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Evidence for complement-mediated bone marrow necrosis in a young adult with sickle cell disease

To the editor,

Bone marrow necrosis (BMN) describes extensive myeloid tissue and medullary stromal necrosis in hematopoietic bone marrow with stromal bone preservation, differentiating it from avascular necrosis (AVN) and aplastic crises [1]. BMN etiologies include chemotherapy, autoimmune disease, and hemoglobinopathies. Sickle cell disease (SCD) has a variety of orthopedic complications, most prominently AVN and osteomyelitis, but BMN is less well-appreciated. While SCD-associated BMN was first described nearly 80 years ago, the incidence is uncertain. One BMN case review reported that 2% had SCD, but a smaller SCD-focused series found BMN in 1 of 6 patients, suggesting the true incidence in SCD may be underappreciated [2,3].

Complement activation is increasingly recognized as a component of SCD pathophysiology. Free heme induces C5a production, producing hemolysis-induced thromboinflammation and vasoconstriction. It also contributes to SCD-related hyperhemolysis, where complement inhibition has been therapeutic [4]. Whether complement activation contributes to BMN is unclear. This case describes an individual with SCD who developed extensive BMN during a vaso-occlusive crisis (VOC) episode refractory to all interventions except eculizumab.

A 21-year-old individual with Hemoglobin SS Disease (HbSS) presented to the emergency department with back and knee pain consistent with previous VOCs. The patient had no preceding illness. Past medical history included recurrent acute chest syndrome, right hip AVN, and recent mild liver transaminase elevation consistent with sickle hepatopathy based on liver biopsy. The patient had never received blood products. Home medications included folic acid, L-glutamine, and voxelotor. Voxelotor had been started 11 weeks prior to presentation; hemoglobin rose from 7.1 g/dL to 11.7 g/dL after initiation. At admission, the hemoglobin was 10.2 g/dL with an absolute reticulocyte count (ARC) of 326 $\times$ 10^9/L, platelet count of 316 $\times$ 10^9/L, and white blood cell count of 15.5 $\times$ 10^9/L. Liver function testing showed alanine aminotransferase (ALT) of 73 U/L, aspartate aminotransferase (AST) of 94 U/L, and total bilirubin of 2 g/dL. Voxelotor was not on hospital formulary so the patient was off therapy until hospital day (HD) 3 once home supply was obtained.

After three uneventful days, laboratory studies on HD4 demonstrated a dramatic onset of marrow dysfunction, with hemoglobin 5.7 g/dL, ARC 68 $\times$ 10^9/L, and platelets 71 $\times$ 10^9/L. Total bilirubin rose to 3 g/dL. AST rose to 383 g/dL while ALT decreased to 51 g/dL. Urine microalbumin was 30 mg/dL (baseline unknown). Virologic workup for an infection-induced aplastic crisis was unrevealing. The patient developed worsening dyspnea, new fevers, and tachycardia with bibasilar opacities on chest radiograph on HD6 and received broad-spectrum antibiotics. COVID-19 was ruled out by polymerase chain reaction testing. Peripheral smear on HD6 showed numerous blister cells (Fig. 2A). The patient refused blood products until reaching a hemoglobin of 3.0 g/dL, at which point chest pain, troponin elevation (0.162 μg/L), and non-specific ST changes on electrocardiogram occurred. At this life-threatening juncture, the patient agreed to blood product use and one 40,000-unit dose of erythropoietin. On HD7, the patient received three packed red blood cell units with transient improvement but required two more on HD9 (Fig. 1C). Voxelotor was also stopped on HD7 and never restarted.

