Case report

A Case of Myelodysplastic Syndrome-Induced Acquired Sideroblastic Anemia

Bremansu Osa-Andrews[1*], John O. Ogunbileje[2], Neil Harris[1], Tung Wynn[1]

[1]*University of Florida, College of Medicine, Gainesville, USA*
[2]*Indiana University; School of Medicine, Indianapolis, USA*

Article Info

Corresponding Author:
Bremansu Osa-Andrews
University of Florida, College of Medicine
Gainesville, FL 32611, USA
E-mail: b.osaandrews@ufl.edu

Keywords

Sideroblastic, anemia, hematological, myelodysplastic

Abstract

Hematological disorders are frequently encountered at the doctor's office and in the emergency room. Sideroblastic anemia, a rare hematological malady, is characterized by ring sideroblasts in the red blood cells due to accumulation of poorly transported and underutilized iron. Unlike primary sideroblastic anemia which can be conclusively diagnosed through genetic testing, the more common secondary form of the disease requires intricate cascading of several preliminary and confirmatory laboratory testing to determine the accurate etiology and provide the appropriate management regimen. The scope of laboratory medicine is broadening; clinical chemists and other laboratorians are tasked with directing broader clinical pathology sections, including Core lab hematology. Understanding the testing dynamics, diagnostic criteria and management of hematological diseases is fundamental to attaining success in consulting with providers to manage diseases such as sideroblastic anemia. Via a relevant case study, we explore the etiology, workup, symptoms, and treatment of myelodysplastic syndrome-induced sideroblastic anemia.

Introduction

Sideroblastic anemia is a rare hematological disorder involving disrupted mitochondrial iron metabolism and of iron transport which inadvertently impacts heme synthesis [1]. By classification, rare diseases affect less than 200,000 individuals in the United States. Primary sideroblastic anemia is usually caused by genetic mutations with three modes of inheritance (Autosomal recessive, maternal and X-linked) [2], while environmental factors are the main features in the acquired form of the disease. Myelodysplastic syndromes with ring sideroblasts (MDS-RS), driven by dynamic alterations in the bone marrow are responsible for the most common forms of acquired sideroblastic anemia. A subtype of MDS-RS, Refractory anemia with ring sideroblasts (RARS) is a low-grade MDS characterized by dyserythropoeises, anemia and at least 15% ring sideroblasts, and the significant involvement of ring sideroblasts is what differentiates RARS from Refractory anemia (RA). RARS has a 3-12% chance of progression to acute myeloid leukemia, even though the elevated ring sideroblasts diminishes the risk of progression to leukemia [3]. Here, we present a clinical case of MDS-RS to highlight the diagnostic criteria, laboratory investigation, and the management rudiments of the disease. This case report is a great resource for clinical chemists, clinical pathologists, and hematologists in understanding the distinct and collective roles of laboratory and clinical teams in working up and resolving a typical secondary sideroblastic anemia involving myelodysplasia in the bone marrow.

Case presentation

A 78-year-old male patient was admitted at a large tertiary academic hospital for cough and weakness for one week. He tested negative for COVID and Influenza. On admission, the patient's hemoglobin level and hematocrit were 4.7 g/dL and 14.1 respectively. His other lab results were white blood cells count (WBC) 1.9 (4.5 to 11.0 ×109/L), absolute neutrophile count (ANC) 0.72 (2.0–7.5×109/L), red blood cells count (RBC) 1.53 x106/uL, red cell width distribution width, 19.2 (11.5-14.5 %) and platelet count was 3,000/µL. The patient had a history of hyperlipidemia and hypertension and was also diabetic, suggesting metabolic syndrome. He had reported being a former smoker but was not currently using alcohol.

