Severe Aplastic Anemia Manifesting After Complete Remission of Acute Promyelocytic Leukemia: Is it a Fortuitous Association?

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Abstract Acute leukemia, secondary myelodysplasia and paroxysmal nocturnal hemoglobinuria evolving from severe aplastic anemia (AA) following immunosuppressive therapy are well recognized. However, severe AA occurring after complete remission of acute promyelocytic leukemia (APL) has been documented only once in 2009. We report a case of 30-year-old male diagnosed with APL who achieved complete cytogenetic remission with all-*trans* retinoic acid based induction regimen and developed severe AA few months later during maintenance therapy.

Keywords Acute promyelocytic leukemia · Severe aplastic anemia · ATRA

Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) that harbors a unique balanced reciprocal translocation between chromosomes 15

and 17 resulting in the generation of promyelocytic leukemia (PML)-retinoic acid receptor alpha (RAR α) fusion gene [1]. Untreated, it runs a fatal course of only weeks, with most succumbing to severe hemorrhagic diathesis. The introduction of all-*trans* retinoic acid (ATRA) in the frontline treatment has revolutionized the management of APL with dramatic improvement in complete remission rate and overall survival [2].

Aplastic anemia (AA) is a clinical syndrome characterized by peripheral pancytopenia and a hypocellular marrow [3]. Acute leukemia, secondary myelodysplastic syndrome (MDS), and paroxysmal nocturnal hemoglobinuria (PNH) frequently evolve from severe aplastic anemia following immunosuppressive therapy [4].

Pham and colleagues in 2009 [5] reported the first, and to the best of our knowledge only case of severe AA occurring few months after completion of ATRA based APL chemotherapy.

We report a case of 30-year-old male diagnosed with APL who achieved complete cytogenetic remission with ATRA based induction regimen and developed severe AA few months later during maintenance therapy.

Case History

A 30-year-old male with history of fatigue, fever, and breathlessness and peripheral pancytopenia was diagnosed with acute promyelocytic leukemia–hypergranular variant, 7 months ago (Fig. 1a, b, c). Fluorescence in situ hybridization (FISH) analysis of the bone marrow cells at the time of diagnosis demonstrated PML/RAR α fusion signal in 96 % cells (Fig. 1d). He was started on an induction regimen comprising of ATRA and daunorubicin. On completion of 3 months of induction therapy, bone marrow

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Fig. 1 Acute promyelocytic leukemia: accumulation of leukemic promyelocytes **a** Bone marrow aspiration (Leishman stain $\times 1000$; *inset* shows intense positivity of leukemic promyelocytes with myeloperoxidase stain, $\times 1000$); **b and c** Bone marrow trephine biopsy (H and E $\times 40$ and H and E $\times 400$ respectively); **d** Fluorescence in situ hybridization analysis detected PML/RAR α fusion signal in 96 % leukemic promyelocytes

quantitative PML/RAR α translocation assay by real time PCR revealed complete remission (CR). He underwent 2 months of consolidation treatment employing ATRA, daunorubicin and mitoxantrone and subsequently put on maintenance therapy with ATRA, 6-mercaptopurine (6-MP) and methotrexate. The patient felt reasonably well and had normal peripheral blood counts.

Two months into his maintenance therapy, he presented back with fatigue and dyspnea. His peripheral blood examination revealed pancytopenia with a white blood cell (WBC) count of $1.1 \times 10^9/L$, hemoglobin of 8 g/dL, platelet count of $40 \times 10^9/L$, and reticulocyte count of less than 1 %. His physical examination was unremarkable for any organomegaly or lymphadenopathy. A relapse of AML was a concern and a bone marrow examination was once again sought. Bone marrow biopsy, however, revealed marked hypoplasia (Fig. 2). There was no evidence of promyelocytes or myelodysplasia. PCR of the bone marrow cells also came back negative for PML/RAR α . A normal serum vitamin B12 and folic acid level excluded the more common nutritional cause of pancytopenia. Coombs test and a host of serological tests for various infectious etiology, notably human immunodeficiency virus (HIV), hepatitis B virus surface antigen, hepatitis C virus, WIDAL, VDRL, dengue IgG and IgM, parvovirus IgG and IgM came back negative. Liver function tests, renal function tests and thyroid function tests were within normal limits. Meanwhile, his clinical condition

Fig. 2 Aplastic anemia, bone marrow trephine biopsy (H and E $\times 40$)

deteriorated and he developed severe bleeding manifestation. The peripheral blood counts continued to drop and the patient received multiple blood and platelet transfusions. The WBC count decreased to $0.2 \times 10^9/L$, hemoglobin dropped to 7.5 g/dL, and platelets fell to $6 \times 10^9/L$. A repeat trephine biopsy once again demonstrated markedly hypoplastic marrow. These findings fulfilled the diagnostic criteria of severe AA [6]. A cytogenetic analysis was

warranted to rule out therapy related hypoplastic MDS. Also assay of the drug metabolizing enzyme, namely thiopurine S-methyltransferase (TPMT) metabolizing 6-MP, was desired to exclude possible drug induced myelosuppression. However neither could be performed as the patient rapidly deteriorated despite supportive treatment and finally succumbed to severe hemorrhagic diathesis 7 months after the initial diagnosis of APL.

