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(CASE REPORT)

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Effects of epoetin alpha subcutaneous injections on MDS patient (Case Report)

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Abstract

Spontaneous splenic rupture is an exceedingly rare condition, with no documented cases occurring in patients with myelodysplastic syndromes (MDS). In this case study, we have reported a patient with low-risk MDS who was treated primarily with Epoetin Alpha subcutaneous injections to manage his Anemia for nearly one year and was subsequently diagnosed with spontaneous splenic rupture in our department, which was treated with urgent splenectomy.

Although spontaneous splenic rupture is rare and infrequently reported, further investigations and data collection are necessary to confirm whether certain drugs can lead to serious complications like spontaneous splenic rupture.

Keywords: Epoetin; Myelodysplastic; Spontaneous; Splenic; Rupture

1. Introduction

Myelodysplastic syndrome (MDS) refers to a diverse collection of closely linked clonal hematopoietic abnormalities frequently observed in the elderly population. All these abnormalities are characterized by one or more peripheral blood cytopenias. While normal bone marrow is typically hypercellular, hypocellular marrow resembling aplastic anemia may occasionally be observed. Dysmyelopoiesis, or abnormal morphology and maturation of bone marrow cells, leads to inefficient blood cell synthesis.

MDS may affect one, two, or all three myeloid hematopoiesis cell lineages—erythrocytic, granulocytic, and megakaryocytic—depending on the subtype and stage of the disease. The heterogeneity of MDS reflects the various cytogenetic processes that occur during its progression. Some patients may develop acute myeloid leukemia (AML) from MDS due to the emergence of additional genetic defects. Consequently, MDS is considered a premalignant condition, despite being clonal. (1)

MDS is an indolent disease for some patients, while others may develop significant cytopenias, with complications such as bleeding and infections accounting for nearly all MDS-related mortality. In some cases, the disease progresses aggressively and evolves into acute leukemia.

The French–American–British (FAB) Cooperative Group, the World Health Organization (WHO), and the MDS Risk Analysis Workshop have collaborated to establish risk classification systems for estimating the prognosis of MDS patients. The FAB classification divides MDS into five categories, distinguishing it from acute myeloid leukemia: (2)

- Refractory anemia (RA)
- RA with ringed sideroblasts (RARS)

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- RA with excess blasts (RAEB; 6%–20% myeloblasts)
- RAEB in transition to AML (RAEB-T; 21%–30% myeloblasts)
- Chronic myelomonocytic leukemia (CMML)

To enhance prognostic categorization, the MDS Risk Analysis Workshop developed the Myelodysplastic Syndrome International Prognostic Scoring System (IPSS), released in 1997 and updated in 2012. (3) The revised IPPS (IPSS-R) score is calculated using five variables: (1) hemoglobin levels, (2) absolute neutrophil count, (3) platelet count, (4) percentage of bone marrow blasts, and (5) cytogenetic category.

The IPSS classifies patients into four risk groups: low, intermediate 1 and 2, and high. The IPSS-R score categorizes patients into five risk groups. The table below clarifies the risk for MDS patients.

Table 1 Risk for MDS

Risk group	Time to develop AML (in years)	Median survival rate (in years)
Very low	No risk	8.8
Low	10.8	5.3
Intermediate	3.2	3.0
High	1.4	1.6
Very high	0.7	0.8

The figure below demonstrates the symptoms of MDS.

