To the editor:

Fatal sickle cell crisis after granulocyte colony-stimulating factor administration

We summarize here a case involving a fatal sickle cell crisis in a patient with previously very mild hemoglobin sickle cell (Hb SC) disease. With granulocyte colony-stimulating factor (G-CSF) priming for peripheral stem cell collection, a crisis developed, followed by death within 36 hours. The case strongly suggests a role for granulocytes in acute sickle cell complications and a need for cautious use of G-CSF in this disease.

The patient was a 47-year-old African American woman who 6 weeks earlier learned that she had Hb SC disease. She had no history of sickle cell crises, although she occasionally had some joint pains that always resolved within a few hours after 1 or 2 doses of aspirin. She had pneumonia as a child, but no history of strokes, lower extremity ulcerations, gallstones, splenic infarctions, hypersplenism, bone infarcts, hip necrosis, blood transfusions, or ophthalmologic problems.

Hb SC disease was diagnosed after a hemoglobinopathy evaluation at the time of HLA typing, done in preparation for her to become a stem cell donor for her sister, who had chronic myeloid leukemia (CML) and mild Hb SC disease. The patient was the only sibling and had a 6 of 6 antigen match. After transplantation committee and ad hoc member reviews and careful discussions with donor and recipient, the patient proceeded with treatment to donate stem cells. She started daily G-CSF injections (400 $\mu g/M^2$) and dexamethasone (10 mg/M^2, starting on day 3) and noted some aches and pains in her back, legs, and shoulders. But on the fourth day of treatment, she awoke with the worst pain of her life, primarily affecting her lower back and thighs. She had no associated fevers, chills, dyspnea, cough, nausea, vomiting, diarrhea, or neurologic symptoms.

The admission physical exam revealed a well-developed and well-nourished woman writhing in pain. The vital signs included a temperature of 37.0°C (98.6°F), a pulse rate of 85, a respiratory rate of 24, and blood pressure of 138/94. The eyes had no scleral icterus. Results of the lung and heart exams were normal. The abdomen was nondistended with normal bowel sounds and flexed muscles but no obvious guarding or tenderness. No masses were noted. Lumbar and sacral spine regions, posterior pelvis, and both femurs were markedly tender. The skin and neurologic exams were normal. Table 1 shows the remarkable admission studies: the white blood cell (WBC) count differential had 72% segmented neutrophils, 21% band forms, 2% metamyelocytes, 2% lymphocytes, and 3% monocytes.

Intravenous hydration, scheduled morphine, and a single dose of ketorolac achieved good pain control. The next morning, the patient felt much improved and easily sat in a chair with only mild back pain remaining. But laboratory evaluation showed evidence of multiorgan injury and profound anemia (see "Hospital day 2" in Table 1). Packed red blood cell transfusions were given. Reevaluation of the abdomen showed the development of massive splenomegaly. The oxygen saturation dropped (95%), with a respiratory rate of 20. The patient received platelet transfusions followed by leukophoresis for both stem cell collection and the potential benefit of leukoreduction. The patient had a marked worsening of her respiratory status and arrested. Although the patient was revived, disseminated intravascular coagulation (DIC) developed and adequate oxygenation became impossible over the next several hours. She arrested a second time and ultimately expired. A postmortem bone marrow stem cell collection was performed to complete the harvest and achieve an adequate number of CD34 cells for transplantation to her sister the next day. The patient's sister has no evidence of CML 12 months after transplantation.

Microbiology cultures and parvovirus studies remained negative. The autopsy showed an enlarged spleen (weight, 1200 g) with infarctions and lacerations and a 1000 mL hemoperitoneum. The lungs were congested (weight, 1540 g), having vascular engorgement by red blood cells and neutrophil infiltrates. The liver had acute centrilobular congestion. No fat emboli were present.

