

Non-gouty arthritis in sickle cell disease: report of 37 consecutive cases

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SUMMARY Arthritis in association with sickle cell disease was seen in 37 patients in a 2½-year period. Cases of gout and of avascular necrosis of the femoral head were excluded. In 12 patients a non-inflammatory effusion occurred during the course of a painful crisis, in 12 patients an ankle effusion occurred in association with spontaneous development or deterioration of leg ulceration, and in 13 patients there was a group of miscellaneous arthritides. Ankle arthritis with leg ulceration has not been previously recognised, and its association with spontaneous ulceration, which is presumed to have a vaso-occlusive origin, is compatible with ischaemic synovial damage. The aetiology may therefore be similar to that believed to account for effusions in association with the painful crisis.

The incidence and pattern of true arthritis in sickle cell disease is largely unknown. Well established causes of arthritis include joint damage associated with avascular necrosis of the femoral head^{1 2} and gout secondary to hyperuricaemia.³⁻⁵ Less common causes include infective arthritis,⁶⁻⁹ migratory polyarthritis,^{10 11} and systemic lupus erythematosus,¹²⁻¹⁴ although it is unclear whether these are causally linked or occur coincidentally with sickle cell disease.

Pains related to the joints commonly occur in the painful crisis, but these are generally attributable to avascular necrosis of bone marrow in the juxta-articular areas of the long bones.^{15 16} A true arthritis may also occur in association with the painful crisis,^{11 17-19} although little is known of its frequency, characteristics, or outcome.

At a large sickle cell clinic in Jamaica 37 patients with sickle cell disease and arthritis unassociated with gout or avascular necrosis of the femoral head have been assessed in a 2½-year period. These have included 12 patients developing arthritis during a painful crisis, 13 with miscellaneous arthritides, and 12 with a newly recognised syndrome of ankle arthritis associated with recent leg ulceration. The characteristics of these groups are presented.

Patients and methods

The patients attended the sickle cell clinic of the University Hospital of the West Indies in Kingston and a group of peripheral sickle cell clinics operated by the staff of the Medical Research Council (MRC) Laboratories during the period March 1980 to November 1982. Patients with arthritis associated with gout or with avascular necrosis of the femoral head were excluded, as were patients with painful limitation of the hip in which early avascular necrosis of the femoral head could not be ruled out. There remained 37 patients in whom the diagnosis of haemoglobinopathy was made by standard criteria.²⁰ Thirty-one had homozygous sickle cell (SS) disease, five had sickle cell-haemoglobin C (SC) disease, and one had sickle cell-beta° thalassaemia (Sβ° thal).

The diagnosis of arthritis was based on objective signs which included warmth, swelling, effusion, and limitation of movement in at least one joint. When possible, joint fluid was aspirated and examined for total white blood cell and differential counts, under polarised light for crystals, and by bacterial culture. If only limited amounts of fluid were obtained, examination was confined to culture and presence of crystals. The viscosity of synovial fluid was assessed semiquantitatively by observing it dropping from the aspiration needle.

Haematological investigations including red cell indices, reticulocyte and irreversibly sickled cell

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(ISC) counts, and estimations of bilirubin and fetal haemoglobin (HbF) were performed as previously described.²¹ Certain of these haematological indices were not normally distributed, and comparison of their distributions in the different groups was performed after transformation to obtain a more normal distribution. These transformations were considered appropriate for HbF, red cell count (RBC), reticulocytes, total bilirubin, and ISC count and the following transformations were used: \log_e (HbF + 1), \log_e RBC, \log_e (retic + 1), \log_e (total bilirubin + 1), and \log_e (ISC + 10). Other tests included serum urate and creatinine, VDRL, liver function tests, and tests for latex fixation, anti-nuclear antibodies, DNA binding, serum complement C₃, C₄, factor B, and immunoglobulins. Radiographs of affected joints were taken, including the sacroiliac joint where indicated.

Results

During the period of the study approximately 1100 patients with SS disease of which seven were known to have gout and 55 were known to have avascular necrosis of the femoral head attended these clinics. Since these complications and the arthritides described in this report were almost confined to patients over the age of 10 years, the population at risk would be of the order of 700 patients with SS disease. These gross assumptions would approximate assessments of the prevalence of gout at 1%, avascular necrosis of the femoral head at 8%, and of other arthritides at 4% of this patient sample.

