

Metachronous occurrence of gastrointestinal stromal tumor and acute promyelocytic leukemia in a patient with ankylosing spondylitis: A case report

Fatemeh Nejatifar^{1,*}, Habib Zayeni², Marjan Yaghmaie³, Narges Akrami⁴

¹Department of Hematology and Oncology, Razi Clinical Research Development Unit, Guilan University of Medical Sciences, Rasht, Iran

²Department of Rheumatology, Guilan University of Medical Sciences, Rasht, Iran

³Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran

⁴Department of Internal Medicine, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

Abstract

Gastrointestinal stromal tumors are the most common mesenchymal tumor of the alimentary canal. Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia. A 57-year-old male patient with a previous record with history of gastrointestinal stromal tumors (GIST) and ankylosing spondylitis, was hospitalized with right ankle and foot swelling and pancytopenia. A diagnosis of APL was made by bone marrow aspiration and cytogenetic study. After a combined treatment with all-trans retinoic acid and arsenic trioxide, the patient achieved cytogenetic and molecular remission. According to past studies, the synchronous or metachronous coexistence of GISTs with other malignancies, such as lymphoma, liver cancer and pancreatic tumors has been widely reported. This study describes a patient with the metachronous occurrence of a CD34 positive GIST and APL. We suggest, the minor alterations in hematological parameters must be taken into consideration for such cases.

Keywords: GIST, Acute promyelocytic leukemia, Ankylosing spondylitis, HLAB27

1. Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia, characterized with promyelocytic proliferation and reveals chromosomal translocation (15;17) and life-threatening coagulopathy. The presence of t(15;17) is considered a diagnostic marker of APL regarding to the blast count, such as our patient. Gastrointestinal stromal tumors (GIST) is the most common of soft tissue sarcoma of gastrointestinal tract and resulting by mutation of the receptor tyrosine kinase KIT (CD 117) [1]. Majority of GIST express CD117 in immunohistochemistry. IHC demonstrates 60-80%

of GISTs express CD34 [1]. The development of APL during imatinib therapy is rare [1, 2]. Kim et al. reported a case of 63-year-old woman, diagnosed with a hepatic GIST and acute myeloid leukemia (AML) with KMT2A gene rearrangement [3]. Gao et al. reported a case of 69-year-old man with synchronous occurrence CD117 positive AML and GIST [1]. We report the case of the metachronous occurrence of a CD34 positive GIST and APL as well as a history of ankylosing spondylitis (AS).

*Corresponding author:

Fatemeh Nejatifar, MD
Razi Hospital, Razi Clinical Research Development Unit,
Guilan University of Medical Sciences, Sardar Jangal Street, Rasht, Iran
Tel/Fax: +98 911 3433101
Email: dr.f.nejatifar@gmail.com
<http://orcid.org/0000-0002-3858-8482>

© The Author(s) 2022



Received: January, 17, 2021
Accepted: February, 01, 2021

2. Case presentation

A 57-year-old male patient suffering from right ankle and foot swelling was admitted in April 2018, to Razi hospital which is the most important referral hospital in Rasht, Iran. The patient on admission revealed right ankle arthritis while the other physical examination was normal. At the time of hospitalization, the patient was pancytopenia. Twelve years ago, the patient was diagnosed with GIST and underwent surgery and treated with imatinib 400 mg/day for a period of 36 months. GIST was 8*6*4 cm in the greater curvature of the stomach and its immunohistochemistry (IHC) staining was reported positive for CD34 and negative for CD117. He has been suffering from arthritis and low back pain for 5 years, and a diagnosis of positive HLA-B27 AS was made based on modified New York criteria [4]. AS was refractory to nonsteroidal anti-inflammatory drugs (NSAID); therefore, he has been under treatment with Infliximab for three years. GIST relapsed after 10 years and imatinib started again because the tumor was unresectable. At the recent hospitalization test revealed that white blood cell counts 1000 cells/ μ l (normal range: 4,000-10,000 cells/ μ l) with 18% for diff neutrophil count, 79% for lymphocyte count hemoglobin level of 7.2 g/ dl (normal range :13-15 g/dl), and platelet count of 61,000 (normal range: 150,000-450,000 platelets/ μ l). The patient's other lab tests reported as follows: ESR: 119 mm/hour, CRP: +1 mg/L, PT: 12.5 sec, INR: 1, PTT: 32 sec, fibrinogen 346 mg/dl, Fe: 39 mg/dl, TIBC: 225 mg/dl, ferritin > 800 ng/ml, Cr: 1 mg/dl, LDH: 278 U/L. The liver function test was normal. In peripheral blood smear, RBCs had mild anisocytosis and rouleaux formation. In addition, WBCs and platelets severely decreased. Also, Giant platelet was observed. However, no immature cells and tear drop was not observed (Figure 1). Pancytopenia persisted even after discontinuation of imatinib, and infliximab, and bone marrow aspiration (BMA), as well as bone marrow biopsy (BMB) revealed a severe hypocellular marrow. Differential counts of BMA were as follows: Blast = 2%, Promyelocyte = 17%, Myelocyte = 15%, Metamyelocyte = 10%, Band = 13%, Segment = 12%, Lymph = 7%, Erythroid series = 30%, Eosinophilic series = 2%, Plasma cell = 5 %. IHC staining was performed but it was not helpful to confirm the diagnosis of APL. The cytogenetic result revealed a