The patient had thrombocytopenia. Bone marrow biopsy was consistent with refractory anemia with ringed sideroblasts and complex cytogenetics were noted. Chest X-ray revealed left lower lobe infiltrate with effusion and enlarged heart. Additional techniques performed to unravel the patient's predominant diagnosis were bone marrow biopsy with Fluorescence In Situ Hybridization (FISH), and neoplastic bone marrow chromosome study with specific neoplastic interphase EGR1, D7S522 with D7Z1, D8Z2 and D20S108 FISH studies performed. The results of the cytogenetic studies showed chromosome 7q locus copy number loss. The patient had been on a hypomethylating agent with Vidaza but demonstrated resistance to the medication. Consequently, he was started on one cycle of Dacogen and was also receiving Procrit but with no response. The rest of the tests performed are itemized in Table 1. He is now receiving supportive care at a hospice facility.

Table 1: Results of tests performed on patient at the time of admission.

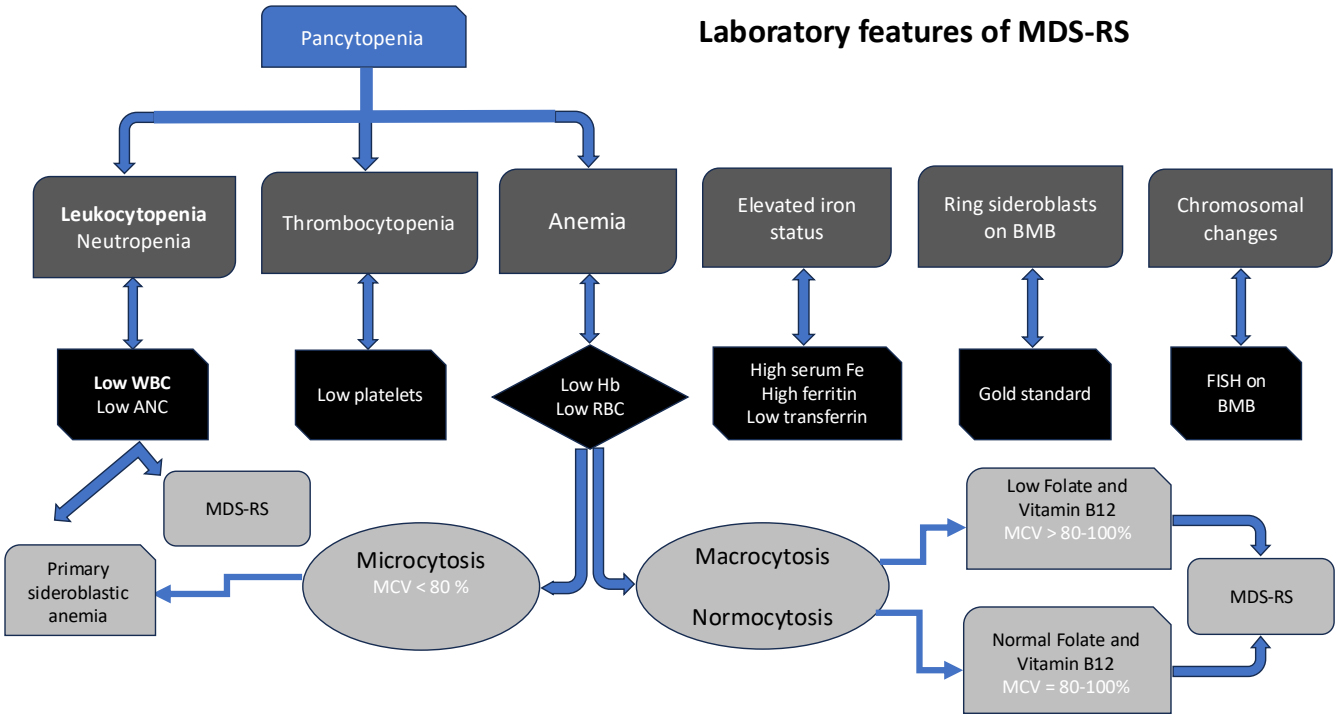
Test	Result	Reference interval
Hemoglobin	4.7	13.9–16.3 g/dL
RBC	1.53	4.30–5.90 x 10^6/µL
WBC	1.9	4.50–11.90 x 10^3/µL
Platelets	3	150–400 x 10^3/µL
Hematocrit	14.1	39–55%
MCV	92.2	80–100%
MCH	30.7	23.4–34.6 pg
MCHC	33.3	31.0–37.0 g/dL
ANC	0.72	2.0–7.5 x 10^3/µL
RDW	19.2	11.5–14.5%
Absolute lymphocytes	0.26	1–3.4 x 10^3/µL
Serum iron	184	65–175 µg/dL
Iron saturation	97	11–46%
Transferrin	133	200–360%
Ferritin	1425	8–388 ng/mL
TIBC	190	260–400 µg/dL
Serum folate	>20	3.1–17.5 ng/mL
Vitamin B12	536	193–986 pg/mL

Normal result, low result, high results.

