Case Study

Transient monosomy 7 associated with bicytopenia in a 9-month-old boy: Report of a case and review of the literature

Guang Yang[1], Ross A. Rowsey[2], Jun Wang[1,*], Rhett P. Ketterling[2], and Ross Fisher[3]

[1]Department of Pathology and Laboratory Medicine, Loma Linda University Medical Center, Loma Linda, California; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; [3]Department of Pediatric Hematology Oncology, Loma Linda University Medical Center, Loma Linda, California, USA.

Abstract: Monosomy 7 or partial loss in the long arm of this chromosome is a recurrent nonrandom cytogenetic finding associated with a variety of hematological disorders. In the present case, a 9-month-old male presented with a febrile illness along with anemia and thrombocytopenia, and achieved spontaneous remission of the bicytopenia and monosomy 7 without any intervention 28 months after initial diagnosis. To our knowledge and literature search, this is likely the first case report of transient monosomy 7 in a patient with only bicytopenia. It is critical to closely monitor patients with monosomy 7 for evidence of spontaneous remission before proceeding to any major treatment.

Keywords: monosomy 7, bicytopenia, spontaneous remission, fluorescence in situ hybridization, karyotype

Introduction

Monosomy 7, the loss of whole chromosome 7, is associated with a variety of hematological disorders in pediatric patients, including myelodysplasias (MDS), acute myeloid leukemias (AML), and myeloproliferative disorders [1]. In 1964, the association between monosomy 7 and myeloid diseases was discussed for the first time [2]. Since then, many studies have revealed a clear association between chromosome 7 alterations, MDS and AML in children and adults, as well as less well-established association with lymphoid malignancies; these alterations of chromosome 7 include monosomy 7 and the partial deletion of the long arm of this chromosome [del(7q)] from bone marrow cells [3].

*Correspondence: Jun Wang MD, 11234 Anderson Street, Room 2151, Loma Linda, CA 92354, USA. Tel: (909) 558-4000 ext. 86001; Fax: (909) 558-0400; Email: JWang@llu.edu

Monosomy 7/del(7q) is by far the most common cytogenetic abnormality observed in children with both adult type MDS and juvenile myelomonocytic leukemia (JMML); it is also the most frequent abnormality of karyotype detected in the bone marrow of children and adults with therapy-related MDS (t-MDS) [4], and in patients during the evolution from aplastic anemia to MDS [5]. Besides a variety of myeloid disorders, monosomy 7/del(7q) are also associated with adult acute lymphoblastic leukemia (ALL), in which they frequently occur as secondary aberrations associated with a Philadelphia chromosome and predict a poor prognosis [6].

Although the overall prognosis for patients who develop hematological disorders associated with monosomy 7/del(7q) is poor, a small number of case reports describing spontaneous remission of hematologic disorders have been published in the literature [4, 7–11]. Here, we report a pediatric patient that

