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Case Report

Chronic myelomonocytic leukemia-1 in a post-renal transplant patient

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ABSTRACT

Azathioprine is a commonly used immunosuppressive agent in renal transplantation. Thiopurine therapy is associated with an increased risk of solid organ malignancies after renal transplantation. There are few reported cases of azathioprine therapy-related myelodysplastic syndrome/acute myeloid leukemia. We describe a case of post-renal transplant patients developing chronic myelomonocytic leukemia-1 associated with monosomy of chromosome 7, possibly related to prolonged exposure of azathioprine.

Keywords: Post-renal transplant, Chronic myelomonocytic leukemia-1, Azathioprine, Monosomy 7

INTRODUCTION

Solid organ transplant recipients have elevated cancer risks, due in part to pharmacologic immunosuppression.[1] Renal transplant is the most common solid transplant worldwide. Management of post-transplant patients entails a thorough understanding of chronic immune suppression and related complications, including secondary malignancies. For most common tumors, for example, colon, lung, prostate, stomach, esophagus, pancreas, ovary, and breast cancer rates are roughly twofold higher after kidney transplantation compared with the general population. Melanoma, leukemia, hepatobiliary tumors, cervical, and vulvovaginal tumors are each approximately five-fold more common. The risk of testicular and bladder cancers increases to approximately threefold, while kidney cancer is approximately 15-fold more common.[2] With increased longevity of renal transplant patients, acute leukemias and myelodysplastic syndromes (MDS) are also becoming more prevalent.[3] Retrospective solid organ transplant data analysis suggests seven-fold and 5-fold increase in the incidence of MDS and acute leukemia, respectively.[3,4]

MDS are a group of neoplastic stem cell disorder characterized by bone marrow (BM) failure with a tendency to progress to acute myeloid leukemia (AML). Chronic myelomonocytic leukemia (CMML) is an indolent rare disease in the category of myelodysplastic and myeloproliferative neoplasms (MDS), which can often evolve into acute leukemic neoplasms in high-risk patients.[5] MDS/myeloproliferative disorders (MPDs) including CMML can occur *de novo* or because of exposure to therapy (tMDS/tCMML). Very few cases of tCMML have been reported in post-solid organ transplant patients.

We report a case of post-renal transplant patients developing tCMML-1 associated with monosomy of chromosome 7, possibly related to prolonged exposure of azathioprine.

CASE REPORT

The patient, a 45-years-old gentleman, was evaluated at nephrology institute in February 2009 for end-stage renal disease due to diabetic nephropathy requiring hemodialysis. He had a history of uncontrolled diabetes for 7 years, diabetic retinopathy and hypertension for 2 years. He subsequently underwent a spousal renal transplant uneventfully on April 17, 2009. He received interleukin-2 receptors blocker (Inj Daclizumab) as induction agent and cyclosporine, azathioprine, and prednisolone for maintenance therapy. Post-transplantation he had good graft function. He remained in good health until 2016 when the patient started developing intermittent low-grade fever. Hemogram done in August 2016 was suggestive of mild leukocytosis and monocytosis. In January 2017, the patient developed febrile neutropenia; immunosuppression was stopped and treated with antibiotics and growth factors. Immunosuppressive medications were restored on recovery of the leukopenia. In November 2017, the patient developed the acute coronary syndrome, requiring percutaneous transluminal coronary angioplasty with drug eluting stent and antiplatelet medications aspirin and clopidogrel were started. Since November 2017 patient developed worsening bicytopenia (anemia and thrombocytopenia) with monocytosis and was referred for hematological evaluation.

On physical examination, the patient had pallor, ecchymotic patches over the skin and mild hepatosplenomegaly.

Blood investigations were as follows: White blood cell was 9.6 × 10^9/L, hemoglobin of 4.6 mmol/L, and platelet level of 168 × 10^9 6 mmol/L. The differential on the complete blood count revealed a monocytic hyperproliferation at 25% with (5%) promonocytes, (20%) lymphocytes, (5%) blast cells, and (45%) segmented neutrophils. Peripheral smear examination was suggestive of anisopoikilocytosis, macroovalocytosis, dysmyelopoiesis, dysmyelopoiesis, and reduced thrombocytes.