Case discussion

The present case explores the laboratory features of MDS-RS (Figure 1). The initial investigation of anemia begins with an order for a complete blood count (CBC). Often associated with low hemoglobin, confirming anemic state is low RBC. The results for hemoglobin and RBC of the patient under review were very low, strongly indicating an anemic state. It's been reported that sideroblastic anemia patients have high RDW as it was in this scenario [2]. Neutropenia is a notable feature of sideroblastic anemia, particularly the primary form. On the other hand, myelodysplastic syndromes are also known to cause diminished neutrophils. The patient's low ANC which typifies neutropenia is therefore consistent with his sideroblastic anemia and potentially the extensive myelodysplastic involvement [4, 5].

Figure 1: Laboratory features of MDS-RS.



Routine CBC is the preliminary laboratory test panel in the work up of sideroblastic anemia. Pancytopenia is a common feature in MDS-RS and corresponds to low RBCs, low platelets, low WBCs. If CBC is ordered with differential, neutropenia, indicated by low ANC may be seen in either primary sideroblastic anemia or myelodysplastic syndromes. Normal to elevated iron status is a key component of sideroblastic anemia since in this condition, iron is present, but the body has a usage problem due to a broken mechanism. It is therefore common to find normal or high iron and ferritin, low transferrin and TIBC. In most cases of acquired sideroblastic anemia like MDS-RS, folate and vitamin B^{12} are normal or may be slightly elevated. On the other hand, microcytosis is frequently associated with primary rather than secondary sideroblastic anemia. Ring sideroblasts on BMB is a key feature in MDS-RS. If 15% or more ring sideroblasts are involved, RARS is often more accurately the diagnosis. Patients with acquired myelodysplastic syndrome with ring sideroblasts often show chromosomal structural changes on BMB through FISH. MDS-RS: Myelodysplastic syndrome with ring siderobasts; BMB: Bone marrow biopsy; ANC: Absolute neutrophil count; MCV: Mean corpuscular volume; CBC: Complete blood count; FISH: Fluorescence In situ Hybridization; RARS: Refractory anemia with ring sideroblasts.

The MCV result of the patient propounds normocytic anemia, often associated with the acquired form of sideroblastic anemia. Microcytic anemia is a common feature of congenital sideroblastic anemia while macrocytic or normocytic anemia is often seen in acquired forms of the disease [6] (Figure 1). The high serum folate and normal vitamin B12 further rule against other causes of macrocytosis. The patient's high serum iron and ferritin are consistent with his normocytic anemia. Further, the patient's markedly elevated iron saturation, low transferrin and low TIBC confirm the overall elevated iron status of the patient. Microcytosis or macrocytosis is not a measure of discrimination to determine if a patient has sideroblastic anemia or not. This suggests that a routine CBC alone is inadequate to untangle the disease.

The gold standard diagnostic criterion for sideroblastic anemia is the visualization of ringed sideroblasts following a bone marrow biopsy examination. Of note, for this patient, three types of samples were retrieved from the bone for the diagnosis: bone marrow core biopsy, bone marrow clot section and bone

marrow aspiration smears. The results from all these specimens were accurately comparable: Myelodysplastic syndrome with features most compatible with refractory anemia with ring sideroblasts. A common complication of myelodysplastic syndromes is thrombocytopenia [7] {Basood, 2018 #4547}, and this is supported by the patient's extremely low platelet count. Myelodysplastic syndrome is the underlying cause of the patient's sideroblastic anemia. By contrast, thrombocytopenia is a rare clinical feature of copper-induced sideroblastic anemia [6]. Linezolid-induced thrombocytopenia in which ringed sideroblasts form has been reported [6], but the drug was not used for the patient. The confirmation of the patient's MDS, in addition to denying alcohol abuse, rules out alcohol as the secondary cause.