translocation between chromosomes 15 and 17 and gain of chromosome 21. (Figure 2). PML/RARA fusion transcript was also positive in bone marrow aspiration by RT-PCR at diagnosis. The treatment started with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) because according to Italian Group for Adult Hematologic Disease (GINEMA) and Spanish PETHEMA group [5], the patient is categorized as low risk. Twenty-eight days later, blood cells became normal and bone marrow study revealed remission. Three months after treatment, PML/RARA was not detected in peripheral blood by quantitative RT PCR. The evaluation of patient after three years revealed hematological and molecular remission.

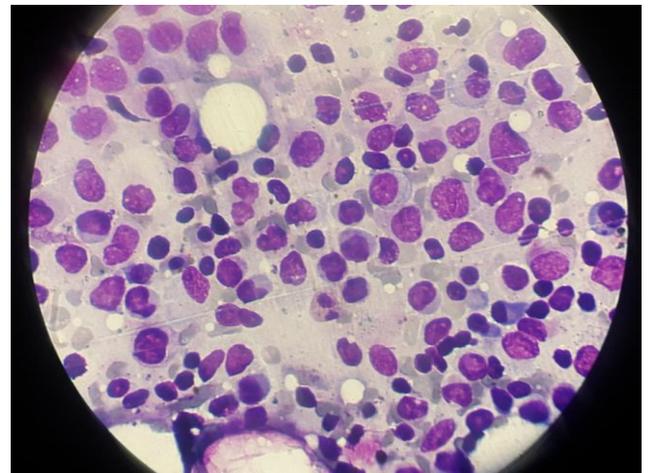


Figure 1. Bone marrow aspiration. Wright Giemsa stain at magnification x100.

3. Discussion

Although there is no known mechanism for imatinib and acute leukemia, sporadic acute leukemia cases and GIST were reported during imatinib therapy for GIST [1, 2, 6-8]. The development of APL during imatinib therapy is rare [1, 2]. It is to our knowledge this is the first case suffering from GIST, APL and HLA-27 positive ankylosing spondylitis simultaneously. Our patient was CD117 negative GIST. CD34 is a hematopoietic stem cell antigen that commonly present in GISTs but is less specific than KIT (CD 117) [9]. Our patient also presented CD34 on GIST tumor cells. CD34, a hematopoietic stem cell antigen, is commonly present in GISTs but is less specific than KIT (CD 117) [10]. The CD34 is also expressed in vascular

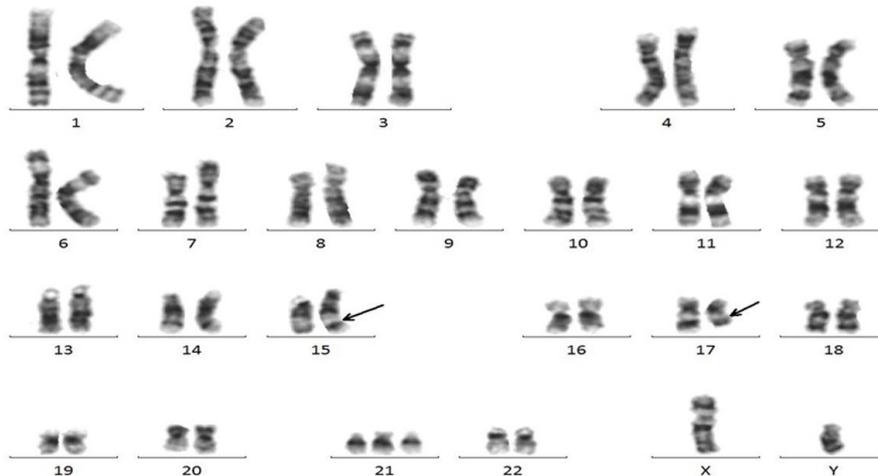


Figure 2. 47, XY, t (15;17) (q24; q21), +21[12]/46, XY [8], Twelve metaphase cells analyzed displayed a translocation between the long arms of chromosomes 15 and 17 and gain of chromosome 21. These results consistent with the diagnosis of APL. t (15;17) (q24; q21) is associated with a good prognosis. t (15;17) is seen often (40%) with additional karyotypic changes.

