Case Report

A Teenager of Myelodysplastic Syndrome with Fibrosis and Monosomy 7

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Abstract: Extensive fibrosis in myelodysplastic syndromes (MDS) is relatively infrequent and associated with worst prognosis. It has been classified as a specific entity by WHO. Moreover, the incidence and prevalence of Myelodysplastic Syndromes in children and adolescents is very low. Herein, we report a case of a 17 years old boy diagnosed as myelodysplastic syndrome with fibrosis along with monosomy 7. Data pertaining relationship between myelodysplastic syndrome with fibrosis and karyotype abnormalities is relatively sparse. This case report will assist in considering better risk adapted therapies.

Keywords: Myelodysplastic syndrome with fibrosis, Monosomy 7, Immunohistochemistry, Fluorescence *in situ* Hybridization (FISH), Acute myeloid leukemia, HIV.

INTRODUCTION

Myelodysplastic syndromes (MDS) are composite groups of clonal disorders represented by peripheral blood cytopenias consequential to ineffective and dysplastic hematopoiesis with predisposition to evolve into acute myeloid leukemia (AML) [1] in upto 30% of patients [2]. In contrast to adulthood, MDS in childhood is seldom seen, constituting 4% of all hematological malignancies with an incidence of 1.8 per one million children per year in the 0-14 year age group [3]. In young adults, it is also rarely reported with worse prognostic implication and majority of the cases being associated with pancytopenia instead of only anemia as in adults. Most of the time, myelodysplastic syndromes are associated with hypercellular bone marrow but in young adolescents, majority of the cases are reported as hypocellular [4].

Myelofibrosis, on the other hand is bone marrow disorder in which the marrow is replaced by fibrous scar tissue. Numerous benign diseases are related to this condition such as infections including HIV and tuberculosis, osteopetrosis, primary and secondary hyperparathyroidism, autoimmune disorders and certain drugs. Many oncological conditions are also strongly associated with marrow fibrosis such as primary myelofibrosis, post polycythemia or essential thrombocythemia myelofibrosis, chronic myelogenous leukemia, chronic myelomonocytic leukemia, acute leukemia, hairy cell leukemia and metastatic carcinomas [5]. Myelofibrosis is generally related with defects in function or number of platelets and megakaryocytes.

Hyperfibrotic MDS or MDS with myelofibrosis is rare [6] and is about 10-15% of all MDS, and are categorized as MDS with fibrosis according to WHO classification of haematopoietic

and lymphoid neoplasms 2017 (Revised). These cases usually have advancing clinical course independent of percentage of blast counts. The morphological knowledge from bone marrow aspiration is mostly insufficient and is complemented by histological data and immunohistochemical staining [7]. Unlike Myeloproliferative neoplasms, MDS with fibrosis is not usually associated with splenomegaly and leucoerythroblastosis and usually has dysplastic megakaryocytic morphology especially micromegakaryocytes [8].

CASE PRESENTATION

We, herein, describe a case of 17 years old boy with no significant past medical or surgical history, presented with generalized weakness, dizziness, shortness of breath and fever for 2-3 months. Examination revealed no visceromegaly or lymphadenopathy. Initial workup was done that showed pancytopenia on complete blood count with Hb of 8.1g/dl, MCV of 95.5 fl, MCH of 30.7pg and MCHC 32.1g/dl. White blood cell count (WBC) was $3.9 \times 10^9/L$ with ANC of $1.5 \times 10^9/L$ and platelet count of $21 \times 10^9/L$. Peripheral film showed dysplastic neutrophils with 03% blast cells and marked platelet anisocytosis as shown in Figs. (1, 2). Biochemical studies were normal, viral serology was negative. Ultrasound abdomen showed no abnormal findings. Bone marrow aspirate and trephine biopsy was performed. Aspirate was hemodiluted (Fig. 3) with occasional blast cells. Trephine biopsy was cellular (80% cellularity) with marked megakaryocytic hyperplasia and features of dysmegakaryopoiesis, like monolobation and hypolobation. Micromegakaryocytes were also identified on trephine biopsy sections (Fig. 4). Trephine biopsy also revealed markedly increased fibrotic activity that was causing streaming of cells and distortion of morphology. Reticulin stain showed MF-2 fibrosis (Fig. 5). Immunohistochemistry was performed that showed CD34 positivity in around 3% of cells while CD61 was positive in megakaryocytes and micromegakaryocytes (Fig. 6). Sample for bone marrow karyotyping was taken twice but could not be performed due to

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culture failure. On FISH analysis, monosomy 7 was identified in 18% of the cells. Deletion 5q was also sent which was negative. According to IPSS-R, our patient was high risk. Such patients have median overall survival of around 1.6 years and increased chance to convert to AML.