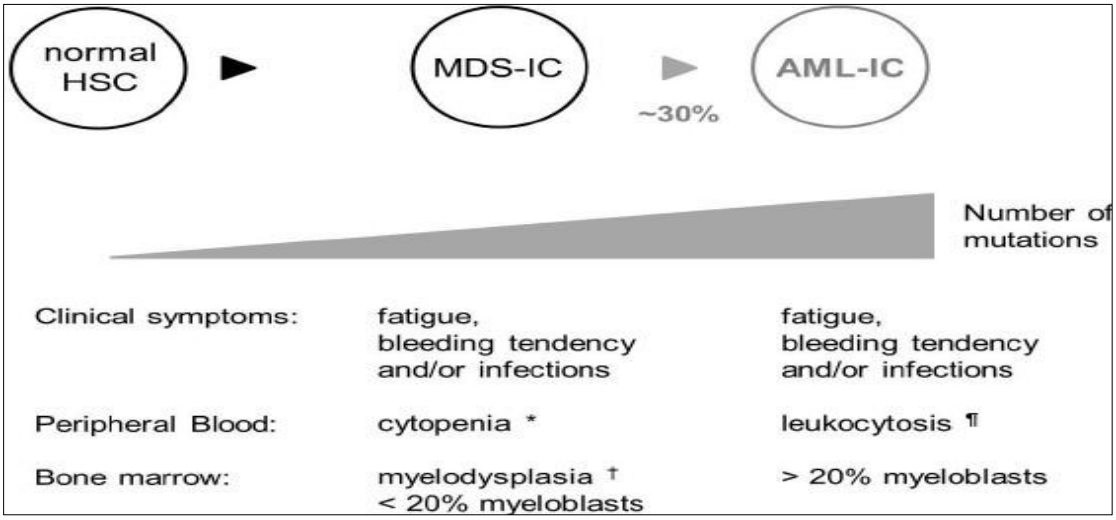

Figure 1 Symptoms of MDS

1.1. Splenic Rupture

Atraumatic splenic rupture is a rare occurrence, often overlooked in the differential diagnosis of abdominal pain in the absence of trauma, which can lead to serious complications. The earliest recorded cases of atraumatic splenic rupture date back to 1861, when Rokitansky coined the term "spontaneous splenic rupture," describing it as a rupture without external force. (4)

In 1966, Knoblish classified non-traumatic splenic rupture into two categories

- Pathological rupture of a diseased spleen, which may be caused by
  - Infections (bacterial, viral, or parasitic), accounting for 30% of cases.

- Hematological neoplasms, contributing to 27% of cases[11] primarily conditions that result in massive splenomegaly such as myelofibrosis and chronic myelogenous leukemia.

A recent systematic review of 613 splenic rupture cases identified 84 cases secondary to hematological malignancies. Acute leukemia and non-Hodgkin lymphoma were the most common causes, followed by chronic and acute myelogenous leukemia. (4)

1.2. Non-traumatic splenic rupture of unknown cause (spontaneous splenic rupture)

Spontaneous rupture refers to the rupture of a normal spleen without external trauma, sometimes also called idiopathic rupture. It is a rare cause of acute abdominal pain and hemoperitoneum, accounting for less than 1% of all splenic rupture cases. And it carries high risk of mortality because of delayed diagnosis. (5)

1.3. Clinical Presentation

A 59-year-old male was diagnosed with multilineage dysplasia (MDS-MLD) following an investigation for pancytopenia through bone marrow aspiration, biopsy, and cytogenetics; the FISH study was negative for chromosome 5 and chromosome 7 deletion, as well as trisomy 8. In November 2022, the patient's IPSS score was classified as low risk. He began receiving Eprex® (Epoetin Alpha) as a subcutaneous injection along with supplements (e.g., folic acid and B-complex) to manage his Anemia, as his baseline Hemoglobin level was approximately 8.00 g/dL. As the patient's Anemia did not improve with a low dose of Eprex® (4000 IU twice weekly), the dosage was gradually increased to 8000 IU three times a week, maintaining his hemoglobin level near 10.00 g/dL between January and April 2023.