Two other publications describe sickle cell disease complications after growth factor administration. One reports a vaso-occlusive pain crisis hours after topical administration of GM-CSF on a leg ulcer,[1] and another, the development of acute chest syndrome following administration of G-CSF before peripheral stem cell collection in a patient with homozygous sickle hemoglobin (hemoglobin SS) disease and a history of multiple sickle cell complications.[2] The latter case shares many similarities with the one presented here. But because the current case involves a patient with no prior history of sickle cell complications, it even more strongly implicates a role for the G-CSF and/or elevated WBC count in precipitating sickle cell complications.

Steady-state elevations of the WBC count have been linked with a worse clinical course.[3] But few data exist regarding the relationship between acute leukocytosis and a sickle cell crisis, even though granulocytes may play an active role in vaso-occlusion.[4] In part, the difficulty in determining the significance reflects the complexity of a sickle cell crisis that may include a concurrent infection and frequent increases in multiple cytokines that can affect inflammation.[5,6] In contrast to the usual clinical situation, these 2 reports involving G-CSF

Table 1. Laboratory studies of patient with Hb SC disease

	Baseline*	Admission	Hospital day 2
WBC count ($\times 10^3$/L)	4.8	57.8	70.9
Hemoglobin (g/dL)	10.5	11.2	5.4
Platelets ($\times 10^3$/L)	155	220	64
Creatinine (μM [mg/dL])	70.7 [0.8]	70.7 [0.8]	159.1 [1.8]
Alkaline phosphatase (U/L; normal, 39-117)	57	194	1364
Aspartate aminotransferase (U/L; normal, 0-31)	20	40	232
Lactate dehydrogenase (U/L; normal 120-240)	ND	ND	13 274
Hemoglobin oxygen saturation (2 L/min oxygen)	ND	99%-100%	95%

ND indicates not done.
*Prior to start of G-CSF.

administration present simpler backgrounds upon which to evaluate the effect of the WBC count. In both cases, complications occurred with the development of marked WBC count elevations a few days after initiating the cytokine treatment in clinically well individuals. These cases suggest that an acute elevation in the polymorphonuclear leukocyte count can promote acute sickle cell complications. Alternatively or additionally, G-CSF–induced changes in granulocyte function, such as increased adhesiveness, might have played a major pathogenic role in the above cases since leukocyte adhesion appears to contribute to the pathophysiology of sickle cell vaso-occlusion.[7] Thus, in the absence of infection, dehydration, or other clinically important conditions, a large number of adherent polymorphonuclear leukocytes might have precipitated the fatal vaso-occlusive event described above.

The present case supports the concept that granulocytes play, or can play, an important role in acute complications of sickle cell disease. The importance of granulocyte number, versus functional characteristics, remains unknown, but understanding the role of granulocytes in acute sickle cell events might provide insights for new therapeutic intervention in this disease. Pending a better understanding of the pathophysiology of vaso-occlusion, patients with sickle cell disease should receive G-CSF with great caution.

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References

1. Pieters R-C, Rojer R-A, Saleh A-W, Saleh A-E-C, Duits A-J. Molgramostim to treat SS-sickle cell leg ulcers [letter]. Lancet. 1995;345:528.
2. Abboud M, Laver J, Blau C-A. Granulocytosis causing sickle-cell crisis. Lancet. 19986;351:959.
3. Platt O-S, Brambilla D-J, Rosse W-F, et al. Mortality in sickle cell disease. New Engl J Med. 1994;330:1639-1644.
4. Fadlon E, Vordermeier S, Pearson T-C, et al. Blood polymophonuclear leukocytes from the majority of sickle cell patients in the crisis phase of the disease show enhanced adhesion to vascular endothelium and increased expression of CD64. Blood. 1998;91:266-274.
5. Duits A, Schnog B, Lard L, Saleh A, Rojer R. Elevated IL-8 levels during sickle cell crisis. Eur J Haematol. 1998;61:302-305.
6. Graido-Gonzalez E, Doherty J, Bergreen E, Organ G, Telfer M, McMillen M. Plasma endothelin-1, cytokine, and prostaglandin E2 levels in sickle cell disease and acute vaso-occlusive crisis. Blood. 1998;92:2551-2555.
7. Hoglund M, Hakansson L, Venge P. Effects of in vivo administration of G-CSF on neutrophil functions in healthy volunteers. Eur J Haematol. 1997;58:195-202.

