Case Report

Co-existent Sickle Cell Disease and Juvenile Rheumatoid Arthritis. Two Cases with Delayed Diagnosis and Severe Destructive Arthropathy

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ABSTRACT. We describe 2 pediatric patients with sickle cell disease (SCD) who developed seropositive juvenile rheumatoid arthritis (JRA). Both patients have severe joint damage, the compound effect of both disease processes. The bone and cartilage destruction, which poses serious therapeutic challenges, highlights the difficulty of making a diagnosis of chronic inflammatory disease in the setting of SCD. There may be a correlation between increased levels of tumor necrosis factor-α in the synovial tissue of joints damaged by arthritis and local sickling. The resultant ischemia and corresponding inflammatory infiltrates could in turn worsen existing synovial proliferation and cartilage destruction as well as trigger further sickling. (J Rheumatol 2001;28:2125–8)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS SICKLE CELL ANEMIA
TUMOR NECROSIS FACTOR

There are several well recognized rheumatological manifestations of sickle cell disease (SCD) including avascular necrosis, dactylitis and septic arthritis. Synovial effusions secondary to adjacent bone infarction occur in almost 20% of acute crises[1]. However, true cases of rheumatic disorders such as rheumatoid arthritis (RA) in association with SCD are rarely described. Definite previous cases that fit American College of Rheumatology classification include a 50 year old man with homozygous S/S disease[2] and 2 others aged 33 and 53 years with sickle trait and sickle S/D respectively[3]. The latter is a compound heterozygous hemoglobinopathy disease due to the presence of hemoglobins S and D (Los Angeles), which is very similar to S/S disease.

We describe 2 pediatric patients with SCD (both classical homozygous S/S) who developed juvenile RA (JRA). We use the term JRA here in the classical sense in that they have juvenile onset of so called adult type seropositive RA. This is equivalent to seropositive juvenile idiopathic arthritis (JIA) in the new nomenclature. The cases both illustrate the difficulty of making the diagnosis of chronic inflammatory joint disease in this setting. The patients have severe joint damage, the compound effect of both disease processes causing bone and cartilage destruction which poses serious therapeutic challenges.

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CASE REPORT

Case 1. Patient 1, a 15-year-old girl, was diagnosed with SCD at the age of 2 after presenting with pneumococcal meningitis associated with an acute vasoocclusive sickle crisis. Since that time she has continued to have about 4 sickle cell crises per year, usually affecting the lumbar spine and chest.

At the age of 14, she developed recurrent pain and swelling of her left great toe. Her uric acid level was normal and symptoms were thought to be due to SCD. A year later, in March 1997, she presented with a 6 week history of pain and morning stiffness of her fingers and wrists and a swollen right knee. Aspiration of the knee showed no growth and she was referred for a rheumatological opinion. When questioned further, she described the recent arthralgias as quite distinct from the symptoms of previous sickle crises. Examination revealed evidence of an active polyarticular arthritis affecting the small joints of the hand, wrists, one knee, and both great MTP

Table 1. Investigations at presentation in 2 patients with SCD who developed JRA.

(Normal range)	Case 1	Case 2
Hematology		
Hb g/dl (11.5–14.5)	6.7	6.7
MCV fl (75–87)	84.9	94.5
WBC × 10^9/l (5–15)	11.1	12.0
Plt × 10^9/l (150–450)	888	426
Sickle testing		
Hemoglobin S	90.4%	68.3%*
Hb F (0.1–1%)	2.5%	1.0%*
Inflammatory markers		
ESR mm/h	135	130
CRP mg/dl	4.4	6.4
Immunology		
ANA	Negative	1:320**
dsDNA	Negative	Negative
Rheumatoid factor	Positive (1:2560)	Positive (1:2560)
C3, C4	Normal	Normal

* Results post transfusion; ** Homogenous and speckled.

Figure 1. The right hip joint of Case 2 at 14 years of age, prior to arthrodesis and before diagnosis of JRA was established. Gross destructive arthropathy is seen with evidence suggestive of avascular necrosis of the femoral head.

joints. Investigations are listed in Table 1 and are consistent with a diagnosis of JRA. Radiographs of her feet showed destructive changes affecting both sides of the 1st DIP joint on the left and the 5th MTP of the right foot, which was associated with a periosteal reaction and soft tissue swelling. Radiographs of her hands, knees, and ankles were reported as normal.

