Journal of Cancer Science & Therapy

Babak et al., J Cancer Sci Ther 2019, 11:7

Case Report Open Access

Refractory Isolated Thrombocytopenia with Trisomy 8

Abdolkarimi Babak[1]*, Karimi Mehran[2], Shahriari Mahdi[3], Mokhtari Maral[4] and Mardani Samira[3]

[1]Department of Pediatrics, Division of Hematology/Oncology, Lorestan University of Medical Sciences Khoramabad, Iran
[2]Department of Pediatrics, Division of Hematology/Oncology, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Pathology, Shiraz University of Medical Sciences Shiraz, Iran

Abstract

Refractory isolated thrombocytopenia (RIT) is an uncommon variant of myelodysplastic syndrome (MDS) that initially presents as chronic pure thrombocytopenia. Because of the lack of distinguishable dysplasia, RIT has often been misdiagnosed as idiopathic thrombocytopenic purpura. We describe a patient with RIT and mosaic trisomy 8 for whom a bone marrow mononuclear cell (BMNC) culture was done for cytogenetic study. This patient exhibited a special pattern of MDS. We suggest that RIT be classified as a subtype of MDS on the basis of its specific molecular property.

Keywords: Thrombocytopenia; Trisomy 8; Myelodysplastic syndrome; Bone marrow; Cell blood counts

Introduction

Isolated thrombocytopenia is a relatively common finding on routine pediatric complete cell blood counts (CBC). The platelet count is usually >20 x 10^9/L and the patient almost asymptomatic. Sometimes this condition is persistent thrombocytopenia in children. The commonest etiology of isolated thrombocytopenia in children is immune thrombocytopenic purpura (ITP), that is a benign situation, but other causes such as congenital or acquired amegakaryocytic thrombocytopenia are adverse etiology.

If dysmegakaryopoiesis presents as an isolated cytopenia it is difficult to differentiate it morphologically from simple ITP, because ITP is diagnosed by exclusion of other diagnoses, and in many patients may be accompanied by megakaryocytic hyperplasia;On the other hand amegakaryocytic thrombocytopenia may be disarranged with ITP but attention to comorbidities with thrombocytopenia is a key full stop for differentiation and diagnosis.

Comorbidities of Isolated thrombocytopenia can also help to put into background potential security signals and ameliorate clinical trial design and planning. Refractory Isolated thrombocytopenia(RIT) despite being a rare disease, is associated with an extremely higher level of mortality risk as well as a vast list of comorbid medical conditions. Comprehension of Isolated thrombocytopenia comorbidities hopefully may assist in improved disease management of isolated thrombocytopenia patients.

Refractory isolated thrombocytopenia (RIT) is an uncommon subtype of myelodysplastic syndrome (MDS) that initially presents as chronic pure thrombocytopenia. Because of the absence of discernible dysplasia, RIT has often been misdiagnosed as ITP. We describe a RIT patient with mosaic trisomy 8 diagnosed on bone marrow mononuclear cell (BMNC) karyotype, which is a rare presentation of MDS patients [1].

However, this RIT patient exhibited an expression pattern distinct from that of other MDS patients. We enforce that RIT be classified as a subtype of MDS on the basis of its specific clinical-hematologic features and specific karyotype.

Case Presentation

A 22 months old female first noted the onset of a petechial rash in August 2014. Laboratory studies performed by her primary care physician revealed a marked thrombocytopenia with platelet count of 6000, a White Blood Cell(WBC) =5380, hemoglobin (Hgb) 10.5 gm/dl. She was treated with two days of IVIG with impression of ITP (1 g/kg per day for 2 days) without improvement in the platelet count. Due to response failure to IVIG bone marrow aspiration and biopsy was done for her.

The peripheral blood smear showed severely decreased platelet count, but neither large platelets nor gray platelets seen. Normal granulocytes cells, with no evidence of myelodysplasia or blast. A bone marrow biopsy showed a mild hypocellular marrow, with normal myelopoiesis and erythropoiesis with about 5% immature mononuclear cells; increased numbers of lymphocytes and mast cells, as well as reduced numbers of megakaryocytes were seen Figure 1. Flow cytometry

