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Spontaneous splenic rupture during induction chemotherapy for acute myeloid leukemia

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Spontaneous splenic rupture (SSR) is a rare life-threatening emergency that can be uniformly fatal if not promptly recognized and adequately managed. SSR in patients with acute myeloid leukemia (AML), especially after initiation of chemotherapy, is a very rare event [1-4]. Here we report a case of SSR with hemorrhagic shock in a patient with AML who was successfully managed, and review relevant literature.

A previously healthy 33-year-old female presented with a 2-week history of a sore throat. Upon presentation, she was found to have a leukocytosis with a white blood cell count (WBC) of 89 310/ μ L (normal range [NR], 4500-11 000). The differential showed 43% blasts, 29% promonocytes, 13% monocytes, 8% lymphocytes and 4% neutrophils. A peripheral smear showed numerous circulating promonocytes and blasts with a monocytoid appearance. Hemoglobin (Hb) was 9.3 g/dL (NR, 13.9-16.3) and platelets were 43 000/ μ L (NR, 150 000-350 000). Acute myelomonocytic leukemia was confirmed by laboratory testing. Renal function, electrolytes, uric acid and coagulation parameters were all within normal limits. The bone marrow (BM) was markedly hypercellular and replaced with blasts with minimal residual hematopoiesis (Figure 1). Flow cytometry showed 25% immature monocytic elements (bright CD33 and CD64 with no CD14) and phenotypically abnormal CD34 + blasts which expressed bright CD33, human leukocyte antigen (HLA)-DR, CD13, CD34, dim CD38, CD64, CD15, CD117 and CD22. No cytogenetic abnormalities were detected, but FLT3 internal tandem duplication (ITD) and NPM1 mutations were observed. The patient had no family history of hematological malignancy. Physical examination noted

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absence of hepatosplenomegaly or lymphadenopathy. Computed tomography (CT) imaging revealed borderline splenomegaly by radiographic criteria (Figure 1), but no other abnormalities.

For cytoreduction, the patient was initiated on hydroxyurea for 36 h without a significant decrease in leukocytosis. She then received cyclophosphamide 60 mg/kg per institutional protocol. The patient began definitive treatment with cytarabine (667 mg/m²/day on day 1-3) and daunorubicin (45 mg/m²/day on day 1-3), 9 days after receiving cyclophosphamide. Immediately prior to starting induction chemotherapy, a repeat CT chest scan performed for neutropenic fevers demonstrated patchy opacities in bilateral lower lung lobes concerning for pneumonia. Additionally, an incidental new finding of a 3 × 2.6 cm rounded hypodensity in the anterior part of the spleen consistent with a splenic infarct was noted (Figure 1). The patient denied abdominal complaints at that time.

On the evening of day 2 after the second planned dose of daunorubicin and 36 h of cytarabine infusion, she developed sudden-onset severe abdominal pain. Systolic blood pressure did not register on an automated non-invasive cuff, and was only documented with manual palpation at 70 mmHg. She became minimally responsive, the emergency response team was called, and she was intubated. Aggressive fluid resuscitation and vasopressor and ventilatory support were initiated. Chemotherapy was immediately discontinued after a total dose of 90 mg/m² of daunorubicin and 1000 mg/m² of cytarabine. The abdominal examination evolved from soft to rigid over 2 h with newly elevated bladder pressures to 36 cmH₂O, consistent with abdominal compartment syndrome. Bedside abdominal ultrasound demonstrated lack of free air in the abdomen, suggesting intestinal rupture was an unlikely cause of the abdominal catastrophe. Repeat blood work performed revealed significant changes from 12 h prior: Hb 5.9 g/dL from 8.3 g/dL, platelet count 15 000/μ L from 37 000/μ L, prothrombin time (PT) 16.6 s from 11.4 s, activated partial thromboplastin time (aPTT) 45.4 s from 27.3 s, fibrinogen 150 mg/dL from 503 mg/dL and D-dimer 7.8 mg/L from 2.2 mg/L, consistent with disseminated intravascular coagulation (DIC) and acute blood loss. The absolute neutrophil count was 0/μL. Arterial blood gas showed severe metabolic acidosis with pH of 6.85 (NR, 7.35-7.45) and the lactate level was 18.7 mmol/L (NR, 0.5-2.2). Given the clinical progression and worsening laboratory markers, an acute intra-abdominal bleed was suspected, and emergent surgical consultation was obtained.

After initial clinical stabilization with aggressive blood product transfusions and hemodynamic support, a CT scan demonstrated a massive hemoperitoneum with a sentinel clot present in the left upper quadrant, implicating SSR as the cause of the bleed (Figure 1). Emergent exploratory laparotomy confirmed the SSR with evacuation of 7 L of blood from the abdominal cavity; splenectomy and abdominal packing with temporary closure were performed. The patient received a total of 38 units of red blood cells, 31 units of plasma, five units of apheresis platelets and 10 units of cryoprecipitate (one dose). The postoperative course was complicated by acute respiratory distress syndrome but she improved rapidly and underwent an abdominal wall closure 5 days later. She was extubated on postoperative day 7 and was transferred back to the leukemia service.