The patient concurrently developed severe thrombocytopenia, reaching a nadir of 3 $\times$ 10^9/L by HD10 (Fig. 1B). Thrombotic microangiopathy (TMA) concerns were raised given the severity of presentation and red blood cell fragments newly seen on peripheral smear (Fig. 2B). Two plasmapheresis treatments (HD9 and 10) provided little benefit. ADAMTS13 testing was normal. Corticosteroids were given on HD9 as an unsuccessful adjunct to plasmapheresis for hyperhemolysis. Four units of platelets were given over the next five days with little improvement. A bone marrow evaluation on HD10 demonstrated extensive BMN (Fig. 3). Given the refractory course to date, a complement-mediated process was considered. Eculizumab (900 mg) was given on HD13. The platelet count rose quickly within two days without further transfusions, reaching 226 $\times$ 10^9/L five days after eculizumab. Hemoglobin and ARC also returned to baseline and the patient was discharged on HD17. Complement testing was unable to be performed before eculizumab but on day 18 of the clinical course, total complement (CH50) was 21.9 U/mL (normal range 39–90 U/mL). C3 and C4 were 204 U/mL (normal range 81–157 U/mL) and 57 U/mL (normal range 13–39 U/mL), respectively, one week after discharge (12 days post-eculizumab). CH50 was > 90 U/mL two weeks post-discharge. The patient has maintained transfusion-independent blood counts without further eculizumab as of fourteen weeks after discharge (hemoglobin 7.4 g/dL, platelets 228 $\times$ 10^9/L).

SCD-associated BMN occurs but the true incidence is unclear and may not be linked to classic SCD symptomatology. Non-HbSS genotypes may be at higher risk for BMN than HbSS, potentially due to higher hematocrit [5]. One potential link to BMN could be the disordered SCD marrow microvasculature. Recent research found that SCD produces disorganized and structurally abnormal marrow vascular networks with congested with erythrocyte aggregates that was reversible with regular transfusions [6].

Complement activation is increased in SCD, including at baseline. To date, complement-mediated cytotoxicity (CMT) in SCD has been associated with circulating free heme, associated endothelial cytotoxicity, and thromboinflammatory effects [7,8]. Hemopexin and hydroxyurea have both been shown to reduce complement activation. Eculizumab, an anti-C5 monoclonal antibody, reduces CMT in disorders like transplant-associated TMA. Eculizumab reduced *in vitro* CMT in a small SCD case series but its use has been limited to treating hyperhemolysis [4]. While CMT contributes to SCD pathogenesis, its role in BMN is uncertain, since this research area generally focuses on peripheral hemolysis. It is not definitively known what triggered BMN in this case but given the rapid recovery after eculizumab, CMT was likely