BM aspiration was hypercellular with overall cellularity of 50–55%, with M:E ratio of 2.2:1, differential counts were suggestive of monocytes 15%, promonocytes 12%, blast 07%. Dyserythropoiesis and dysmyelopoiesis are shown in Figure 1. BM biopsy revealed infiltration by atypical cells which were large, having vesicular nuclei with prominent nucleoli in many of them with moderate to abundant cytoplasm [Figure 2].

BM flow cytometry was as follows: About 21.3% monocytic cells with partial dim CD56 expression, 7.6% myeloid blasts, 0.1% mature b-lymphoid cells, and 5.2% mature t-lymphoid cells with rest of the cells being maturing myelocytes.

Fluorescence *in situ* hybridization (FISH): Monosomy 7 was observed in 90% cells [Figure 3]. Monosomy 5, chromosome

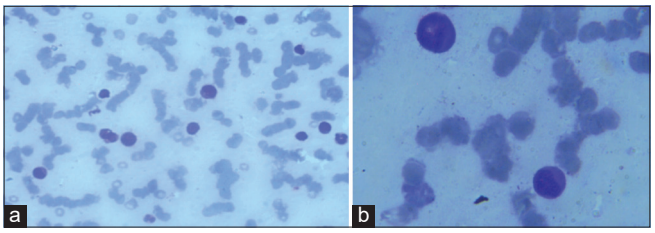

Figure 1: (a) Bone marrow aspiration ×400 (b) bone marrow aspiration ×1000.

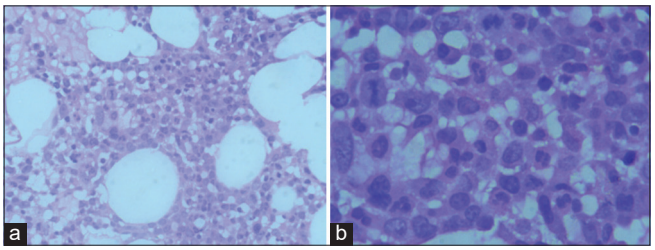

Figure 2: (a) Bone marrow biopsy ×400 (b) bone marrow biopsy ×1000.

8 abnormality, Del 20, *BCR/ABL1*, *FIP1L1-PDGFRA,* and *ETV6/PDGFRB* translocations were negative.

CMML was diagnosed based on the peripheral monocyte proliferation >1 × 10^9/L documented for 3 months, <20% blasts, and BM pathological findings consistent with both myeloproliferative and dysplastic features. The absence of Philadelphia chromosome and of a PDGFRA rearrangement on FISH along with clonal cytogenetic abnormality of Monosomy 7 in the bone marrow confirms the diagnosis of CMML.

The patient was treated with azacitidine and supportive care. He received two cycles of azacitidine. The clinical course was complicated with febrile neutropenia, transfusion dependence, labile hyperglycemia, and worsening of renal function. After the second cycle of chemotherapy, patient developed lower respiratory tract infection and succumbed to acute respiratory distress syndrome.

DISCUSSION

CMML is a rare disease. As per the WHO classification, CMML is classified under the category of myelodysplastic/MPD (MDS/MPD).[5] MDS/MPDs, including CMML, can occur de novo or as a result of exposure to therapy. tMDS/AML have been reported after exposure to alkylating agents, topoisomerase II inhibitors and radiation therapy.[6] These chemotherapy agents and radiation therapy are conventionally used to treat a variety of primary malignancies such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute leukemia, sarcoma, breast, ovarian, and testicular cancers. The median time to develop tMDS/AML is 3–5 years. However, the incidence of secondary malignancies