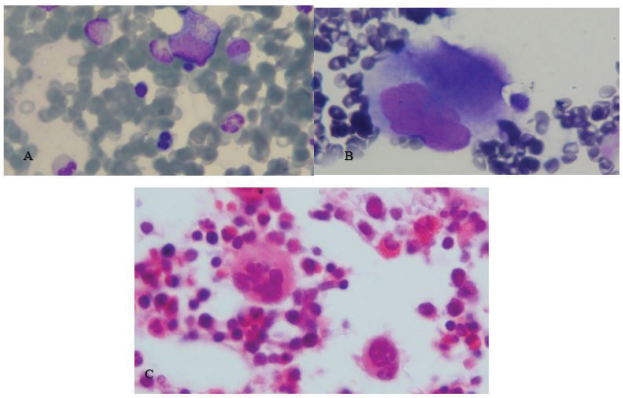

Figure 1: (A) Bone marrow aspiration shows dysplastic erythroid cell, Wright stain, oil immersion, **(B)** a dysplastic megakaryocyte, wright stain, oil immersion and **(C)** bone marrow biopsy show mild hypocellularity with dysplastic megakaryocytes, H&E stain, oil immersion.

***Corresponding author:** Abdolkarimi Babak, Assistant Professor, Department of Pediatrics, Division of Hematology/Oncology, Lorestan University of Medical Sciences, Khoramabad, Iran, Tel: +98-713632306; E-mail: b.abdolkarimi@yahoo.com

Received June 06, 2019; **Accepted** July 11, 2019; **Published** July 18, 2019

Citation: Babak A, Mehran K, Mahdi S, Maral M, Samira M (2019) Refractory Isolated Thrombocytopenia with Trisomy 8. J Cancer Sci Ther 11: 228-231.

Test	Value	Definition
Hb	9	g/dl
WBC	13800	mm^3
platelet	70000	mm^3
Retic count	1	%
D-Deimer	400	Unit*
PT	12	minutes
PTT	32	minutes
fibrinogen	300	mg/dl
LDH	3996	mg/dl
T. Bil	3.5	mg/dl
D. Bil	2.5	mg/dl
BUN	12	mg/dl
Creatinine	0.4	mg/dl
FDP(fibrin degradation product)	35	micrograms per milliliter (**mcg/ml)** **Normal Values:** The result is normally less than 10 micrograms per milliliter (mcg/mL).
Direct coombs	Negative	
Indirect coombs	Negative	
ANA(Antineutrophilic antibody)	Normal	
[1]Anti-SSA	Normal	
[2]Anti-RNP	Normal	
C3	0.4	C3 0.65 - 1.65 g/L;
C4	0.32	C4 0.16 – 0.60 g/L
CH50	350	** total level of the blood complement(CH50) should be 41 to 90 hemolytic units
Anti-DNA	Normal	
Haptoglubolin	70	**Normal Values: 27-139 mg/dL**
Cold agglutinin	Negative	
[3]p-ANCA	Normal	
[4]c-ANCA	Normal	
ESR	65	mm/hr
G6PD	Normal	
HBSAg	Negative	
Anti-HCV Ab	Negative	
Anti-HIV Ab	Negative	
EBV-VCA-IgM	Negative	
CMV-IgM	Negative	
Blood culture	Negative	
Serum B12	Normal	
Serum Folate	Normal	
Parvo virus B19	Negative	
EBV-VCA-IgM	Negative	
CMV-IgM	Negative	
Blood culture	Negative	
Serum ferritin	145	
CD55,CD59	Negative	
Ham test	Negative	

[1]Anti-SSA autoantibodies (also called anti-Ro, or the combination anti-SSA/Ro or anti Ro/SSA autoantibodies)
[2]Anti-Ribonucleoprotein 3,4. Anti-neutrophil cytoplasmic antibodies (ANCAs)
P: peripheral, C: core, * D- Dimer: In Conventional Units: ≤ 250 ng/mL D-dimer units (DDU); In SI Units: ≤ 0.50 mcg/mL fibrinogen equivalent units (FEU); ** CH50 Values % of Reference values Interpretation: <100(0-50%) Absent or low; 100-300(51 to 150%) Normal; >300 (>150%) High

Table 1: Paraclinical patient evaluation for MDS.

of the marrow aspirate failed to reveal any clonal lymphocytes or phenotypically abnormal cells in the myeloid or monocyte lineages.