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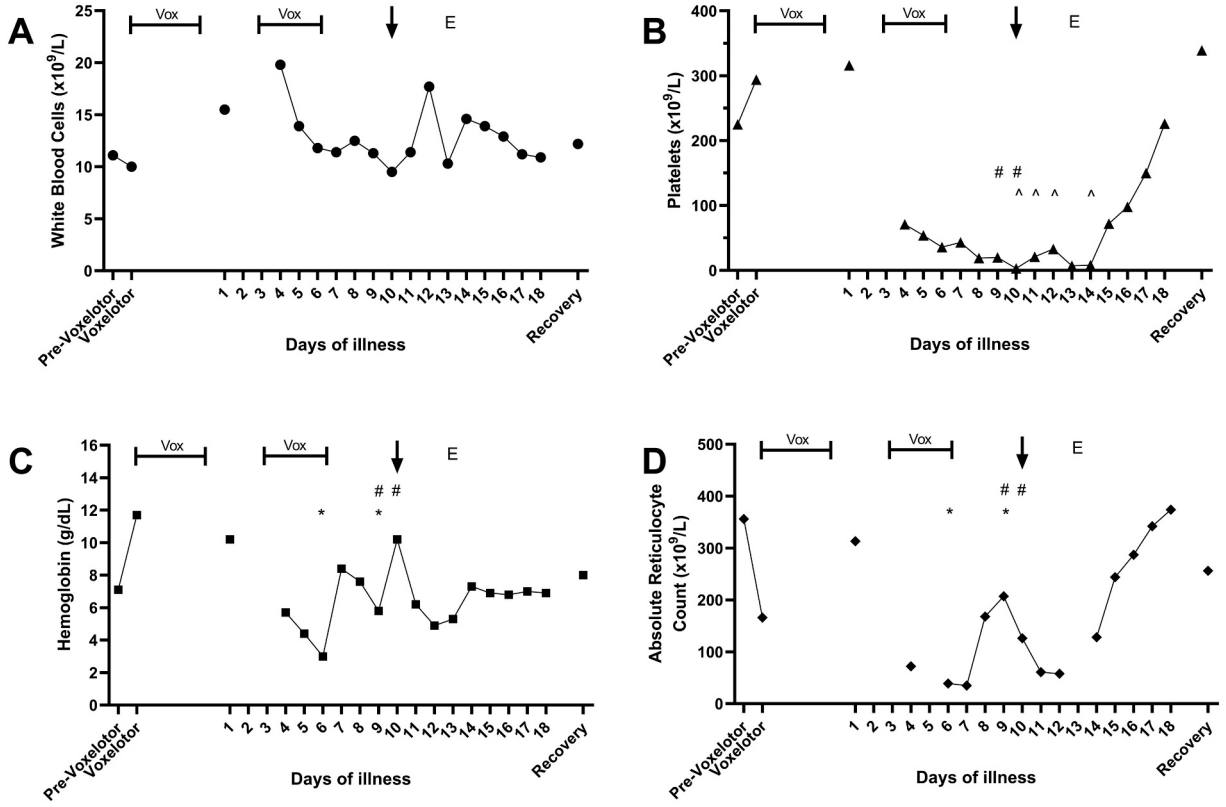

Fig. 1. Severe refractory hypoproliferative anemia and thrombocytopenia was successfully treated with eculizumab. White blood cell count, platelet count, hemoglobin, and absolute reticulocyte count (A-D, respectively) trends are shown, including pre-voxelotor averages and while on voxelotor. On the x-axis, the gap between "voxelotor" and the first day of illness represents 76 days. The time after discharge and the "recovery" time point is 41 days. "Days of illness" represents hospital course. # represents plasma exchange (1.5 episodes since the first had to be stopped early due to dyspnea). * represents packed red blood cell transfusion (5 units total; 3 on the first marked day and 2 on the second). ^ represents platelet transfusions (4 units total, one daily). The black arrow marks the day of bone marrow biopsy. The "Vox" bars represent the time frame on voxelotor, including a three-day gap without it early in admission. E represents the eculizumab dose, 900 mg. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