Of the 37 patients with arthritis, 12 had arthritis in association with the painful crisis (group I), 12 had arthritis of the ankle associated with leg ulceration (group II), and 13 had a systemic, infectious, or degenerative type of arthritis (group III).

Group I. Arthritis associated with painful crisis. Arthritis during the course of a painful crisis was observed in 12 patients (11 SS, 1 SC) of which 6 were male and 6 were female with a mean age of 26.9 years (range 16–40 years). A monoarthritis affected the knee in eight, and the ankle in two, one patient had an oligoarthritis involving both knees and one ankle, and the other a polyarthritis involving elbows, knees, and ankles. These 12 patients were all seen by one observer (K. de C.) during a period when the same observer assessed 64 patients in painful crisis suggesting a prevalence of arthritis of approximately 20% in those attending clinic for painful crises.

All patients had typical painful crises with symptoms maximal around the affected joint. The involved joints were swollen, but with only slight limitation of movement, and the point of maximal

tenderness was over the epiphyses rather than the joint space. Radiographs at the time of pain did not reveal changes different from those in the steady state and on convalescence there were no radiological features of avascular necrosis of bone. Synovial fluid was generally non-inflammatory and without crystals (Table 1).

The arthritis usually resolved within 2–3 weeks, though it persisted for four months in one patient. The prognosis was excellent, all patients healing without residual functional impairment.

Group II. Arthritis associated with leg ulceration. Arthritis limited to the ankle and which affected the same area as a typical malleolar ulcer occurred in 12 patients. All had SS disease. There were 4 males and 8 females with a mean age of 27.2 years (range 18–41 years).

The arthritis appeared simultaneously or shortly after the development of a spontaneous leg ulcer in seven patients or at the same time as the spontaneous deterioration of an existing ulcer in five patients. In two patients ulceration and arthritis were bilateral. There was usually extreme limitation of ankle movement which impaired walking. Joint fluid was typically non-inflammatory, with predominantly mononuclear cells, sterile, and without urate crystals (Table 1). In one patient the synovial fluid leucocyte count was $15.3 \times 10^9/l$, but only 2% were polymorphonuclear cells, the serum urate was 0.56 mmol/l, and no crystals were seen in the joint fluid. The diagnosis of gout was considered unlikely and rapid resolution of the arthritis attended healing of the leg ulcer. Radiology in this group failed to show any acute changes.

Arthritis associated with leg ulceration was usually chronic (mean duration 7.7 months, range 1–26 months) and resolved with improvement of the leg ulcer. Swelling and limitation of movement markedly improved with conventional non-steroid

Table 1 *Synovial fluid analysis in arthritis in SS disease*

| | Normal | Arthritis with painful crisis (n=8) | Arthritis with leg ulceration (n=7) |
|--|-------------------|-------------------------------------|-------------------------------------|
| Appearance | Clear, colourless | Yellow | Yellow |
| Abnormal viscosity | 0 | 0/8 | 3/7 |
| Nucleated cells ($\times 10^9/l$) (mean-range) | <0.2 | 2.5 (0.7–6.1) | 4.3 (0.6–15.3) |
| % polymorphonuclear leucocytes (mean range) | <25 | 9 (0–18) | 13 (2–34) |
| Crystals | 0 | 0 | 0 |
| Culture | Sterile | Sterile | Sterile |

anti-inflammatory drugs. Resolution was usually complete with full function and without radiological abnormalities.

Group III. Miscellaneous arthritides. Thirteen patients (8 SS, 4 SC, 1 S β° thal) presented with a variety of systemic arthritic disorders. All were female and the mean age was 29 years (range 7–69 years). Typical systemic lupus erythematosus (SLE) with non-deforming arthritis, erythematous skin rash, alopecia, high DNA binding, and low serum complement occurred in one patient, and in two others there was a chronic non-deforming polyarthritis with positive antinuclear antibody test (ANA) but without other features of SLE. Other causes included seropositive erosive rheumatoid arthritis in one, arthritis associated with ulcerative colitis in one, osteoarthritis of the knee in two, gonococcal arthritis in one, self-limiting flitting polyarthritis with negative antistreptolysin O titre and negative bacteriology in two, and chronic seronegative monoarthritis of the knee with quadriceps atrophy in two. One patient with SC disease had severe rheumatic heart disease and a chronic arthritis of the right hip.