A sonography of the abdomenopelvis was unrevealing with the exception of a mildly enlarged spleen. At that time because the history was compatible with an immune thrombocytopenia, high dose methylprednisolone (30 mg/kg day for 3 days) was started, but no response was seen during 4 weeks. Because of rarity of MDS in children prednisone 0.5 mg/kg every other day was started for endothelial stabilization and serum folate and B12 levels were checked. Then trial of B12 1000 microgram shots as 3 times in week for 1 week, then weekly for 1 months, then monthly plus folic acid 1 mg/day were started. Serum folate and B12 levels were reported to be normal. Patient had no significant improvement in her platelet count after 4 months. During

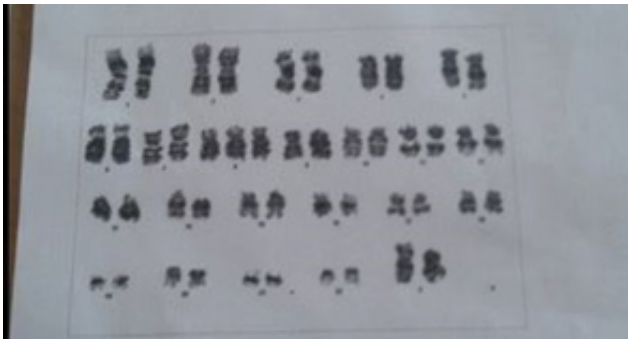

Figure 2: Bone marrow mononuclear cells cytogenetic study showed trisomy 8 in 10 of 25 metaphases (mosaic).

this time the patient received random donor platelet and sometimes single donor platelet because of many petechial and purpura during training of walking and running. Other work up for thrombocytopenia causes were negative (Table 1). Cytogenetic studies showed mosaic triosomy 8 (Figure 2).

Discussion

Myelodysplastic syndrome (MDS) compose a heterogeneous category of clonal stem cell disorders, characterized by ineffective hematopoiesis in one or more cell lineages, producing anemia, leukopenia, and thrombocytopenia. When evidences are insufficient, then diagnosis of MDS is difficult [2]. RIT is an unusual variant of MDS that initially presents as chronic pure thrombocytopenia. Because of the bereavement of discernible dysplasia, RIT has often been misdiagnosed as ITP [3]. Cytogenetic abnormalities have been detected in 40-60% of patients with de novo myelodysplastic syndrome (MDS). Some reports infer that Asian and Western MDS patients have different cytogenetic features [4]. Triosomy 8 like monosomy 7, is one of the most reiterated numerical aberration in MDS. Trisomy 8 is the most common numerical chromosomal abnormality in myelodysplastic syndromes (MDS).

Some MDS patients with triosomy 8 perhaps progress rapidly to acute leukaemia and have shorter survival [5]. Despite Monosomy 7, prognostic importance of trisomy 8 is controversial. Some reports have suggested that trisomy 8 should be categorized into poor risk cytogenetic group, but based on Revised International Prognostic Scoring System for Myelodysplastic Syndrome triosomy 8 is in intermediate risk group with median survival 26 months and median transformation time for AML 78 months [6].

MDS can be attendant with paraneoplastic syndromes related to autoimmune processes, particularly when MDS overlaps with myeloproliferative neoplasms (such as chronic myelomonocytic leukemia, often associated with splenomegaly). These may be dermatologic (psoriasis or Sweet's syndrome), rheumatologic (vasculitis, ulcerative colitis), pulmonary infiltrates, hematologic (hemolytic anemia or Glanzmann's thrombastenia), or endocrinologic disorders (hypothyroidism, diabetes insipidus).

Trisomy 8 captive in myelodysplastic syndromes is a risk factor for Behçet's syndrome, intestinal ulcers and thrombosis. Also this situation with all-trans-retinoic acid (ATRA), can develop to paroxysmal nocturnal hemoglobinuria (PNH) with normal karyotype. In our patient all of work up for such systemic disease were normal (Table 1) [7]. Trisomy 8 in MDS is oscillating, and this fluctuation was not related to the percentage of the blasts in the bone marrow or progression of disease. However, sometimes metaphase cells with trisomy 8 disappeared when their anemic state recovered [8].

Trisomy 8 aneuploidy is an early event in MDS. These small clonal populations could induce a cytotoxic T cell lymphocyte (CTL) response to trisomy 8 cells, therefore causes destruction of normal cells as bystanders and can present as cytopenia. The persistence of trisomy 8 cells, despite immune attack, would be attributed to their increased proliferation relative to normal cells, failure to fully undergo programmed cell death, or immune escape. If thrombocytopenia or bicytopenia was still present, suggests that the decrease in the number of BM cells with trisomy 8 reflects hematologic features in some MDS patients [9].