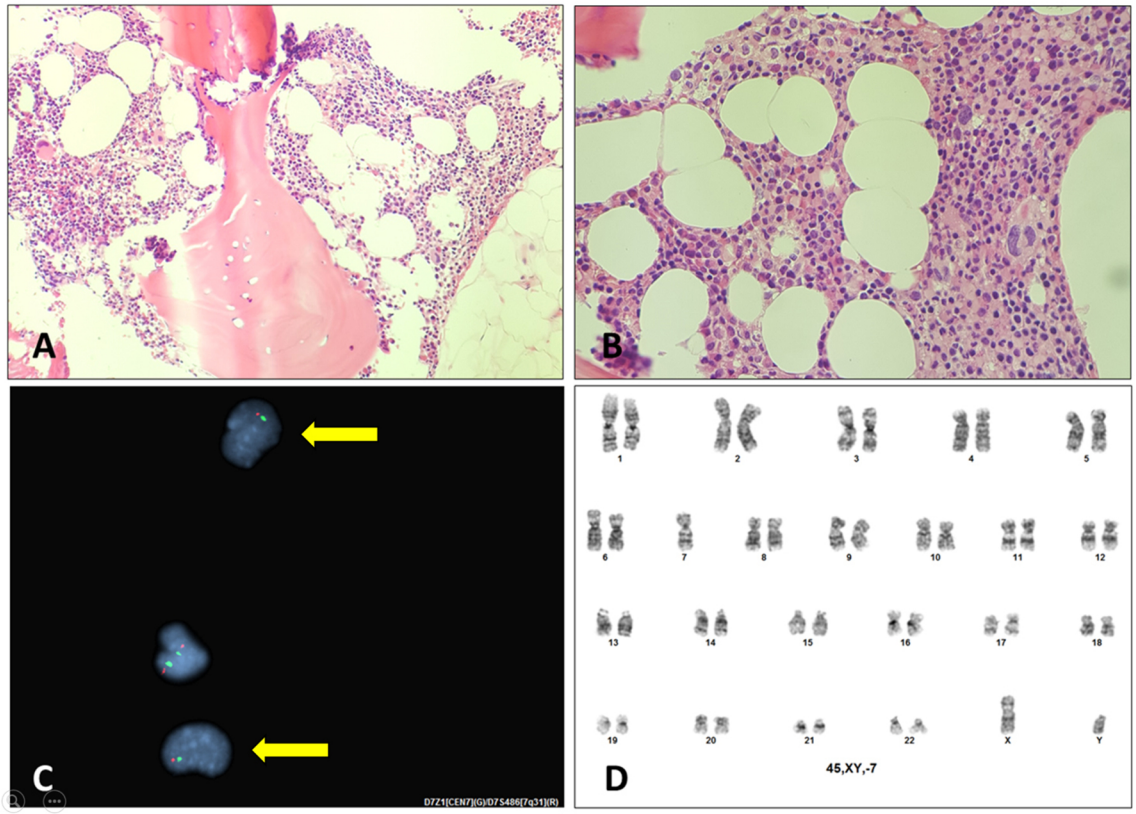

Figure 1: (A) Bone marrow biopsy showing normocellular to slightly hypocellular for age marrow (Hematoxylin and Eosin stain, magnification x100). (B) Bone marrow biopsy showing active trilineage hematopoiesis with no overt dysplasia (Hematoxylin and Eosin stain, magnification x400). (C) Monosomy 7 clone in FISH (yellow arrows) [chromosome 7 centromere in green, D7S486 (7q31) in red]. (D) Chromosome analysis of the patient's bone marrow revealing monosomy 7.

presented with only anemia and thrombocytopenia with monosomy 7 and achieved spontaneous remission without any intervention 28 months after initial diagnosis. The clinical features of these cases with spontaneous remission [4, 7–11], and the current study are summarized in Table 1.

After carefully searching the literature, we believe the present case is most likely the first example of transient monosomy 7 associated with only bicytopenia; it illustrates the importance of a period of close observation of these patients before proceeding to any major treatment such as hematopoietic stem cell transplant (HSCT).

Case Report

A 9-month-old male, previously healthy except for congenital heart murmur, presented to a community hospital after 2 weeks of intermittent fevers (maximum temperature 102 °F, axillary), non-bloody, non-bilious emesis, mucous-containing watery stools, dry cough, rhinorrhea, decreased appetite, increased fussiness and decreased activity level. According to the patient's mother, no signs of tachypnea, shortness of breath, wheezing, increased breathing difficulties, and no rashes or bruising were observed. Laboratory tests showed mild leukocytosis, anemia, thrombocytopenia and the patient was transferred

Table 1: Clinical Features of the Cases with Spontaneous Remission of Monosomy 7/del(7q)

Reference	Number of cases	Age	Gender	MDS	Duration of remission
4	4	8 months to 10.5 years	All male	2 cases with *de novo* MDS, 2 cases with therapy related MDS	14+ to 108+ months
7	1	3 years	Male	*de novo* MDS	30+ months
8	1	19 years	Female	therapy related MDS	Unknown
9	1	8 months	Female	*de novo* MDS	72+ months
10	1	13 months	Female	*de novo* MDS	Unknown
11	1	14 months	Male	Unknown	Unknown
Current study	1	9 months	Male	anemia and thrombocytopenia	14+ months

Note: MDS: Myelodysplastic Syndrome.

to Loma Linda University Medical Center for ruling out leukemia.

