

## Sickle cell disease associated with uric acid deposition disease

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**SUMMARY** The infrequent occurrence of gout in patients with sickle cell anaemia contrasts with the high incidence of hyperuricaemia and impaired renal function. This report records the third case of synovial membrane uric acid deposition and the first case of tophaceous deposits in haemoglobin SS patients. The limitations of a diagnosis of gout on the basis of hyperuricaemia and arthritis are confirmed. Analysis of reported cases suggests the existence of 2 forms of arthritis associated with sickle cell anaemia—noninflammatory and inflammatory. Paradoxically, gout appears to be associated with the former, in which the pathophysiological changes probably prevent or diminish the acute inflammatory response.

Secondary gout is a well recognised complication of disorders characterised by increased nucleic acid catabolism and disordered renal function. Its notable rarity in patients with haemoglobinopathies, such as sickle cell anaemia, stimulates speculation on certain aspects of the pathogenesis of gout. The frequency of hyperuricaemia and impaired renal function in sickle cell disease is not accompanied by the expected incidence of gouty arthritis. Ball and Sorensen's report<sup>1</sup> of a 37-year-old black male with haemoglobin SS disease and arthritis involving the ankles, elbows, knees, and feet appears to be the only previous identification of uric acid crystals in joint fluid in a patient with sickle cell anaemia. Patel<sup>2</sup> identified uric acid crystals in the synovial membrane of a 48-year-old black male with haemoglobin SS disease and gonarthrosis, while unable to demonstrate crystals in the synovial fluid. Ransone and Lange's report<sup>3</sup> of tophi in a 79-year-old male with haemoglobin CC disease appears to be the only previous report of tophi in association with any haemoglobinopathy. Other synovial fluid parameters have not been reported in these cases.

The association of sickle cell disease with hyperuricaemia and the response of the associated arth-

ritis to colchicine has been reported as indicative of gouty attacks. However, the response of the arthritis of sickle cell anaemia to colchicine has not been evaluated and a nonspecific effect on that arthritis rather than a specific 'antigout' effect may be operative. Two cases of uric acid deposition disease in patients with haemoglobin SS disease are presented.

### Case reports

#### CASE 1

A 49-year-old black male with haemoglobin SS, by electrophoretic pattern and solubility, presented with 5 weeks' pain and swelling of his left hip, left knee, and both ankles. The arthritis progressed to pain and swelling of his shoulders, wrists, and second and third metacarpophalangeal joints bilaterally. His first right metatarsophalangeal joint became swollen, red, hot, and 'so tender I could not put the sheet over it'. Previous medical history revealed aseptic necrosis of the left femoral head 4 years prior to this admission, and mitral regurgitation with cardiac failure diagnosed 2 years previously. The patient had not been transfused in 22 years in spite of a marked chronic anaemia and a haematocrit of 12% for the past year.

Physical examination revealed a middle-aged black male in moderate distress, febrile to 38°C. Both shoulders, elbows, wrists, knees, ankles, the

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left hip, metacarpophalangeal, and proximal interphalangeal joints were tender. Decreased range of motion was noted in both shoulders and the right wrist. The left elbow, knee, ankle, and right third metacarpophalangeal joints were swollen. Physical examination was otherwise unremarkable with the exception of scleral icterus, clubbing of the nails, pallor of mucous membranes, and a grade IV/VI holosystolic murmur radiating to the axilla.

Laboratory examination revealed haematocrit of 10.5%, reticulocyte count 8%, white blood count  $12\,300/\text{mm}^3$  ( $12.3 \times 10^9/\text{l}$ ) with 47% polymorphonuclear leucocytes and 53% lymphocytes. Serum creatinine was 3.7 mg/100 ml (327  $\mu\text{mol/l}$ ), blood urea nitrogen 57 mg/100 ml (normal 6–23), LDH 668 IU/ml, colorimetric uric acid 14.1 mg/100 ml (normal <8), Westergren erythrocyte sedimentation rate 20 mm/h, and urine analysis revealed 3+ protein. Arthrocentesis of the left knee revealed clear fluid with a good mucin clot, less than 200 leucocytes/ $\text{mm}^3$  ( $0.2 \times 10^9/\text{l}$ ), and no crystals or organisms. Arthrocentesis of the left knee revealed clear fluid with a good mucin clot, 1994 leucocytes/ $\text{mm}^3$  ( $2 \times 10^9/\text{l}$ ) with 94% mononuclear cells and 6% polymorphonuclear leucocytes, and strongly negative birefringent crystals morphologically identical to monosodium urate crystals. The patient responded to indomethacin therapy with resolution of symptoms.