The patient with ulcerative colitis received systemic corticosteroids and developed severe recurrent painful crises until the treatment was stopped. The gonococcal arthritis responded dramatically to intravenous penicillin. The non-infectious polyarthritides were well controlled on ibuprofen.

Investigations. Synovial fluid findings in the group with arthritis associated with painful crises and with leg ulceration are shown in Table 1.

The haematology in individuals during the period of arthritis showed no consistent differences when compared with their own steady state values. The steady state haematology in patients developing arthritis did not differ from that in SS controls of similar age (Table 2).

Serum immunoglobulin and complement components also showed no significant differences in the groups with arthritis.

Discussion

The symptoms of sickle cell disease are not infrequently misdiagnosed as 'rheumatism' or arthritis, because the painful crisis, a characteristic manifestation of the disease, usually causes pain referred to the joint areas. It is now recognised that the painful crisis generally results from a limited avascular necrosis of bone marrow in the intermediate zone, a 'watershed' of blood supply between the distribution of branches of the main nutrient artery and the small perforating synovial vessels. Pain in the painful crisis is therefore maximal in the juxta-articular areas of the long bones, and patients frequently refer to joint pains affecting the knees, ankles, elbows, and wrists, although on examination the point of maximal tenderness overlies the bone rather than the joint space.

A true arthritis is recognised in association with the painful crisis,^{11 17–19} but is thought to be uncommon. Part of the reason for this is that the joint swelling may be minimal and that the symptoms of the effusion are overshadowed by the clinical features of the painful crisis. The present study suggests that such an arthritis may be much commoner than previously recognised, since it occurred in one-fifth of patients seen with painful crises.

No assessments of the prevalence of arthritis in the painful crisis has been possible in previously reported cases. Three out of five cases described by Hanissian and Silverman¹⁰ were in association with a painful crisis, and one of these had unusual features with bilateral avascular necrosis of the femoral heads at the age of 9 years, a reticulocyte count of

Table 2 Comparison of steady-state haematological values in controls (aged 25–30 years) and in patients developing arthritis associated with the painful crisis and with leg ulceration. Bracketed figures refer to means re-expressed in original units

| | Control values | | | Arthritis with painful crisis | | | Arthritis with leg ulceration | | |
|--|----------------|-----------|------|-------------------------------|-----------|------|-------------------------------|------------|-----|
| | n | mean | SD | n | mean | SD | n | mean | SD |
| Log _e (% Hb F + 1) | 69 | 1.5 (3.6) | 0.6 | 11 | 1.7 (4.3) | 0.7 | 11 | 1.8 (5.1) | 0.4 |
| Total Hb (g/dl) | 86 | 8.8 | 1.5 | 11 | 8.5 | 1.3 | 11 | 7.9 | 1.2 |
| MCHC (g/dl) | 86 | 34.3 | 2.3 | 11 | 34.6 | 2.5 | 11 | 33.8 | 2.4 |
| Log _e (RBC × 10 ¹² /l) | 86 | 1.1 (2.9) | 0.2 | 11 | 1.1 (2.9) | 0.1 | 11 | 0.9 (2.6) | 0.2 |
| MCV (fl) | 86 | 89 | 8.9 | 11 | 84.5 | 10.3 | 11 | 89 | 6.6 |
| Log _e (% reticulocytes + 1) | 85 | 2.4 (9.9) | 0.5 | 11 | 2.3 (9.1) | 0.4 | 11 | 2.6 (12.0) | 0.6 |
| Platelets (× 10 ⁹ /l) | 73 | 416 | 194 | 9 | 346 | 134 | 7 | 377 | 64 |
| Log _e (total bilirubin + 1) | 82 | 1.5 (3.3) | 0.4 | 11 | 1.1 (2.1) | 0.5 | 11 | 1.3 (2.7) | 0.3 |
| Log _e (% ISC + 10) | 35 | 2.9 (7.3) | 0.33 | 10 | 2.8 (6.3) | 0.2 | 11 | 2.9 (7.8) | 0.2 |