She was given oral methotrexate (MTX) at 20 mg/week, high dose ibuprofen and regular physiotherapy. These failed to bring about satisfactory control of her disease. It has been difficult to increase the dose of MTX because of recurrent episodes of abnormal liver function tests. She has had intraarticular steroid injections on 5 occasions without complications producing moderate, though temporary responses. Her medication was changed to subcutaneous MTX in April 1999, but her arthritis has remained active with recurrent flares often following painful sickle crises. When last seen she had synovitis of both wrists and elbows with radiographic evidence of progressive joint disease.

Case 2. Patient 2 is a 16-year-old girl with a strong family history of SCD, 2 siblings having died from sickle related complications. She was diagnosed with SCD aged 18 months following an episode of dactylitis. She had sickle crises about once a year, and at the age of 10 years had a presumed acute crisis involving the right hip. Since then she has had increasing pain and loss of movement in that hip, and a pelvic radiograph taken 3 years later showed a grossly deformed right sided capital epiphysis (Figure 1). This was thought to be secondary to avascular necrosis resulting from SCD and she was then admitted to hospital for arthrodesis of the right hip in July 1998.

At this admission she was noted to have a 30° fixed flexion deformity of the hip with no rotation of the joint permitted and a 3 cm leg length discrepancy. The histology of the femoral head showed degenerative arthrosis though no synovial tissue was included in the biopsy and therefore no specific diagnosis was confirmed. Postoperatively she had persistent fevers and was noted to have swollen proximal interphalangeal (PIP) joints and she was referred for a rheumatology opinion. Subsequently, a detailed clinical history revealed a 3 year history of intermittent swelling of hands and wrists associated with morning stiffness. Examination at this stage showed that she had synovial thickening of MCP joints, fixed flexion deformities of both elbows and knees, with ankle effusions. Investigations are listed in Table 1 and were consistent with JRA. Plain radiographs of both hands at that time showed periarticular osteopenia, loss of joint space particularly of the carpometacarpal and PIP joints (Figure 2). These radiographic changes were consistent with an inflammatory arthropathy with little definite evidence of bone destruction due to SCD. Other radiographs were reported to be normal.

She received 6 pulses of intravenous methylprednisolone and intensive physiotherapy with improvement in her disease. She was discharged on oral prednisolone, 20 mg/day but her disease flared again and she was given 2 further courses of methylprednisolone. Thirty-six hours after this, she presented with a cerebral sickle crisis requiring exchange transfusion. A magnetic resonance image (MRI) of the brain showed altered signals in the temporal and parietal regions consistent with ischemia. She had a stormy convalescent period with persistent sickling and relapse of her arthritis. Abnormal liver function tests occurred after the first dose of MTX, which were thought to be related to the drug. She had previously had intermittent elevation of liver function tests both during sickle crises and at other times. Our concern and parental anxiety about an additional risk factor for liver damage led to changing her disease modifying antirheumatic drug to cyclosporine.

Oral prednisolone was also continued in an attempt to control her inflammatory arthritis. She was eventually discharged from hospital in December 1998.

She has continued to have severe, treatment resistant arthritis, requiring multiple corticosteroid joint injections, which produced substantial but temporary improvement only and sulfasalazine was added to her treatment in November 1999. Shortly after this she developed an ulnar nerve neuropathy distal to the left elbow, confirmed on neurophysiological testing. An MRI of the left elbow (Figure 3) showed severe erosions of the

Figure 2. Plain radiographs of both hands of Case 2 at 15 years indicating gross destructive arthropathy of the carpus and wrist joint with periarticular osteopaenia evident in the MCP and IP joints.