Upon admission, there was no hepatosplenomegaly or lymphadenopathy on physical examination. This patient's complete blood cell count (CBC) showed white blood cells (WBC) count of 17.32 x 10^9/L with a differential of 36% segmented neutrophils, 8% bands, 50% lymphocytes, 3% monocytes, 1% variant lymphocytes, 1% myelocytes, and 1% promyelocytes, red blood cells (RBC) count 3.14 x 10^{12}/L, reticulocyte percentage (Retic) 0.2%, hemoglobin (HGB) 8.8 g/dL, hematocrit (HCT) 25.8%, mean corpuscular volume (MCV) 82.2 fL/cell, mean corpuscular hemoglobin (MCH) 28.0 pg/cell, mean corpuscular hemoglobin concentration (MCHC) 34.1g/dL, red cell distribution width (RDW) 15.3%, and platelets (PLT) 47 x 10^9/L. The absolute neutrophil count (ANC) was 7.8 x 10^9/L. Other laboratory tests demonstrated a normal coagulation profile, metabolic profile, lactate dehydrogenase and uric acid as well as a negative result for blood culture except a positive respiratory viral nucleic acid test for Rhinovirus. His chest x-ray was unremarkable.

A bone marrow aspirate and biopsy revealed slightly hypocellular (~85% overall cellularity) for age with active trilineage hematopoiesis; morphologically, there was no overt dysplasia observed in myeloid, erythroid and megakaryocytic series with a myeloid to erythroid ratio of ~3:1 [Figure 1A & 1B]. Flow cytometry showed no evidence of aberrant antigen expression, acute leukemia, abnormal T cells, or monotypic B cells. Conventional cytogenetic analysis revealed monosomy 7 in 25% of metaphases examined (5 of 20), and fluorescence in situ hybridization (FISH) was done as confirmation, which showed monosomy 7 in 20.5% of nuclei [Figure 1C & 1D]. Parvovirus B19 IgG antibodies, instead of IgM, were found positive, which suggested past infection. The patient greatly improved after antibiotics treatment

Table 2: Hemoglobin, platelets, percentage of monosomy 7 by FISH and abnormal karyotype in chronological order

	Time after initial presentation (months)					
Tests	**0**	**1**	**4**	**9**	**15**	**28**
Hemoglobin (g/dL)	8.8	8.6	11.5	11.5	10.1	12.1
Platelet (10^9/L)	47	219	159	188	258	290
Monosomy 7 clone FISH (%)	20.5	24.5	13.0	6.5	5.5	1.5
Abnormal karyotype of 20 Cells (%)	5 (25)	4 (20)	6 (30)	1 (5)	0 (0)	0 (0)

