Case report

Arthritis in β thalassaemia trait: clinical and pathological features

BONNIE B. DORWART AND H. RALPH SCHUMACHER

From the 1Department of Internal Medicine, Division of Rheumatology, Jefferson Medical College and Lankenau Hospital, Philadelphia, and the 2Department of Internal Medicine, Section of Rheumatology, University of Pennsylvania, and Veterans Administration Hospital, Philadelphia, USA

SUMMARY A 33-year-old white female of English descent with β thalassaemia trait developed painful recurring bilateral knee effusions at age 15 years. Trauma was denied. Synovial analyses revealed noninflammatory effusions with normal complement, no inclusions, and no crystals. Knee x-rays normal at ages 18 and 26, showed mild osteoarthritic changes at age 33. Laboratory tests for other known causes of arthritis were repeatedly normal or negative. Bone densitometry was below normal. Light microscopy of the synovial membrane showed no significant abnormalities and no iron deposition. Electron microscopic findings included multilamination of vascular basement membranes and large amounts of thin fibrils surrounding many connective tissue cells. Treatment with salicylates did not prevent recurrence of effusions, and quadriceps strengthening and joint rest were moderately successful in relieving pain. Intra-articular corticosteroids on 2 occasions were not helpful. Whether her knee arthritis is purely secondary to the para-articular bone thinning from the chronic marrow expansion remains to be determined.

Arthritis in patients having both thalassaemia and sickle cell haemoglobinopathy1,2 or in thalassaemia major alone3,4 has been reported. One series has also described arthritis in 7 patients with β thalassaemia minor (trait) alone.5 However, prolonged clinical follow-up and studies of joint fluid and synovial membrane have not been reported. We describe a patient with β thalassaemia trait in whom no other known cause has been determined for 18 years of intermittent knee pain and effusion and 4 years of lumbar pain.

Case report

Clinical Characteristics
This well developed, well nourished white woman first experienced knee swelling and pain at 15 years of age, without antecedent trauma. Painful effusions recurred in no identifiable pattern, in one or both knees, often persisted several days to 3 months at a time, and disappeared spontaneously with joint rest. There was no morning stiffness. Pain was worse after prolonged standing or walking. Two normal pregnancies at age 22 and 24 had no influence on her joint complaints. At age 29 vague aching in the lumbar spine was noted, worse after prolonged standing.

Menses have been normal, with normal oestrogen activity on vaginal cytology. No serositis, mucocutaneous abnormalities, cardiopulmonary abnormality, morning stiffness, iritis, involvement of the gastrointestinal tract, neurological disease, or joint laxity has appeared. Her habitus and body proportion were normal. Joints were normal on examination except for cool moderate effusions in each knee.

Family history was negative for musculoskeletal abnormality except for her mother, who had mild primary fibrositis for 20 years.

Chronic anaemia was present since childhood, with a haemoglobin of 11g/dl, not responsive to oral iron administration. Transfusions had not been given.

Therapeutic measures were largely ineffective. Salicylates administered to give serum levels of 20–30 mg/100 ml (1.45–2.17 mmol/l) afforded some relief of pain but did not decrease the size of synovial

Accepted for publication 25 March 1980
Correspondence to Dr Bonnie B. Dorwart, Lankenau Medical Building, Philadelphia, Pennsylvania 19151, USA.

Annals of the Rheumatic Diseases, 1981, 40, 185–189
effusions. Ibuprofen in doses of 2400 mg daily had no effect on pain or fluid formation. Physiotherapy, including heat packs and quadriceps strengthening was judged minimally effective by the patient. Joint rest, by means of a posterior splint, bed rest, or cane, afforded modest but definite relief of pain. Intra-articular prednisolone acetate, 40 mg at the time of arthrocentesis, was ineffective twice.

LABORATORY TESTS
At age 31 through 34 the patient was seen during 5 episodes of knee pain and swelling. Most laboratory determinations were performed at least twice. These were within normal limits or negative: rheumatoid factor, HLA B27, antinuclear antibody, serum complement (C3, C4), sedimentation rate (Westergren), antistreptolysin O titre, lipids, creatine phosphokinase, electrolytes, SGOT, SGPT, serum protein electrophoresis, immunoglobulins, uric acid, T3 and T4, calcium, phosphorus, and alkaline phosphatase.

At age 32 she was referred to a haematologist for investigation of chronic anaemia often attributed previously to iron deficiency because of microcytosis of her erythrocytes (mean corpuscular volume (MCV) of 66 µm³). However, the failure to respond to iron raised the possibility of a haemoglobinopathy. A diagnosis of β thalassaemia trait was then made on the basis of these laboratory results: haemoglobin 10·7 g/dl, massed cell volume 69, leucocytes 6·5 × 10⁹/l, reticulocytes 0·7%, serum iron 134 µg/100 ml (24 µmol/l) saturation of iron 33%, starch gel electrophoresis showing haemoglobin F 1·0% (normal less than 2%), haemoglobin A₂ 5·79% (normal 1·8-3·3), haemoglobin A 93·21%, and paper electrophoresis revealing presence of haemoglobin A and haemoglobin A₂.