Fig. (1). Peripheral Film Showing Platelet Anisocytosis and Clumping.

Fig. (2). Peripheral Film Showing Dysplastic Neutrophil.

Fig. (3). Trephine Biopsy Section Exhibiting Megakaryocytic Proliferation and Dysplasia.

Fig. (4). Reticulin Stain Showing Extensive Fibrosis.

Fig. (5). CD61 Immunohistochemistry on Trephine Biopsy Section.

Fig. (6). CD34 Immunohistochemistry on Trephine Biopsy Section.

At present, our patient is planned for treatment by hypomethylating agents followed by bone marrow transplant by HLA matched donor. Good supportive care in the form of blood product transfusion and antibiotic prophylaxis is also being instituted.

DISCUSSION

Myelodysplastic syndrome is a rare entity and is generally considered as a disease of elderly. Though uncommon in young patients, MDS has been affiliated with overall poor

prognosis and decreased overall survival rates. Myelofibrosis (reticulin/collagen) can occur in huge variety of malignant and non-malignant conditions of the bone marrow, including MDS [9]. Patients having MDS-F (Myelodysplastic syndrome with fibrosis) has generally poorer outcome than those having little or no fibrosis [10, 11]; however, this is also questionable and requires more data analysis [12, 13]. A large retrospective study of 352 MDS patients showed a median survival of 9.6 months in patients with fibrosis and 17.4 months in those without fibrosis [10]. Reticulin fibrosis is often revocable after therapy however, collagen fibrosis is less likely to be reshaped by treatment. Classical data implied that bone marrow fibrosis modify hematopoietic reconstitution after allogeneic stem cell transplantation. Increased graft failure, delayed neutrophil engraftment and increased risk of relapse were all associated with fibrosis after allogeneic stem cell transplantation [14].

Karyotypic abnormalities have been associated with diagnostic and prognostic significance of Myelodysplastic syndrome from previous times. Globally, less than 50% of MDS patients display an aberrant karyotype, of which del (5q) is the most common cytogenetic abnormality displaying in 10 to 20% of adult MDS patients [15]. However, loss of chromosome 7 is the most common cytogenetic aberration in pediatric population accounting for around 10-15% of cases. MDS with monosomy 7 has poor outcome, while isolated del (7q) has a better prognosis comparatively [16]. Monosomy 7 has also been associated with familial myelodysplastic syndrome and GATA 2 mutations and has high propensity to transform to AML. Such patients mostly carry ASXL-1 mutations [17]. Therefore, in young patients, genetic analysis should be performed in routine in order to diagnose, prognosticate and plan treatment accordingly. Myelodysplastic syndrome with fibrosis has not been linked with any specific cytogenetic abnormality though some case reports mention different cytogenetic aberrations associated with poorer outcomes.

22 patients with myeloid malignancies and isochromosome 17q were associated with myelodysplastic and myeloproliferative features, including pseudo-Pelger-Huet-anomalies, micromegakaryocytes, hypercellularity, fibrosis, and osteosclerosis [18]. This study concluded that disorders with isolated isochromosome 17q represent a specific entity having myelodysplastic and myeloproliferative features, with increased chances of transformation to leukemia and presence of wild-type TP53 [19]. Though deletion 17p is much commoner in acute myeloid leukemia and myelodysplastic syndrome, isolated deletion 17q is a rare abnormality.

Treatment of such patients should be aggressive and majority of the studies emphasize on upfront allogeneic HLA matched stem cell transplantation which is the only alleviative option and is associated with better overall and disease free survival. To the best of our literature search, this is the first case of its kind reporting the presence of Myelodysplastic syndrome

along with fibrosis and presence of monosomy 7.

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CONFLICT OF INTEREST

Declared none.

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