# A Case of Hemoglobin SE Presenting with Sickle Cell Crisis: Case Report And Histological Correlation

**Dear Editor**,

A 66-year-old Bangladeshi woman with a 10-year history of rheumatoid arthritis (RA) presented with acute sharp rib and upper back pain of 2 weeks' duration. This was aggravated by movement and relieved by rest, without preceding trauma. Her RA was previously diagnosed based on the physical findings of active synovitis of her metacarpophalangeal, knees, ankles and metatarsophalangeal joints associated with high titre rheumatoid factor (RF) of 251 IU/ml, erythrocyte sedimentation rate (ESR) 32 mm/hr and C-reactive protein (CRP) 13 mg/L. Previous DMARD therapy included methotrexate, sulfasalazine and leflunomide. She had long standing microcytic anemia (baseline Hb10.2g/dL) attributed to compound heterozygosity for haemoglobin E and sickle cell (HbSE) confirmed on haemoglobin electrophoresis. Previous investigations also showed a negative Direct Coombs test and a reactive bone marrow with erythroid hyperplasia on bone marrow examination.

At presentation, her RA was quiescent on prednisolone 7.5mg daily. Physical examination revealed focal tenderness at the T12/L1 region. Pain intensified and spread within a day to involve the chest wall, shoulder and pelvic girdles. There was no active synovitis of her joints. She was febrile (temperature 38 °C) and tachypnoeic with hypoxaemia on room air ($PaO_2$ 46.5 mmHg). Blood investigations showed microcytic anaemia (9.3 g/dL), normal platelet count (174 x $10^9$/L), absence of leukocytosis (7960/$mm^3$) but elevated ESR (80mm/hr) and CRP (90mg/L). Peripheral blood film showed mildly microcytic and hypochromic red blood cells, but no sickle cells. Reticulocyte count was elevated at 113.4 x $10^9$/L (29.13-112.60). Unconjugated bilirubin and lactate dehydrogenase were 32 umol/L (5-25) and 2478 U/L (300-700) respectively. Chest radiograph and electrocardiogram were normal. Haemoglobin electrophoresis (at alkaline and acid pH) and high performance liquid chromatography demonstrated presence of HbE and HbS, with HbS at 61.2% and HbF at 7.2%. This was confirmed with thalassaemia genotyping and sickling tests. Pulmonary embolism was excluded by CT pulmonary angiography which showed bilateral basal collapse-consolidation. Magnetic resonance imaging (MRI) showed multiple levels of disc desiccation and avascular necrosis of both femoral heads, without fragility fractures. A bone scan revealed multiple hot spots in the thoracolumbar spine, bilateral ribs, hemipelves, humeri and femoral heads. CT guided biopsy of the right sacral ala showed markedly hypocellular bone marrow with extensive areas of necrosis and haemorrhage, suggesting that the hot spots visualised on the bone scan were bone infarcts secondary to preceding vasoocclusive bony crisis. (Fig. 1). The patient was treated with empiric antibiotics for community acquired pneumonia. In view of her history of HbSE, severe bone pain with bone infarcts and acute respiratory symptoms with hypoxaemia, a diagnosis of acute vasoocclusive bony crisis and acute chest syndrome was made. She improved clinically with 2 units of red blood cell concentrate transfusion, supplemental oxygen, intravenous hydration and opioid analgesia. Hydroxyurea was started and she remains well to date with no further episodes of vasoocclusive crisis.

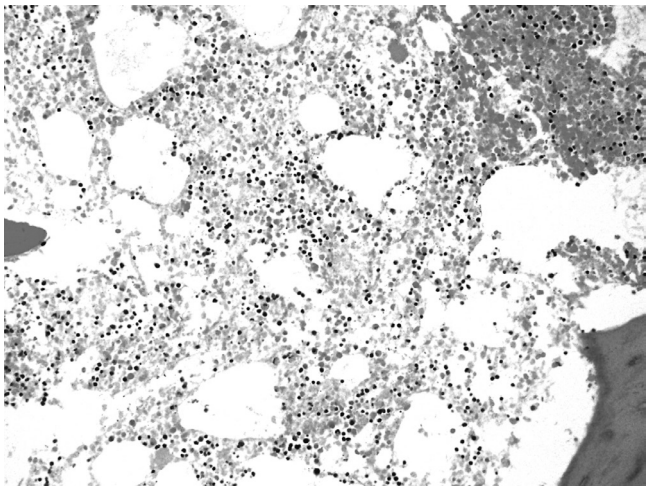

Fig. 1. Hypocellular bone marrow with extensive areas of necrosis and haemorrhage. Trilineage hematopoiesis is seen in the more viable areas.

## Discussion

Double heterozygosity for HbS and HbE is rare as evident by a paucity of literature. We report vasoocclusive crisis and bony infarcts in a patient with RA with previously asymptomatic HbSE disease. Musculoskeletal abnormalities in sickle cell disease are well described. Sickle cell crisis is often associated with periarticular and joint pain, tenderness, warmth and effusion due to ischaemia and infarction of synovium and adjacent bone and bone marrow. This has resulted in reports of delayed diagnosis of RA in patients

with sickle cell disease.[1] Conceivably, sickle cell disease can mimic RA. Our patient's chronic inflammatory arthritis with evidence of synovitis, high-titer RF and response to DMARD therapy was compatible with RA. Our index of suspicion for an alternative diagnosis was high at this presentation as the distribution of pain was atypical (severe, generalised and requiring intravenous opioids) and synovitis was absent. Osteoporotic vertebral fracture was excluded by MRI. However, our patient had osteonecrosis of the femoral heads. Widespread osteonecrosis or infarction of bone marrow involving the axial skeleton and ribs is unusual for chronic steroid use. Investigations to exclude an underlying malignancy were negative as over 90% of cases of bone marrow infarction are associated with malignancy.[2]

Unlike sickle cell anaemia, HbSE is regarded as a benign condition with mild asymptomatic anaemia. The disease tends to follow a benign course in childhood, with sickling complications more likely to develop in adulthood.[3,4] There are anecdotal reports of severe clinical presentations, such as vasoocclusive crisis, osteonecrosis and bone marrow infarctions.[3,5,6] The hallmark of sickle cell disease is painful vasoocclusive disease, culminating in infarcts and bone necrosis. Bone marrow is particularly vulnerable due to microcirculation occlusion.[2,6] The clinical features of acute chest syndrome (ACS) are almost indistinguishable from community acquired pneumonia, which may be co-existent.

Our patient received empirical antibiotics. Fever, cough, chest pain, tachypnoea, pain in the limbs, ribs, sternum or abdomen are common symptoms at diagnosis of ACS. Interestingly, sickling crisis in HbSE disorder may occur in the absence of sickle cells in the peripheral blood, hence the importance of clinical acumen when there is no diagnostic test.[5] The rapid resolution of acute generalised pain with supportive treatment and opioid analgesia lends credence to the diagnosis of an acute pain episode and ACS in sickle cell disease as the cause of the current presentation. Hydroxyurea has been shown to decrease the rate of acute painful episodes and episodes of ACS.[7] Our patient was started on hydroxyurea for pharmacologic induction of HbF in view of her severe presentation of vasoocclusive crisis and acute chest syndrome. Our case underscores the importance of vigilance, recognition and appropriate treatment of patients with HbSE disease when they develop sickling-related symptoms and complications.

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