RADIOGRAPHIC DATA
X-rays at age 33 were taken of the skull, lumbosacral spine, and both knees. The skull showed 'hair on end' appearance described previously in thalassaemia trait, and the lumbosacral spine, including sacroiliac joints, was negative. Knees showed no abnormality other than prominence of the tibial spines and early narrowing of the medial joint space bilaterally (Fig. 1). Knee x-rays taken 15 and 7 years before were normal.

BONE DENSITOMETRY
Bone density was determined at the right radius and ulna at ages 33 and 34 with a Norland-Cameron densitometer as described by Hahn and Hahn. Normal ranges, as reported by Boyd et al., are 0·71 to 0·81 g/cm³. Values for the patient were subnormal both at 0·68 g/cm³ initially and 0·67 g/cm³ 1 year later. Unfortunately it was not technically possible to measure bone density at the knee itself.

As described by Hahn and Hahn, studies to rule out premature menopause, inadequate vitamin D or calcium intake, intestinal malabsorption, renal tubular disease, excessive antacid ingestion, hyperparathyroidism, exogenous or endogenous hypercortisonism, thyrotoxicosis, or malignancy have been normal.

SYNOVIAL FLUID STUDIES
Arthrocentesis was done initially at 31 years of age, yielding 18 ml of group I fluid. Colour was clear and light yellow, viscosity and mucin clot were good, white cell count was 200/µl with 92% mononuclear and 8% polymorphonuclear cells. Cytoplasmic inclusions were absent by light microscopy on examination of a wet smear, and no crystals were found under compensated polarised light microscopy. Subsequent examinations of joint fluid have shown similar results.
SYNOVIAL BIOPSY
Needle biopsy of the left knee was performed as described by Schumacher and Kulka. Specimens for light microscopic study were placed in buffered formalin. Those for electron microscopy were put into half-strength Karnovsky’s medium (glutaraldehyde–paraformaldehyde), diced into 1 x 1 mm pieces, fixed for 4 hours at room temperature in glutaraldehyde–paraformaldehyde, postfixed in osmium tetroxide, dehydrated in alcohol and embedded in Epon, as described by Agudelo and Schumacher.

The synovial membrane was normal in most areas, with 1–2 layers of synovial lining cells. There was occasional mild perivascular fibrosis. Prussian blue stain showed no abnormal iron deposition. Electron microscopic findings included small vessels with some abnormally dark endothelial cells and multiple layers of basement membrane and surrounding...

Fig. 2  Electron micrograph of a synovial venule with an erythrocyte in the lumen (L). Normal endothelial cells (E) are contrasted with some abnormally dark cells that may be degenerating. Note the multiple layers of basement membrane (arrows). C=mature collagen. P=pericyte. (× 7700).
pericytes (Fig. 2). Connective tissue cells had prominent glycogen and rough endoplasmic reticulum. There were masses of thin filaments between the cells and the adjacent 64 nm banded thicker collagen fibres (Fig. 3).

Discussion

We describe a young woman with irregularly recurrent painful knee effusions to whom 18 years of follow up have not revealed a cause for her arthritis. As in the other case report of joint abnormalities in β thalassaemia trait, our patient had chronic pauciarticular, non erosive seronegative disease. Unlike the patients of Schlumpf et al. ours does not yet have radiographically evident osteopenia of the spine. However, it is known that visible osteopenia on x-ray is a late sign and represents a loss of one-third of normal bone mass. Bone densitometry is a more sensitive indicator of lost bone mass, and was below normal in our young patient, raising the possibility that lumbar compression fractures may appear in the future.

Schlumpf did not report joint effusions in his series. Synovial fluid in our patient was noninflammatory and similar to that described by Gratwick et al. in β thalassaemia major.

The multilaminated basement membranes and dark endothelial cells seen by electron microscopy are not seen in normal joints but can be seen in a...
variety of inflammatory or noninflammatory joint diseases. No specific pathogenetic significance other than some type of microvascular injury has been found. The thin fibrils were not identified biochemically but might be immature collagen or proteoglycans and would fit with increased production or delayed removal or maturation of these.

Because the synovial fluid and synovial membrane findings are still limited and may be nonspecific, we consider that they may be compatible with minor trauma somehow secondary to underlying bone disease. The early onset of osteoarthritis at age 33 presumably also is a consequence of marrow hyperplasia into long bones and perhaps microfractures of subchondral bone adjacent to weight bearing joints as seen in thalassaemia major.

We have not yet seen osteonecrosis in our patient. This has been reported in patients having thalassaemia trait.

This work is supported in part by the Arcadia Foundation and the Barsumian Fund.

References