Pathologic examination of the resected ruptured spleen showed no evidence of leukemia (Figure 1). The spleen weighed 173 g and measured $14.3 \times 8.3 \times 4$ cm. A large portion of the capsule was stripped from the spleen and no masses or lesions were identified. The hilum and parenchyma were unremarkable. Repeat abdomen CT on postoperative day 14 confirmed complete resolution of the hemoperitoneum. The patient was discharged 1 month after the initial admission date. The complete blood count (CBC) on discharge showed WBC $2120/\mu\text{L}$, Hb 9.9 g/dL and platelet count of $360\,000/\mu\text{L}$ with a normal differential. BM evaluation on day 22 demonstrated normocellularity with trilineage hematopoiesis with no evidence of leukemia and disappearance of the FLT3-ITD mutation. The patient has now completed high-dose cytarabine consolidation therapy and is currently undergoing a myeloablative allogeneic stem cell transplant.

Our patient had a new diagnosis of AML with monocytic differentiation and FLT3-ITD mutation, which are associated with inferior survival. While undergoing induction chemotherapy, she suffered a SSR leading to a massive hemoperitoneum. SSR, also referred to as atraumatic splenic rupture, is a rare life-threatening event that requires prompt diagnosis and management [5]. SSR presents universally with severe abdominal pain, distension, left shoulder pain due to diaphragmatic irritation (Kehr's sign) and hemodynamic instability due to hemorrhage [1,4]. Without emergent splenectomy or splenic artery embolization, mortality in these patients approaches 100% [2-4,6]. The most common causes of SSR include infections and hematologic and non-hematologic neoplasms [2]. A recent systematic review of reported cases found neoplastic diseases to be the most common cause (30%) of SSR [7]. Acute leukemias accounted for 34-40% of cases among patients with hematologic malignancies [2-4,6]. SSR as the presenting symptom in patients with AML has been rarely reported [2,5,6,8,9]. Possible mechanisms for this phenomenon include distension of the spleen due to leukemic infiltrates especially in the capsule; splenic infarcts resulting in capsular hemorrhage; and AML-associated coagulopathy [5,6,10]. SSR in AML after initiation of chemotherapy is even less reported [2,11,12], including one report of fatal SSR in a patient with AML receiving induction chemotherapy with recombinant human granulocyte-macrophage colony-stimulating factor [11] and another patient with acute promyelocytic leukemia who developed SSR on day 2 of all-*trans*-retinoic-acid and idarubicin [12]. Reports suggest that male gender, age > 20 years, presence of splenomegaly and use of cytoreductive therapy are associated with an increased risk of SSR in patients with hematologic malignancies [3-5]. However, splenomegaly is not a prerequisite for SSR, as several autopsies have demonstrated normal sized spleens [2,6]. The most important factor in predicting survival after SSR was timely and appropriate surgical intervention, while splenomegaly and older age were associated with increased mortality [4,7].

Our patient did not receive growth factors or biologic therapy, and she had no pathologic evidence of splenomegaly or splenic involvement by leukemic infiltration. However, the examination occurred 10 days after cytoreductive therapy. The DIC noted at the time of clinical deterioration was not observed earlier that day, suggesting that the coagulopathy could be a result rather than a cause of the SSR. Our patient had an incidental new finding of a splenic infarct on CT imaging done the day before the SSR. Splenic infarction occurs when the splenic artery or one or more of its sub-branches becomes occluded with an

infected or bland embolus or clot [13]. Affected patients classically present with acute left upper quadrant pain and tenderness, although atypical presentations are common. Our patient was asymptomatic. Nonetheless, splenic infarction is an extremely rare cause of splenic rupture and has been mostly reported in patients with chronic renal failure undergoing dialysis treatment [2,7,13]. It is unclear what caused the splenic infarct in our patient and what contribution this made to the SSR.

The prompt initiation and implementation of the institutional massive transfusion protocol (MTP) played a very important part in the successful resuscitation of this patient. The MTP aims to facilitate ordering and provision of blood and blood components for patients experiencing massive blood loss in a timely fashion with an appropriate ratio of products in an effort to reduce the risk of mortality and improve clinical outcomes. Observational data have shown that such protocols may reduce the morbidity and mortality associated with hemorrhagic shock [14]. Although MTP is typically used in cases of hemorrhagic shock due to trauma or during surgery, this case illustrates that such a protocol can also be useful for massive hemorrhage in patients with hematologic malignancies, including those with profound cytopenias from AML or chemotherapy.

In summary, although SSR in patients with AML is very rare, a high index of suspicion is required for prompt diagnosis. Aggressive resuscitation, including timely and liberal use of blood products, and emergent surgical intervention are essential elements for successful management of this otherwise fatal condition.

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Figure 1.

Computed tomography (CT) imaging of the abdomen and pelvis showing (A) spleen at presentation, (B) spleen showing infarction, day 1 and (C, D) horizontal and coronal views of the ruptured spleen, day 2. (E, F) Pathologic specimens. (E) The diagnostic bone marrow aspirate (top, Diff-Quick $\times 40$) and corresponding biopsy (bottom, hematoxylin and eosin [H & E] $\times 40$) showing sheets of blasts with high nuclear cytoplasmic ratio, fine chromatin and prominent nucleoli. A subset of the cells show more abundant gray cytoplasm and convoluted nuclei consistent with monocytic features. (F) Spleen with pool of blood

consistent with rupture (arrowhead) and apoptotic white pulp (arrow) and congested red pulp (top, H & E $\times$ 4) and a higher magnification with arrow indicating white pulp apoptosis involving the left portion of a Malpighian body (bottom, H & E $\times$ 20). The spleen was not involved by leukemia. This was confirmed by negative immunohistochemical marking for CD34.