#### CASE 2

A 28-year-old black male with haemoglobin SS presented with pain and swelling in his left second metacarpophalangeal joint which progressed over 24 hours to involve wrists, elbows, shoulders, knees, ankles, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints.

Physical examination revealed a thin black male in moderate distress, febrile to 39.2°C. Both wrists, elbows, shoulders, knees, ankles, all metatarsophalangeal, metacarpophalangeal, and proximal interphalangeal joints were warm and tender. Effusions were present in both knees, both wrists, the second through fifth metacarpophalangeal joints bilaterally, and in the proximal interphalangeal joints. Examination of the neck revealed decreased range of motion, and tenderness was present over most of the long bones. Examination was otherwise unremarkable with the exception of a tophus on the antihelix of the right ear and a low pitched systolic ejection murmur at the lower left sternal border with radiation to the neck.

Laboratory examination revealed haematocrit 23%, reticulocyte count 36%, uncorrected white cell count  $18\,500/\text{mm}^3$  ( $18.5 \times 10^9/\text{l}$ ) with 89% polymorphonuclear leucocytes, 5% lymphocytes,

and 6% monocytes, colorimetric uric acid 10.0/100 ml (normal <8), blood urea nitrogen 11 mg/100 ml (normal 6–23), creatinine 1.1 mg/100 ml (97  $\mu\text{mol/l}$ ), and a creatinine clearance of 55 ml/min. Arthrocentesis of the right knee revealed intracellular, strongly negative birefringent, needle-shaped crystals, as did the right third metacarpophalangeal joint. Roentgenographic examination showed multiple lytic bone lesions around the left fifth metatarsophalangeal joint and erosions of the lateral aspect of the right first metatarsophalangeal joint and medial aspect of the right second metatarsophalangeal joint (Fig. 1). The third metacarpophalangeal joints had erosions with overhanging edges typical of Martel's 'overhang' sign (Fig. 2). The acute arthritis responded to indomethacin therapy with resolution of symptoms.

#### Discussion

The arthritis associated with sickle cell disease tends to be polyarticular (84%) and symmetrical



Fig. 1 Anterolateral projection of foot radiographs in case 2 demonstrate erosive changes of the metatarsophalangeal joints.



Fig. 2 Postero-anterior projection of hand radiograph in case 2 demonstrates erosive changes of the third metacarpophalangeal joint with overhanging edges typical of Martel's 'overhang' sign.

(65%), with a predilection for large joints and the lower extremities, and generally lasting less than 1 week (range 3–10 days).<sup>4</sup> In the review by Espinoza *et al.*<sup>4</sup> a monocyclic pattern predominated (66%), though the length of follow-up observation was not stated. Synovial fluid examination has revealed yellow, clear or haemorrhagic fluid of a non-inflammatory<sup>5</sup> or a mildly inflammatory<sup>6</sup> nature. Espinoza *et al.*<sup>4</sup> reported synovial fluid findings in 12 patients with sickle cell anaemia.

We noted that these patients could be divided into 2 groups. Six were noninflammatory (less than 2000 cells per 100 ml) and 8 were inflammatory, 2 of the latter being purulent. The inflammatory effusions contained sickled red blood cells, whereas the noninflammatory ones did not. The non-inflammatory fluids had lower synovial fluid total haemolytic complement ( $CH_{50}$ ) than inflammatory fluids, 22–40 U/ml (mean 30), versus 50–80 U/ml (mean 70 respectively, significantly different by Student's *t* test ( $P > 0.001$ )).

This suggests 2 types of arthritis in sickle cell anaemia. The first produces a transudate and the second an exudate. Schumacher's cases of sickle cell arthritis are all of the first type. The synovial fluid findings in reported patients with sickle cell anaemia and associated uric acid deposition disease are also of the first type. Schumacher *et al.*<sup>5</sup> observed pathological changes in sickle cell arthritis of congestion and thrombosis of small vessels with thickening and occasional multiamination of their basement membranes.