These findings indicate that trisomy 8 in our MDS patient was possibly not the primary event in the disease development, but maybe there is a racing between a normal karyotype clone and a trisomy-8-positive clone. Presence of a clone with trisomy 8 is not always a sign of disease progression or poor prognosis in MDS patients.

In contrast, in patients with monosomy 7 and 5q- syndrome, association of trisomy 8 with MDS has relatively better prognosis and it's a way for escaping from leukemia. Similar to Aplastic Anemia (AA), MDS can be successfully treated with cyclosporine (CsA) and antithymocyte globulin (ATG). De novo MDS with trisomy 8 paticularly often shows hematologic improvement after immunosuppressive therapy (IST). If a MDS patient develops AA, associated with trisomy 8 has relatively good prognosis, and cytopenias show sustained response to IST [10].

Therefore if we consider that our presented patient is a MDS patient, administration of CsA and ATG may be a chance for her before HSCT, but allogeneic HSCT, the only potentially curative approach to MDS. Unfortunately our patient has no HLA matched stem cell donor. At this time MDS diagnosis is base on morphologic findings or cytogenetic deletional or exess chromosomal abnormalities panel such as 3q-,-5,-7,-7q,+8,+9,-11q,-12p,18,+19,-20q,+21. In absence of morphologic criteria, MDS specific cytogenetic chromosomal abnormalities can be diagnostic.

Conclusion

We suggest that RIT be classified as a subtype of MDS on the basis of its characteristic clinical-hematologic features and specific molecular basis. Natural history for RIT with trisomy 8 is acute myeloblastic leukemia within 1-5 years; therefore this patients should be treated with allogenic HSCT as soon as possible after complete evaluation for occult systemic disease. In absence of morphologic criteria, MDS specific cytogenetic chromosomal abnormalities such as trisomy 8(+8) can be diagnostic.

References

1. Qian J, Xue Y, Pan J, Cen J, Wang W, et al. (2005) Refractory thrombocytopenia, an unusual myelodysplastic syndrome with an initial presentation mimicking idiopathic thrombocytopenic purpura. Int J Hematol 81: 142-147.
2. Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, et al. (2013) Diagnosis and treatment of primary myelodysplastic syndromes in adults: Recommendations from the European LeukemiaNet. Blood 122: 2943-2964.
3. Pozdnyakova O, Miron PM, Tang G, Walter O, Raza A, et al. (2008) Cytogenetic abnormalities in a series of 1,029 patients with primary myelodysplastic syndromes: A report from the US with a focus on some undefined single chromosomal abnormalities. Cancer 113: 3331-3340.
4. Paulsson K, Johansson B (2007) Trisomy 8 as the sole chromosomal aberration in acute myeloid leukemia and myelodysplastic syndromes. Pathol Biol 55: 37-48.

5. Bowles KM, Warner BA, Baglin TP (2006) Platelet mass has prognostic value in patients with myelodysplastic syndromes. Br J Haematol 135: 198-200.

6. Koguchi-Yoshioka H, Inokuma D, Kanda M, Kondo M, Kikuchi K, et al. (2014) Behçet's disease-like symptoms associated with myelodysplastic syndrome with trisomy 8: A case report and review of the literature. Acta Derm Venereol 94: 355-356.

7. Wang SA, Pozdnyakova O, Jorgensen JL, Medeiros LJ, Stachurski D, et al. (2009) Detection of paroxysmal nocturnal hemoglobinuria clones in patients with myelodysplastic syndromes and related bone marrow diseases, with emphasis on diagnostic pitfalls and caveats. Haematologica 94: 29-37.

8. Sugimori C, List AF, Epling-Burnette PK (2010) Immune dysregulation in myelodysplastic syndrome. Hematol Rep 2: e1.

9. Sloand EM, Mainwaring L, Fuhrer M, Ramkissoon S, Risitano AM, et al. (2005) Preferential suppression of trisomy 8 compared with normal hematopoietic cell growth by autologous lymphocytes in patients with trisomy 8 myelodysplastic syndrome. Blood 106: 841-851.

10. Olney HJ, Le Beau MM (2007) Evaluation of recurring cytogenetic abnormalities in the treatment of myelodysplastic syndromes. Leuk Res 31: 427-434.