Discussion

Hillestad is credited with the first description of APL as a distinct clinical entity in 1957 who observed it to be the most malignant form of acute leukemia. It is a morphologically unique subtype of AML that is classified as AML M3 by the old French–American–British (FAB) system and APL with $t(15;17)(q22;q21)$ by the World Health Organization (WHO) [1]. The resultant PML/RAR α fusion protein inhibits differentiation at the promyelocyte stage [7]. Other rare translocations observed in less than 2 % of APL cases include $t(11;17)(q23;q21)$, $t(5;17)(q35;q21)$ and $t(11;17)(q13;q21)$ [1, 7]. APL has two morphologic variants: a hypergranular variant found in 75 % of cases and a less frequent microgranular variant. Clinically, most patients of APL present with severe coagulopathy ascribed to disseminated intravascular coagulation (DIC) and hyperfibrinolysis [7]. The introduction of ATRA in 1985 has become a paradigm of molecular targeted therapy and transformed a once highly fatal disease to the most curable subtype of adult AML. Evidences from several randomized clinical trials indicate that maximal improvement in the CR rate, disease free and overall survival is obtained from a combination of ATRA plus cytotoxic chemotherapy [1, 2]. A similar treatment strategy was employed in our patient.

AA is a non-malignant hematopoietic disorder characterized by peripheral blood pancytopenia and a hypocellular bone marrow [6]. It can result from either inherited or acquired causes. Fanconi anemia, dyskeratosis congenita, Diamond–Blackfan syndrome, and amegakaryocytic thrombocytopenia are the four major inherited causes of AA [8]. Acquired AA is now increasingly being recognized as an immune-mediated disorder. Environmental exposure to chemicals and drugs or viral infections may be the antigenic determinants driving the pathologic immune response. The immune-mediated stem cell destruction may perhaps also be triggered by endogenous antigens generated by genetically altered bone marrow cells [6]. The usual causes of acquired AA were ruled out in our patient by an exhaustive panel of investigations.

Hypoplastic MDS, which presents with pancytopenia and features a hypocellular marrow, may mimic AA. Subtle dysplastic morphologic features and abnormal

cytogenetics help distinguish between hypoplastic MDS and severe AA [6]. But in 20 % of MDS cases, chromosome testing may have normal results or be unsuccessful because of low number of cells [9]. Moreover, therapy related MDS (t-MDS) is a long-term complication in APL. Separate studies by Lobe et al. and Singh et al. [10, 11] reported average latency period of 46.5 and 62 months from onset of therapy for the primary hematological malignancy to the development of t-MDS respectively. Our patient manifested with severe marrow hypoplasia only 7 months after the diagnosis and initiation of APL treatment arguing against a possible diagnosis of t-MDS.

The 6-MP metabolizing enzyme TPMT exhibits genetic polymorphism stemming from single nucleotide polymorphisms (SNPs) in the TPMT gene located on chromosome 6p22.3. However, TPMT SNPs fails to explain all myelosuppressive events and, therefore, TPMT measurements may supplement but not substitute continued monitoring of blood counts in 6-MP treated patients [12]. Moreover, Nabhan and Radhakrishnan, [13] in their review article emphasized the fact that no published literature exists till date implicating 6-MP or methotrexate in causing severe AA even when these agents were employed for therapy of other disorders. Also Latagliata and co-authors in their report of five cases of t-MDS-AML following APL treatment in a cohort of 77 patients who achieved CR, suggested that APL treatment is not relevant in inducing the onset of secondary non-hematological malignancies [14].

Dameshek, [15] way back in 1967, postulated a hypothesis indicating a commonality between AA, PNH and “hypoplastic” leukemia. The evolution of other clonal disorders such as PNH, MDS and AML in AA patients treated with immunosuppressive therapy has since been well recognized [3, 4, 6]. Similarly secondary MDS or AML developing following treatment of APL is also documented in the literature [10, 14]. A primary insult to the bone marrow could simultaneously lead to several abnormal hematopoietic cell clones, with one dominating and others present below the threshold of detection. Brodsky and Jones [4] termed this phenomenon ‘field leukemogenic effect’. Disease specific targeted therapy is ineffective in suppressing the other abnormal clones allowing them to expand and become detectable.

Pham and colleagues, in 2009, reported the first case of a 32-year-old male who underwent treatment for APL and developed AA 7 months after completion of maintenance chemotherapy. He made a complete recovery following successful matched sibling allogeneic stem cell transplantation [5]. In the review article by Nabhan and Radhakrishnan [13] on the same case described by Pham and colleagues, the author duo raised the question as to whether the secondary AA is possibly attributable to APL treatment regimen, or whether the patient to begin with harbored both

APL and AA clone with AA surfacing following successful treatment of APL. Nissen and Stern [16] put forth an interesting theory in which they proposed that acquired AA in patients with hematological malignancies could be consequent to collateral damage to adjacent normal hematopoietic tissue by the ongoing anti-tumor immune reaction.

A similar dilemma occurred in explaining the pathophysiology of severe AA manifesting in our patient during the maintenance therapy of APL after successful cytogenetic remission. He could either have been an unfortunate victim of the Dameshek riddle or the APL treatment regimen may have influenced the secondary AA. Regardless, more studies are required to further elucidate the pathophysiology of AA following APL therapy.

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