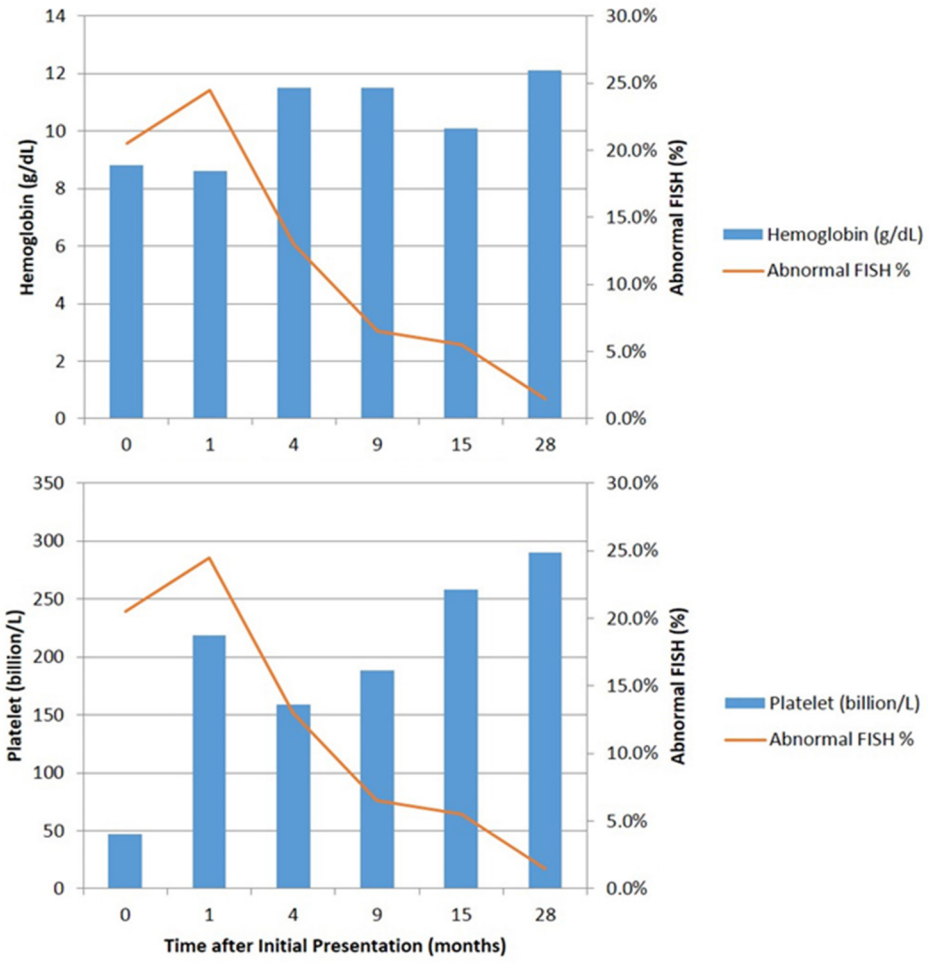

Figure 2: Correlations between hemoglobin levels, platelets levels and monosomy 7 clone FISH percentages.

and supportive measures.

About one month after this discharge, this boy was doing well with no further fevers; his CBC had improved with a leukocyte count of 12.24 x 10^9/L with 70.9% lymphocytes, an absolute neutrophil count of 7.8 x 10^9/L, mild anemia (RBC 3.26 x 10^{12}/L, HGB 8.6 g/dL), and normal PLT count of 219 x 10^9/L. A follow-up bone marrow examination revealed a normocellular marrow for age (~90-100% marrow cellularity) with trilineage hematopoiesis and mild megakaryocytic hyperplasia; flow cytometry was again negative. Cytogenetic studies still detected monosomy 7 in 20% of cells analyzed (4 of 20) and FISH detected monosomy 7 in 24.5% of interphase nuclei examined.

Three months later, this patient was asymptomatic with normal RBC (4.27 x 10^{12}/L) and HGB (11.5 g/dL), mild neutropenia (2.0 x 10^9/L, 16% of leukocytes) and mild lymphocytosis (9.5 x 10^9/L, 75% of leukocytes). Karyotyping still observed the -7 clone in 30% of the unstimulated bone marrow cells (6 of 20), and FISH detected an overall decrease in percentage of cells showing monosomy 7, to 13% (Table 2, Figure 2).

Since then, this boy continued to be doing well with a normal physical examination and stable

CBC except persistent mild lymphocytosis. Multiple follow-up bone marrow examinations revealed mildly hypocellular to normocellular marrow for age (~70-95% cellularity) with active trilineage hematopoiesis, and there was no overt dysplasia observed. Conventional cytogenetic studies showed continuously decreasing numbers of metaphases with monosomy 7, with 5% (1/20) detected at 9 months after the initial presentation, and none observed at 15 and 28 months after the initial presentation. Similarly, FISH revealed gradually decreasing percentages of monosomy 7 from 6.5%, 5.5% to 1.5% of scored nuclei (Table 1, Figure 2). On the last follow-up (approximately 30 months after initial presentation) his physical examination and CBC were normal.