Figure 3. MRI using T-1 weighted sequence without gadolinium, of the left elbow is demonstrated in Case 2 at 16 years of age. Erosive joint damage of the humeral condyle and radial head evident and gross synovial hypertrophy (upper arrow) surrounded by fat pad (lower arrow).

humeral condyles, radial head and olecranon. A large synovial mass was present, and likely to be causing compression of the ulnar nerve. She recently stopped treatment with sulfasalazine and cyclosporine because of inefficacy and intolerance. Currently, both therapy with etanercept (anti-tumor necrosis factor-α [TNFα]) and bone marrow transplantation are being considered as therapeutic options. Her unaffected sister is a 10/10 HLA match.

DISCUSSION

The prevalence of RA (both JRA and RA) in patients of African origin is approximately 0.3%, less than a third of that in Caucasians[4]. This difference may be explained in part by the lower frequency of the risk allele HLA-DR4 in the former population[5]. Nevertheless with the common occurrence of SCA in people of African origin, one would expect a greater number of coexistent cases with RA than described in the literature. Our report illustrates the difficulty and delay in making the diagnosis of an inflammatory arthritis in the context of another disease potentially affecting the joints. It may be that many similar cases are still going unrecognized.

In distinguishing an inflammatory arthritis from the underlying SCD, particular attention needs to be paid to the nature and chronicity of joint symptoms as well as clinical evidence of synovitis especially in a small joint distribution (rare in SCD).

While SCD is known to have musculoskeletal manifestations including bone pain and infarction in crises, dactylitis (the hand-foot syndrome) and osteomyelitis, a chronic inflammatory polyarthritis would be unusual. Bony crises at or near the diarthrodial joint would be expected to cause some reactive synovitis, but chronic involvement with synovial thickening and progressive destruction of joints would be highly unlikely. The eventual typical symmetrical polyarthritis of both small and large joints, together with persistent elevation of both erythrocyte sedimentation rate (ESR) and rheumatoid factor, and the evidence of polyarticular destructive changes on radiological examination are very consistent with the clinical diagnosis of JRA (or seropositve polyarticular JIA). While elevation of ESR might be expected in SCD particularly at time of crises due to acute phase reactants, persistent elevation to such a degree as seen in these cases would be highly unusual, except perhaps in the case of systemic infection. Neither patients had evidence of this clinically.

Difficulty in radiological interpretation may pose a diagnostic problem. Changes such as avascular necrosis and eventual destructive arthropathy are seen in SCD but the latter, at least, are usually late in the course after repeated crises and documented joint disease. Specific erosions, loss of joint space, bony damage on both sides of a joint are more consistent with an inflammatory arthropathy. Regardless, modern imagery (particularly MRI) is able to reveal pathognomonic synovial proliferation and enhancement (with gadolinium), as was seen in Case 2, which would not be expected with SCD.

MTX was started in both cases as the first line agent, but its effective use has been hampered by disturbance of liver function tests, to which they may have been predisposed as a result of the SCD. Intraarticular steroid injections were used to good effect and appeared to be safe contrary to previous reports of causing sickle crises[3]. However the second child developed a cerebral crisis 36 hours after intravenous methylprednisolone. Given other similar reports[6], we would suggest that intravenous steroids should be given with caution in patients with SCD.

Both children have severe ongoing polyarthritis that has failed to respond to standard treatment. Their flares of arthritis often coincided temporally with sickle crises suggesting a possible common pathophysiological link. Recent experimental studies have demonstrated that increased microvascular red cell transit time is critical for sickling[7]. TNF-α has been shown to increase expression of endothelial adhesion molecules[8], increasing red cell transit time and so causing local sickling. There are clear data proving that TNF-α levels are grossly elevated in the synovial tissue of joints affected with arthritis[9]. It is possible that the potentiation of joint disease seen in our cases is mediated by TNF-α causing local sickling. The ensuing ischemia and corresponding inflammatory infiltrate could

worsen existent synovial proliferation and cartilage destruction as well as trigger further sickling.

Clearly it would be imperative to suppress this pathway if this hypothesis is true. The central role of TNF in inflammatory arthritis has already been demonstrated by the profound effect of anti-TNF agents in these diseases[10]. In the patients we have described, anti-TNF provides the exciting possibility of bringing both diseases under control. Finally if this proves unsuccessful, allogenic bone marrow transplantation remains as a potential cure for both diseases.

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