after exposure to anti-metabolite has not been well defined. Azathioprine is a purine anti-metabolite which is used for immune-suppression in post-solid organ transplant and autoimmune disorders including rheumatoid arthritis, multiple sclerosis, lupus nephritis, inflammatory bowel disease, and chronic refractory immune thrombocytopenia. These patients are usually treated with azathioprine for a long duration. Usual side effect of the medication is BM suppression with opportunistic infection. However, the incidence of secondary malignancies has not been well defined after prolonged use of azathioprine.[7] It has been estimated that 1 in 300 individuals has a very low thiopurine s-methyltransferase (TPMT) activity, and individuals with a low TPMT activity may be at an increased risk of thiopurine toxicity and an association with the development of t-MDS–AML.[8]

Two major mechanisms of the development of malignancies in solid organ transplant recipients have been described. One involves the direct tumorigenic effect of the currently used immunosuppressive regimen and the second is based on the diminished immunologic surveillance secondary to the suppressed T- and B-cell mediated immunologic response. DNA damaging therapies, such as azathioprine and mycophenolic acid directly interfere with DNA synthesis and select for cells with mutated p53, a tumor suppressor gene involved in cell growth control and DNA repair.

Our patient underwent a renal transplant and received azathioprine for the past 8 years. There were no rejection episodes, but unfortunately developed myeloid neoplasm with cytogenetic abnormalities.

Confavreux *et al*. reported a case–control study to assess the long-term risk of neoplasia in azathioprine treated multiple sclerosis patients using Lyon Multiple Sclerosis database.[7] Out of 1191 patients analyzed, four patients developed hematological malignancies with total increased risk cancers of 2 (95% confidence interval, 0.4–9.1) with the treatment of 5–10 years of azathioprine.

Knipp *et al*. have described a case series of 14 patients developing tMDS after prolonged exposure of azathioprine.[9] Out of these 14 patients, 2 developed CMML with chromosome 7 abnormality and both succumbed to the disease. Their data suggested a 100 fold increase risk of MDS in patients after prolonged use of azathioprine compared to the general population. Even short-duration exposure also increased the risk of secondary malignancies. Both of these CMML cases were associated with chromosome 7 abnormalities and had a poor outcome.

Therapy-related MDS/AML is generally divided into two types. Type I t-MDS, which is related to alkylating agents, occurs years after exposure with a latency period of several years. Monosomy 5 or 7 is the characteristics of this type. Type II t-MDS is associated with topoisomerase II agents and occurs earlier after exposure with no latency period. The 11q23 cytogenetic abnormality is the characteristic abnormality seen in Type II t-MDS.[10] Interestingly, in t-MDS or t-AML, the abnormalities 5q−/−5 and 7q−/−7 are closely related to previous therapy with alkylating agents.[10,11] Total of eight alternative genetic pathways have been proposed in t-MDS and t-AML.[12] Pathway I comprises patients with 7q−/−7 but normal chromosomes 5 and without balanced aberrations. They frequently have point mutations of *AML1* which are significantly associated with subsequent progression to overt t-AML.[13] Other candidate genes postulated are asparagine synthetase gene in 7q21.3-q22.1; acetylcholinesterase, erythropoietin, and PLANH1 (plasminogen activator inhibitor 1) in 7q22 and MET in 7q31.2–31.3.[14,15] These mutations are associated with high-risk tMDS/AML.

Overall tMDS/AML have a poor prognosis with dismal outcome in part due to high-risk mutations also underlying medical conditions pose a significant challenge. Our patient had multiple comorbidities including labile diabetes and ischemic heart disease. These comorbidities become an important confounding factor in overall survival outcomes of tMDS/AML patients. Our patient, unfortunately, succumbed to LRTI with multi-organ dysfunction post 2nd cycle of azacytidine.

In summary, in post-solid organ transplant therapy-related hematological malignancies are less common but a recognizable entity. Close follow-up of hematological parameters is essential for diagnosis and treatment, which at times get confounded by associated BM suppression due to immunosuppressive therapy. Antimetabolites have been shown to increase the risk of malignancies and judicious use is imperative.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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