To the editor:

Acquired and inherited risk factors for splanchnic venous thrombosis

We read with great interest the paper of Janssen et al.[1] They reported an increased risk for Budd-Chiari syndrome (BCS) or portal vein thrombosis (PVT) among carriers of factor V Leiden or inherited protein C deficiency. Overall, in 58% of their patients a possible inherited or acquired cause of thrombophilia was found; in 14% of cases there was the coexistence of inherited or acquired risk factors. In particular, there was an associated overt chronic myeloproliferative disease (CMD) in 28 (21%) of 135 patients. The authors did not consider the patients as affected by a CMD who did not meet all the diagnostic criteria but in whom the presence of spontaneous endogenous erythoid colonies (EECs) was detected. Indeed, such approach has repeatedly been reported as a useful diagnostic tool for identifying a CMD at very early stages.[2]

The association of unusual or latent forms of CMD diagnosed by means of the EECs assay has been reported in a large number of patients with BCS or PVT.[3-6] Review of 51 published cases with BCS and 69 cases with portal and/or mesenteric vein thrombosis showed the presence of an overt CMD in 49% of the patients with BCS and 23% of the patients with portal/mesenteric vein thrombosis; the inclusion of patients with latent CMD as defined by the presence of EECs increased the diagnostic yield to 78% among patients with BCS and 48% among patients with portal/mesenteric vein thrombosis.[7] Therefore, we suggest that the exclusion of latent CMD as possible underlying cause of splanchnic vein thrombosis could have overestimated the role of inherited thrombophilia as a single risk factor for BCS or PVT. In our series of 11 patients with BCS and 45 patients with portal/mesenteric vein thrombosis, 14 (25%) of 56 had inherited thrombophilia (1 had antithrombin III deficiency; 2, protein C deficiency; 8, factor V Leiden mutation; and 3, prothrombin G20210A), in good agreement with the 23% reported by Janssen et al.[1] Among the 31 patients assayed for the presence of EECs, 18 (58%) were considered to be affected by CMD, in 4 cases in association with inherited thrombophilia. An overt polycythemia vera or primary thrombocythemia was present in 7 (22%) of 31 such patients, in 4 cases at the time of thrombosis. Three of the patients with EECs as the only sign of CMD at the time of thrombosis later developed an overt thrombocythemia. Thus, in 14 patients the presence of a CMD even at early stages should have been missed not applying the EECs assay at the time of thrombosis. Among the 13 patients with no detectable EECs, 4 had inherited thrombophilia (3, factor V Leiden mutation; 1, prothrombin G20210A) and 4 had an acquired cause of thrombosis (1 case each of antiphospholipid antibodies, puerperium, trauma, and surgery). Therefore among the 31 patients exhaustively investigated, 26 (84%) had an inherited or acquired cause of thrombophilia or both. This percentage is higher than that reported by Janssen et al[1] and reflects the improvement in detection of CMD as underlying cause of thrombosis, confirming that a thorough search for CMD is mandatory in evaluating patients with splanchnic venous thrombosis. Diagnostic yield of atypical or precocious forms of CMD can be substantially increased by the use of the EECs assay or novel additional assays such as the megakaryocyte expression of the thrombopoietin receptor (c-*mpl*), whose decrease has been recently reported as a hallmark of polycythemia vera.[8]

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References

1. Janssen HLA, Meinardi JR, Vleggaar FP, et al. Factor V Leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis: results of a case-control study. Blood. 2000;96:2364-2368.
2. Westwood NB, Pearson TC. Diagnostic applications of hematopoietic progenitor culture techniques in polycythaemias and thrombocythaemias. Leuk Lymphoma. 1996;22(suppl 1):95-103.