In April 2023, the patient was admitted to the ward due to progressive Anemia, with a Hemoglobin level dropping to 5.00 g/dL. An investigation for upper gastrointestinal bleeding (GIB) revealed normal results during upper endoscopy. During hospitalization, the patient began to experience hiccups accompanied by diffuse abdominal pain and swelling, which was identified as ascites by abdominal ultrasound. Paracentesis revealed blood. Consequently, an urgent abdominal CT scan was performed, which indicated hyperdense massive ascites, a subcapsular heterogeneous collection (10 × 4 cm), and a subcapsular splenic collection with heterogenous attenuation, highly suspicious for splenic rupture. The patient underwent urgent exploratory laparotomy with splenectomy. His recovery was rapid, and he was discharged after three days with a stable hemoglobin level (around 10.00 g/dL). Histopathology revealed a spleen with a ruptured capsule measuring 14 × 11 × 11 cm, with a dusky cut surface showing hemorrhagic material. The section revealed splenic tissue exhibiting capsular tears with subcapsular hemorrhage and neutrophilic infiltration. The red pulp was cellular, with some foci of extramedullary hematopoiesis and hemosiderin-laden macrophages. The patient denied any history of trauma. A review of his medications revealed no associations with spontaneous splenic rupture.

2. Discussion

Spontaneous splenic rupture is uncommon in medical practice and is often not diagnosed, particularly in the absence of trauma. It typically occurs when there is splenic infiltration due to hematologic diseases causing splenomegaly, along with other risk factors such as splenic infarction, coagulation disorders, and male gender. (6)

Patients often present with left upper quadrant pain and hemodynamic instability, which may include Kehr's sign—left shoulder tip pain caused by diaphragmatic irritation. If a high suspicion of splenic rupture exists, an abdominal CT scan is essential for diagnosis, as it can reveal splenic laceration and intraperitoneal or subcapsular hemorrhage. (7)

Given that our patient had no obvious risk factors for spontaneous splenic rupture, we hypothesize that his case may be related to his medication, primarily Eprex®. Since there is no published data about any correlation between MDS and splenic rupture. Thus, splenic rupture is often reported in hematological disease like myeloproliferative because of massive splenomegaly or thromboembolic disorders which is not presented in patient with myelodysplastic syndrome. (8)

The recommended Eprex® dosage for myeloid malignancies, including MDS, is 150 IU/kg as a subcutaneous injection three times per week. This dosage can be increased to 300 IU/kg if the patient's hemoglobin level does not rise to at least 10.00 g/L after four weeks of administration. If no response is observed with the increased dosage, it is unlikely that the patient will respond to treatment. (9)

The most common side effects of Eprex® include increased blood pressure, diarrhea, nausea, vomiting, pyrexia, and headache, along with a higher risk of thrombotic vascular events and hypersensitivity reactions. Less frequent side effects include asthenia, nasopharyngitis, and dyspnea. (9) Moreover, the lately reviewed leaflet of the Eprex® does

not mention any side effect (even in rare side effects) on the spleen while all mentioned drug – drug interactions are not applicable on this patient case, since the patient is not taking any chronic medications. (10)

While spontaneous splenic rupture is not a well-known side effect, but the patient's case may be associated with subcutaneous Eprex® injections, as no other risk factors were identified.

In patients who frequently use Eprex® (e.g., those with chronic kidney disease), several cases of spontaneous splenic hematoma and rupture have been reported, with an incidence ranging from 0.1% to 0.5%. The causes of such cases in hemodialysis patients may vary from heparin infusion to uremic coagulopathy, infection, or amyloidosis, making it challenging to pinpoint the exact cause. (11)

Although no clear relationship has been established in these cases, we argue that Eprex® could be implicated, potentially representing a rare side effect of the drug. Similarly, certain drugs used in hematology, such as filgrastim, have been associated with splenic rupture, as reported in 100 out of 58,000 patients in a study conducted in the United States. (12)

3. Conclusion

Spontaneous splenic rupture is a rare but potentially life-threatening condition, often associated with splenic infiltration due to hematologic diseases and related risk factors like splenomegaly or coagulopathy. In our case, the absence of these typical risk factors suggests an alternative cause.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from the patient included in this case report.

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