukemic cell infiltration. This is a rare type of interstitial nephritis,[10] known to result from drug hypersensitivity, infection, vascular or glomerular disease, inert particles, etc.[11] Based on the clinical course of this patient, drug-induced hypersensitivity was suspected. Although all drugs except ATRA, including antibiotics and non-steroidal anti-inflammatory drugs, were administered continuously or re-administered during consolidation therapy, the renal function did not decline during this time. It is common in drug-induced interstitial nephritis that withdrawal of the suspicious agent results in resolution of acute renal failure.[12] Because the patient developed renal failure, he was begun on corticosteroid therapy, which has been recommended for suspected cases of ATRA syndrome,[2] as well as Fragmin therapy since thrombotic complications are usually fatal even if laboratory data do not suggest a hypercoagulable state.

In conclusion, the renal biopsy specimen provided definitive evidence of the mechanism for acute renal failure in this case. We believe that this case of ATRA-induced granulomatous tubulointerstitial nephritis is a complication of ATRA therapy which has not been previously reported.

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