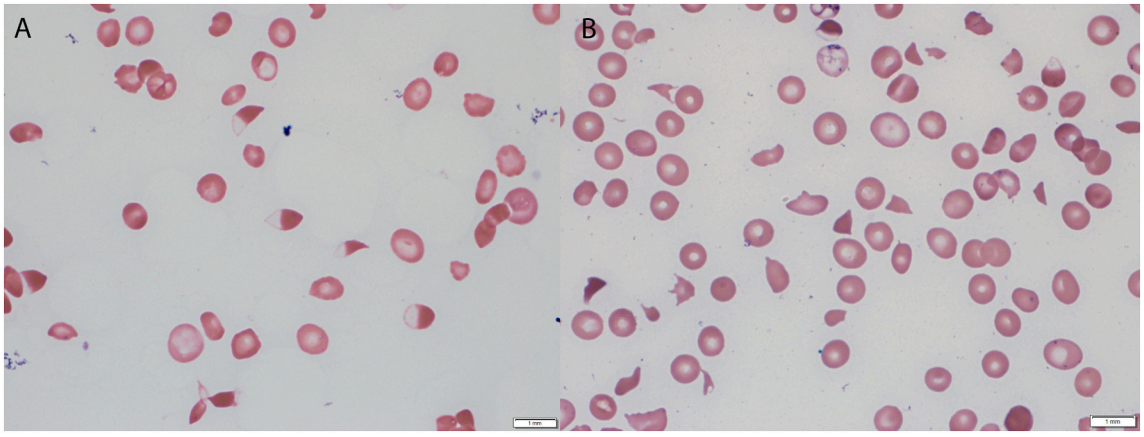

Fig. 2. Peripheral blood smear findings for HbSS patient in vaso-occlusive crisis with progressive anemia and thrombocytopenia. Peripheral blood smears collected on hospital day (HD) 6 and HD9 (A and B, respectively), both stained with Wright Giemsa, with 1000× magnification using an oil immersion lens. (A) On HD6, blister cells, characterized by what appears to be a peripherally located vacuole within the erythrocyte with the hemoglobin condensed on one side of the cell and the thin cell membrane visible outlining the "blister." (B) On HD9, although blister cells can still be seen, red blood cell fragments, including schistocytes, red blood cells characterized by three sharp points and a lack of central pallor, are easily identified. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a major factor.

The authors are unaware of any previous CMT-associated BMN reports or those describing eculizumab use to treat BMN in SCD or otherwise. While pre-treatment complement levels were not obtained to help corroborate the suspected BMN pathogenesis, the robust response suggests a complement-mediated etiology. Reassuringly, the patient has not had any BMN relapses to date. This case reinforces complement's role in SCD pathogenesis as well as a novel association with BMN.

CRediT authorship contribution statement

MA, SS, and AAB drafted the original manuscript. SW provided

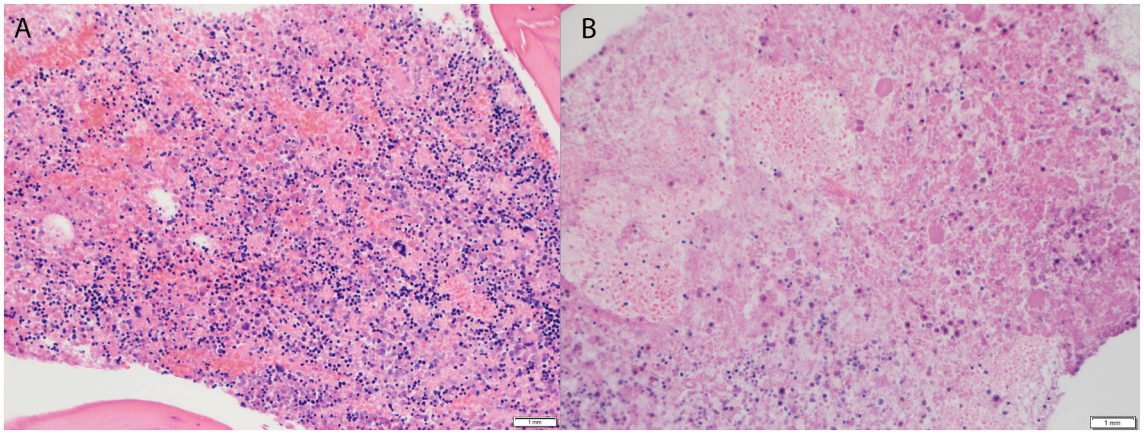

Fig. 3. Bone marrow necrosis present on bone marrow trephine core of a HbSS patient with vaso-occlusive crisis with progressive anemia and thrombocytopenia. Bone marrow biopsy collected on hospital day 10 showed variable stages of coagulative necrosis of hematopoietic elements on adjacent high power fields. Erythroid nuclei are still identifiable in (A), with more extensive necrosis in (B) with only outlines of cells identifiable. Both images are paraffin-embedded hematoxylin and eosin, 500× oil immersion lens.

pathology images and analysis. SW and GMV contributed to manuscript revisions. All authors approved the final manuscript.

Declaration of competing interest

The authors have no disclosures pertinent to this manuscript.

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