One possible hypothesis for the limited observation of gout in sickle cell disease is based on Schumacher's report of pathological findings in synovium in

sickle cell disease.<sup>5</sup> Congestion and thrombosis of small vessels, with resultant circulatory impairment, may prevent white blood cells from responding to the chemotactic stimulus of uric acid crystals. Acute gouty attacks require the presence of polymorphonuclear cells<sup>7–9</sup> and may be impaired either directly because of the vasculopathy of sickle cell disease or indirectly via impaired generation of chemotactic factors.<sup>10</sup>

Penny<sup>11</sup> reported on interference of colchicine with leucocyte migration from blood vessels, suggesting a similar mechanism to the one presented herein for reducing inflammation. The activity of polymorphonuclear leucocytes is greatly reduced under anaerobic conditions,<sup>12</sup> and they may not be able to initiate inflammation under conditions which have been shown to be present in sickle cell anaemia.<sup>13</sup>

Another reason why gout may not occur so often in the haemoglobinopathies in spite of hyperuricaemia is that aging in the joints and degenerative changes set the stage for urate crystallisation in joint fluids and tissues that are only moderately supersaturated with urate, and sickle cell patients usually do not live long enough for this to occur. Our case 1 is an exception to this prognosis, having lived to age 49 with a reasonably good cardiopulmonary status, so he might represent a high haemoglobin F syndrome. As in our case 2, when hyperuricaemia is very severe, aging and degenerative changes in the joints do not seem to be necessary for acute gouty arthritis. It is also possible that the azotaemic state in some way inhibits the inflammatory response.

Most reports of the association of gout with sickle

Table 1 Uric acid deposition disease associated with haemoglobinopathy

Profile	Hgb	Joint involvement	Tophi	Hct	UA	WBC	%P	Crystals	Syn bx
37 B (M)	SS	Ankle, knee, elbow, feet	—	20	11	NA	NA	+	NA
48 B	SS	Knee	—	NA	13.8	NA	NA	—	+
79 B (M)	CC	Knee, ankles, feet	+	19	11	NA	NA	NA	NA
49 B (M)*	SS	Ankle	—	10.5	14.1	200	10	—	NA
		Knee	—			1994	6	+	NA
28 B (M)*	SS	MCP, knee	+	23	10.0	NA	NA	+	NA

Hgb = Haemoglobin electrophoresis. UA = Serum uric acid level. Hct = Haematocrit. %P = Percent polymorphonuclear leucocytes. Syn bx = Presence of crystals on synovial biopsy. WBC = White blood count. \*Cases reported here.

cell anaemia are based on the presence of hyperuricaemia and response to colchicine,<sup>14-16</sup> not on demonstration of crystals.<sup>5 15 16</sup> This response to colchicine is nonspecific. Some cases of sarcoidosis, pseudogout, familial Mediterranean fever, and rheumatoid arthritis have been reported to improve dramatically with colchicine therapy. The arthritis of sickle cell anaemia may itself be responsive to colchicine.

Table 1 characterises the previously reported cases of uric acid deposition disease in association with a haemoglobinopathy and compares them to the cases reported herein. The joint involvement has generally been of an additive nature, superimposed on a chronic arthritis.

The presence of a left shift in sickle cell anaemia, as seen in case 2, should suggest the presence of an additional causality for the episode. Sickle cell anaemia in crisis is not associated with a left shift (Diggs, personal communication). Metatarsophalangeal, metacarpophalangeal, and proximal interphalangeal involvement is not found after age 15 (Diggs, personal communication) in sickle cell disease and crisis, and involvement of such joints should prompt search for an alternative cause.

The presentation in the reported cases is classic for gout. The low white blood cell counts in the synovial fluid at time of evaluation, and the absence of ingested crystals in the first case, suggest that the crystals might be incidental to the arthritis and that one is observing one end of the spectrum of sickle cell arthritis, that is, the transudative, noninflammatory type rather than gouty arthritis in a patient with sickle cell disease. Case 2 is the first reported case of the association of tophaceous gout with haemoglobin SS disease.

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