Retinoic Acid Syndrome Presenting as Acute Renal Failure

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Abstract

Renal failure can occur as part of the ATRA differentiation syndrome in acute promyelocytic leukaemia in conjunction with other organ involvement primarily the lungs. The prognosis is poor if there is a delay in initiation of appropriate treatment. Isolated renal failure is very rare and the diagnosis maybe difficult. We present a case of isolated renal failure due to retinoic acid syndrome in a case of therapy related acute promyelocytic leukaemia which responded very well to dexamethasone even though the diagnosis was delayed.

Introduction

Acute Promyelocytic Leukaemia (APL) represents 10% of acute myeloid leukaemia. It is characterized by specific morphology of the blast cells (M3 in the FAB classification), the t 15;17 translocation that fuses the PML gene on chromosome 15 to the Retinoic Acid Receptor (RAR) gene on chromosome 17 and by a coagulopathy. The leukaemia shows exquisite sensitivity to Anthracyclines and All-Trans Retinoic Acid (ATRA) induces differentiation of the APL blasts. The cure rate is as high as 90% but there is a high early mortality due to the coagulopathy and ATRA syndrome [1]. APL generally occurs de novo without known cause. Occurrences of therapy related APL after chemotherapy for neoplasm is increasingly being described and the prognosis is not significantly different from those with de novo APL [2].

Keywords: Acute Promyelocytic Leukaemia; All-Transretinoic Acid; Retinoic Acid Syndrome; Renal Failure

Case Report

A 68 year old man presented with symptomatic anaemia. The blood count was: WBC 0.15 x 10⁹/l, Neutrophils 0.11 x 10⁹/l, Hb 9.1g/l, Platelets 35x10⁹/l and the creatinine was 88umol/l. Bone marrow analysis revealed 50% infiltration by hypergranular pro-myelocytes. The t15;17 was identified. Three years previously, he was treated for colonic adenocarcinoma with chemotherapy and radiotherapy. The patient was now treated with 4 cycles of chemotherapy according to the PETHEMA protocol: Induction cycle with daunorubicin 60mg/m² days 2,4,6,8 and ATRA 45mg/m2/day until complete remission was documented. Consolidation cycle 1: daunorubicin 25 mg/m² days 1,2,3,4 and ATRA 45 mg/m² x 15 days. Consolidation cycle 2: Mitoxantrone 10 mg/m² days 1,2,3 and ATRA 45 mg/m² x 15 days. Consolidation cycle 3: Daunorubicin 60 mg/m² day 1 and ATRA 45 mg/m² x 15 days. One week into induction, the patient was feverish, urine culture revealed the growth of E. coli and antibiotic therapy was commenced. On the day 15 of induction, the blood count recovered but the creatinine and CRP started to rise, reaching a peak of 337umol/l five days later. This was initially attributed to dehydration, aminoglycoside toxicity and contrast nephrotoxicity. Dialysis was considered but the patient then responded dramatically to the introduction of intravenous dexamethasone 10mg BD on day 20 without the need for discontinuation of ATRA. The Acute Renal Failure (ARF) was attributed in retrospect to the Retinoic Acid Syndrome (RAS). The patient achieved molecular remission after the final consolidation cycle and is now on maintenance.

Discussion

The incidence of the RAS is 15% (6-27%) [3]. Differences in prophylactic measures account in part for the variable incidences among series. The pathophysiology is poorly understood but there are likely to be changes in the cytokine secretion and adhesive qualities of the APL cells during ATRA induced differentiation. Organ infiltration by APL cells suggests that ATRA induces APL cells to acquire leukaemia cell- endothelial cell adhesion followed by extravascular extravasation [4].

ATRA syndrome is defined by the presence of unexplained
fever (81%), weight gain (50%), respiratory distress (89%), interstitial pulmonary infiltrates (81%) and pleural (47%) or pericardial effusions (19%) with or without leucocytosis [3]. No single sign or symptom is considered diagnostic of the syndrome. Because the diagnosis of RAS is purely clinical, it may be difficult to distinguish from other complications of the disease, particularly sepsis.

Renal failure has been documented in 39% of cases in retinoic syndrome [3] in conjunction with the other more common manifestations, 3-5% requiring dialysis and a mortality of 5-20%. In another series [5], the incidence of both RAS and ARF were increased with 20.7% of patients requiring dialysis and a higher mortality of 37.9%. This was attributed to late diagnosis with treatment being started 14 days after onset of ATRA as compared to day 7 in the previous series. Isolated renal failure is very rare [6] and is due to extensive infiltration by the leukaemia cells.

In our case, the isolated ARF due to the RAS in a case of therapy-related APL responded completely to the introduction of dexamethasone without the need for dialysis even though the diagnosis and initiation of treatment were so delayed.

References