endothelial cells and has been shown leading to signal transduction and enhanced adhesiveness of CD34⁺ hematopoietic cells. Normal promyelocyte do not have CD34 while leukemic promyelocyte have overexpression this marker. Our patient also presented CD34 on GIST tumor and leukemic cells. We assume the concomitant of the CD34 expression on APL and GIST cells may be a reason of diagnosis of these two cancers in our patient. Joo et al., reported a case of 63-year-old woman of synchronous occurrence of KIT-positive AML and GIST [6]. Miettinen et al's reported 9 (0.48%) myeloid leukemia in 1892 GIST patients, suggesting an apparent nonrandom association between GIST and myeloid leukemia [7]. There were six patients with AML including one case of promyelocytic and three patients with chronic myeloid leukemia (CML). All patients, in that study, developed leukemia after GIST, with the time interval varying from 1.7 to 21 years [7].

Yu et al reported a 49-year-old woman with CD117 and CD34 positive GIST given which was treated with imatinib. After one year the patient developed APL. The PML/RARA fusion gene was positive and kit mutation was negative [8]. A genetic linkage to HLA B27 has been demonstrated to increase the risk of developing hematological malignancies in patients with AS [11]. Despite of the

presence of autoimmune disease prior immunosuppression therapy, and infliximab, they suggest prompt evaluation for patients who develop hematological abnormalities after being treated with infliximab. It is probably hard to determine which plays a more important role in developing leukemia. However, we suggest, the small changes in hematological parameters must be taken into consideration for such cases. A fundamental study is needed to investigate the possible mechanism of this relation.

This study reports the case of a patient with the metachronous occurrence of a CD34 positive GIST and APL. We suggest, the small changes in hematological parameters must be taken into consideration for such cases.

Acknowledgments

We would like to thank the patient for allowing us to share his details, and thank to oncology ward staff.

Authors' contributions

FN: haematologist and medical oncologist managed the patient and participated in the drafted manuscript. HZ: rheumatologist managed the patient. MY: medical genetics and carried out cytogenetic study. NA: collected data and

participated in the drafted manuscript. All the authors read and approved the final manuscript.

Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical declarations

Ethical approval to report this case was obtained from the Ethical Committee of Guilan University of Medical Sciences with this code: IR.GUMS.REC.1400.159.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying image. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Financial support

Self-funded.

References

1. Gao NA, Guo NJ, Yu WZ, Wang XX, Sun JR, Yu N, et al. Synchronous occurrence of gastrointestinal stromal tumor and acute myeloid leukemia: A case report and review of the literature. *Oncol Lett.* 2016; 11(5):2977-80.
2. Hechtman JF, DeMatteo R, Nafa K, Chi P, Arcila ME, Dogan S, et al. Additional Primary Malignancies in Patients with Gastrointestinal Stromal Tumor (GIST): A Clinicopathologic Study of 260 Patients with Molecular Analysis and Review of the Literature. *Ann Surg Oncol.* 2015; 22(8):2633-9.
3. Kim HJ, Baik SK, Maeng CH, Kim SY, Park TS, Han JJ. Acute myeloid leukemia with t(11;19)(q23;p13.1) in a patient with a gastrointestinal stromal tumor undergoing imatinib therapy: A case report. *World J Clin Cases.* 2020; 8(7):1251-6.
4. Ranatunga S, Miller AV. Active axial spondyloarthritis: potential role of certolizumab pegol. *Ther Clin Risk Manag.* 2014; 10:87-94.
5. Sanz MA, Lo Coco F, Martín G, Avvisati G, Rayón C, Barbui T, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood.* 2000; 96(4):1247-53.
6. Joo YB, Choi SH, Kim SK, Shim B, Kim MS, Kim YJ. Synchronous development of KIT positive acute myeloid leukemia in a patient with gastrointestinal stromal tumor. *Korean J Hematol.* 2010; 45(1):66-9.
7. Miettinen M, Kraszczyńska E, Sobin LH, Lasota J. A nonrandom association between gastrointestinal stromal tumors and myeloid leukemia. *Cancer.* 2008; 112(3):645-9.

8. Yu YP, Song P, Mei JG, An ZM, Zhou XG, Li F, et al. [Acute Promyelocytic Leukemia Developed during Imatinib Therapy for Gastrointestinal Stromal Tumors]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2017; 25(2):358-64.

9. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor. *J Surg Oncol.* 2011; 104(8):865-73.

10. Muroi K, Nakamura M, Amemiya Y, Suda T, Miura Y. Expression of c-kit receptor (CD117) and CD34 in leukemic cells. *Leuk Lymphoma.* 1995; 16(3-4):297-305.

11. Wick RR, Nekolla EA, Gaubitz M, Schulte TL. Increased risk of myeloid leukaemia in patients with ankylosing spondylitis following treatment with radium-224. *Rheumatology (Oxford).* 2008; 47(6):855-9.