FISH is a technique used to evaluate the complete set of chromosomes by using a fluorescent dye-tagged probe that identifies and binds to specific complementary sequences on the chromosomes [8]. Interpretation of the FISH results revealed an abnormal cell population containing an isolated clonal chromosome 7q (long arm) deletion (breakpoints of 7q22 and 7q34), among ten of twenty metaphase cells examined by conventional cytogenetic techniques. A copy number loss for a chromosome 7q31 locus specific-probe signal, consistent with the chromosome 7q deletion as identified, was also demonstrated in cells examined by interphase and metaphase FISH methods. A loss of chromosome 7 long arm material (e.g., del(7q) or monosomy) is among the most frequently reported solitary aberrations observed in AML (3% of cytogenetically abnormal cases) but is also common in MDS and chronic myeloproliferative disorders. In addition, a loss of chromosome 7 long arm material is a frequent observation in therapy-related disease and as a secondary chromosomal aberration, especially in the setting of when an alkylating agent is used in the chemotherapy regimen or with radiation treatment affecting the bone marrow [9].

All the laboratory tests described here (Figure 1) are useful to evaluate the initial, differential and final diagnosis of both types of sideroblastic anemia (congenital/primary and acquired/secondary). But contrary to acquired sideroblastic anemia, the diagnosis of the congenital form of the disease almost always requires genetic testing to identify the specific mutation responsible for the pathological consequences. The different genetic tests are not described here since the current article is focused on acquired form of the disease. Most types of anemia including, but not limited to iron deficiency anemia, anemia of chronic disease, macrocytic and even megaloblastic anemia have many common clinical manifestations. Hence, these may constitute differential diagnosis of sideroblastic anemia and can pose minimal diagnostic conundrum. Care must therefore be taken in the work up of sideroblastic anemia in order to distinctively decipher the disease from other forms of anemia. Identification of ring sideroblast in bone marrow is a key that dichotomizes sideroblastic anemia from all other forms of anemia, and chromosomal testing with FISH isolates MDS-RS from other acquired forms.

Treatment of the patient commenced with 10 mL oral guaiFENesin-codeine, and opioid cough suppressant, to relieve his acute cough, being among the primary symptoms he presented with at the time of admission. The patient was treated with 2g of intravenous cefepime, a broad-spectrum cephalosporin antibiotic which functions by preventing the growth of both gram positive and negative bacteria [10]. This medication was important because of the patient's neutropenia which restricts the body's ability to fight infections. The patient's neutropenia may also have been partly responsible for his acquisition of Pseudomonas pneumonia infection. The patient benefited from blood transfusion, which, as noted earlier, is a standard approach for patients with severe cases of sideroblastic anemia [2, 11]. Transfusion is essential for patients with pancytopenia and severe anemia such as the current patient. The geriatric patient was also prescribed a multivitamin (1 tablet orally daily). The multivitamin treatment was essential to provide some necessary cofactors (of particular interest being pyridoxine-Vitamin B6) for the normal enzymatic activity in heme synthesis within the mitochondria. Critical to the patient's management is the administration of epoetin alfa (3000 units intravenously), an effective medication for bone marrow failure-induced anemia [12] to activate erythropoiesis in the bone marrow. The patient is currently in geriatric hospice care and is being closely followed and monitored.