40%, and a recurrent arthritis even involving the first metatarsophalangeal joint. Uric acid levels were not available. The case described by Orozco-Alcala and Baum¹⁸ had a synovial fluid leucocyte count of $176 \times 10^9/l$ with 97% polymorphonuclear cells, and, although septic arthritis could not be confirmed on culture, the rapid improvement in synovial fluid cell count following antibiotic therapy was compatible with that diagnosis. The report by Espinoza *et al.*¹¹ is difficult to evaluate, since not all patients had sickle cell disease, and the report concerned joint symptoms rather than effusions or other evidence of arthritis. In seven patients in whom effusions occurred in association with a painful crisis the leucocyte count in synovial fluid exceeded $20 \times 10^9/l$ in four, two of whom had raised uric acid levels, and in two levels were not recorded. Although no crystals were seen, a diagnosis of gout was possible in these cases, since crystals are not always present on single synovial fluid examination in this condition.^{22 23} Of the seven patients reported by Schumacher *et al.*¹⁷ five developed arthritis during the course of a painful crisis, and synovial fluid in the four sampled cases was of a non-inflammatory character.

As in the cases in the present report, there is a pattern of non-inflammatory effusions in association with some painful crises. The term 'sympathetic effusion' has been applied, but it is unclear whether this represents a passive synovial response to adjacent bone damage or whether there is a primary ischaemic involvement of the synovium. The blood supply to the bone marrow is compromised during the painful crisis, and it is possible that a similar avascular process affects the synovium. Synovial histology in arthritis during the painful crisis is usually normal or shows only local lining cell proliferation and minimal inflammatory cell infiltration.^{11 10} Congestion and occlusion of small synovial blood vessels has been observed,¹⁷ and such damage could increase permeability of capillaries, leakage of plasma into the synovium, and a secondary inflammatory reaction. The extent of such vessel obstruction could determine the degree of synovitis and hence the variable findings in synovial fluid of arthritis associated with the painful crisis.

In this context the newly recognised arthritis occurring in association with spontaneous leg ulceration is of interest. Leg ulceration presents two basically different patterns in sickle cell disease, some lesions being clearly traumatic and others spontaneous. These latter ulcers are assumed to result from skin infarction, the evidence for this being the absence of trauma, their natural history, and the fact that these ulcers occur more frequently than expected in patients with high vaso-occlusive

indices.²⁴ The association of arthritis with this type of ulceration therefore supports the possibility of synovial ischaemia. The longer duration of ankle arthritis would also be compatible with this, since lymphoedema and the higher venous pressure at this site probably contribute to vaso-occlusion. Confirmation of the aetiology of the arthritis with leg ulceration must await pathological studies or the development of diagnostic techniques capable of detecting localised synovial ischaemia or necrosis.

The miscellaneous arthritides represent a heterogeneous group of conditions some of which occur coincidentally with sickle cell disease. The association with gout is well established because of the tendency to hyperuricaemia in SS disease, but such cases were excluded from the present report. The susceptibility to some infections suggested that an increased prevalence of septic arthritis might occur, but such events appear to be uncommon. A chronic synovitis leading to joint destruction has been reported in sickle cell disease,²⁵ and two patients in the present study had a chronic monoarthritis, but it is unclear whether the complication was aetiologically related. Systemic lupus erythematosus also occurs in sickle cell disease, but there are insufficient data to determine whether this association is coincidental. SLE-like syndromes occur in patients with genetic complement deficiencies, and abnormal complement function in SS disease²⁶ raises the possibility of an immune basis for arthritis.²⁷ Immune complex disease such as poststreptococcal glomerulonephritis²⁸ and autologous immune complex nephritis²⁹ have both been described in sickle cell disease. Establishment of any statistical association between these conditions and sickle cell disease must await more extensive data on their prevalence.

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