Discussion

In the present case, the patient first presented with a febrile illness along with anemia and thrombocytopenia with only normocellular to slightly hypocellular for age bone marrow; FISH and conventional cytogenetic studies detected monosomy 7 in bone marrow cells. About 28 months after the initial presentation, spontaneous remission of bicytopenia and monosomy 7 was achieved. During his clinical course, the improvements of clinical signs, as well as of the HGB and PLT levels in the blood, are closely correlated to the declining monosomy 7 percentages of in the bone marrow [Figure 2]. Based on the bicytopenia and normocellular to slightly hypocellular bone marrow alone but without dysplastic changes, this patient might not meet the strict criteria for a diagnosis of classic MDS. However, when compared with adult MDS, bilineage cytopenias, hypocellular bone marrow and monosomy 7 are most commonly observed in pediatric MDS [12]. Therefore, we believe that this case may represent an early stage of MDS when the dysplastic changes are still subtle.

For pediatric patients, monosomy 7/del(7q) is the most frequent abnormality in myeloid disorders and it is also found in 30% of the MDS and in 4% of the AML. 90% of children with this anomaly are younger than 5 years, with a majority of those being males with monosomy 7 as the sole cytogenetic abnormality. In individuals older than 5 years, monosomy 7/del(7q) is more often associated with additional cytogenetic anomalies, and is more frequently seen in females [13]. Monosomy 7 and del(7q) occur in three general contexts: *de novo* MDS and AML; leukemia associated with a constitutional predisposition or with aplastic anemia; and therapy-related MDS or AML (t-MDS/t-AML) [14]. Although the association between monosomy 7/del(7q) and different hematological disorders is still not completely understood, it has been hypothesized that there is a tumor suppressor gene on chromosome arm 7q that contributes to the pathogenesis of these diseases, and several chromosomal bands have been identified that contain commonly deleted segments, including 7q22 and different non-overlapping regions in 7q31-q35 [15].

It is believed that MDS and AML arise after a susceptible immature hematopoietic cell acquires a sufficient number of genetic alterations and as such attains a growth advantage [4]. The mechanism behind the spontaneous resolution of the clinical signs and transient monosomy 7 can be explained by the fact that the aberrant clone was unable to maintain its proliferative advantage in vivo [4]. Based on this theory, two hypotheses were proposed: 1) the "second hit" hypothesis: the majority of leukemic clones are believed to contain multiple genetic alterations, and loss of chromosome 7 or its long arm was insufficient to induce full malignant transformation; in other words, loss of one copy of a critical 7q tumor suppressor gene can lead to a transient growth advantage, but ultimately regress if there is no "second hit" that inactivates the other allele; or 2) the "limited self-renewal capacity" hypothesis: the hematopoietic cells with monosomy 7/del(7q)-related initiating mutation only have limited self-renewal capacity; therefore, although the aberrant clone was able to dominate hematopoiesis and to produce many progenies for a specific period of

time, the disorder was self-limited because it did not involve the stem cell pool [4]. These theories about the mechanism of spontaneous remission of the cases with transient monosomy 7 may improve our knowledge of leukaemogenesis.

Monosomy 7 in pediatric patients with AML or MDS is associated with poor event-free survival when treated with conventional chemotherapy, immunosuppression or supportive measures; HSCT has been proven to be effective therapy for these patients [16]. One study has even concluded that HSCT improved the outcomes for patients with monosomy 7 and should be offered early in the course of the disease [17]. However, HSCT is a highly specialized, resource intensive and costly medical procedure [18]. In addition to the drawback of the difficulty finding a timely suitable donor, HSCT is also associated with a high treatment-related mortality in the recipient, and the major complications include veno-occlusive disease, mucositis, infections, graft-versus-host disease and the development of new malignancies. Therefore, Mantadakis *et al* suggested to observe young children closely who are doing well clinically, do not require transfusions, and do not have a matched sibling donor for bone marrow transplantation. If the clinical status improves or worsens in these patients, a bone marrow examination with cytogenetics should be obtained [4].

In conclusion, we presented here a rare case of a 9-month old boy achieving spontaneous remission of bicytopenia and monosomy 7 without any intervention. This case illustrates the importance of a period of close surveillance of patients with monosomy 7/del(7q) and without evidence of dysplastic changes before proceeding to any major treatments.

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