Learning points

Thorough understanding of the work up of sideroblastic anemia is essential, not only for diagnostic and treatment purposes, but also pertinent to deciphering the specific etiology of the disease. The existence of many other types of anemia with convergent symptoms further complicates investigation of sideroblastic anemia and meticulous diagnostic process cannot be overemphasized. Some patients may end up in the emergency room with complications from sideroblastic anemia, augmenting the need for time-sensitive management. In addition, up to 12% of patients with RARS may develop leukemia, making laboratory-testing-based disease monitoring paramount. Complete blood count with differential is probably the most important preliminary test panel. Pancytopenia, normocytosis, macrocytosis or microcytosis are discernable on the CBC and these inform the need for further work up of the disease. Identification of ring sideroblasts on a peripheral blood smear or more effectively, on bone marrow biopsy is the definitive diagnosis for sideroblastic anemia but it still falls short of determining the actual etiology. Measurement of analytes such as copper, zinc, lead and certain drugs can exclude causes of such acquired forms of the disease. If clinically indicated, iron studies are recommended, since RARS, a form of MDS-RS is usually refractory to iron. FISH technology identifies chromosomal changes and thus, confirms MDS-RS.

Laboratory medicine is evolving and the need for clinical chemists to cover core laboratory and hematology is ever increasing. It is therefore imperative for chemists to thoroughly familiarize themselves with the work up and diagnosis of hematological diseases such as sideroblastic anemia. This will enhance proper stewardship and effective clinical consultation between lab directors and providers or hematologists, who will also benefit from precise test selection.

Declaration of conflicts

The authors declare no conflict of interest.

Ethical Approval

The University of Florida waves ethical approval if the manuscript involves only one clinical case.

Author contributions

Bremansu Osa-Andrews: Conceptualization, writing, reviewing, editing.
John O. Ogunbileje: Reviewing, editing.
Neil Harris: Reviewing, editing.
Tung Wynn: Reviewing, editing.

References

1. Ogunbileje JO, Harris N, Wynn T, Kashif R, Stover B, Osa-Andrews B. ATP-Binding Cassette Transporter of Clinical Significance: Sideroblastic Anemia. J Pers Med. 2024;14(6):636.
2. Abu-Zeinah G, DeSancho MT. Understanding Sideroblastic Anemia: An Overview of Genetics, Epidemiology, Pathophysiology and Current Therapeutic Options. J Blood Med. 2020;11:305-318.
3. Cioc AM, Nguyen PL. 18 - Myelodysplastic Syndromes. In: Hsi ED, editor. Hematopathology (Second Edition). Philadelphia: W.B. Saunders; 2012. p. 523-546.
4. Wahed A, Quesada A, Dasgupta A. Chapter 3 - Red blood cell disorders. In: Wahed A, Quesada A, Dasgupta A, editors. Hematology and Coagulation (Second Edition): Academic Press; 2020. p. 31-50.
5. Kasprzak A, Andresen J, Nachtkamp K, Kündgen A, Schulz F, Strupp C, et al. Infectious Complications in Patients with Myelodysplastic Syndromes: A Report from the Düsseldorf MDS Registry. Cancers (Basel). 2024;16(4):808.
6. Rodriguez-Sevilla JJ, Calvo X, Arenillas L. Causes and Pathophysiology of Acquired Sideroblastic Anemia. Genes (Basel). 2022;13(9):1562.
7. Mittelman M, Platzbecker U, Grosicki S, Lawniczek T, Zhu Z, Selleslag D. Long-Term Safety and Efficacy of Eltrombopag for Advanced Myelodysplastic Syndromes or Acute Myeloid Leukemia and Severe Thrombocytopenia: Results of the ASPIRE Extension Study. Acta Haematol. 2023;146(5):373-378.
8. Amalia Dutra Ph.D. THGP. Fluorescence In Situ Hybridization (FISH) 2024. Available from: https://www.genome.gov/genetics-glossary/Fluorescence-In-Situ-Hybridization. Accessed: 10/21/2024
9. Boquoi A, Banahan SM, Mohring A, Savickaite I, Strapatsas J, Hildebrandt B, et al. Therapy-related myeloid neoplasms following treatment for multiple myeloma-a single center analysis. Ann Hematol. 2022;101(5):1031-1038.
10. Eranki. AOCMJLAP. Cefepime: StatPearls 2022.
11. Chhabra. DAA. Sideroblastic Anemia: StatPearls 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538287/. Accessed: 10/21/2024
12. Patel. SPJB. Epoetin Alfa: StatPearls; 2023.