DESTRUCTIVE JOINT CHANGES FOLLOWING KIDNEY TRANSPLANTATION

Report of a Case

PAUL AICHROTH, A. C. BRANFOOT, E. C. HUSKISSON and
LAVINIA W. LOUGHRIDGE, LONDON, ENGLAND

From the Westminster Hospital, London

More frequent and longer survival of patients receiving kidney transplants has led to the recognition of a number of new diseases. Among these is a condition usually affecting the hip joint and characterised by avascular necrosis of the femoral head. Similar changes have been reported less commonly in the knee and shoulder.

We have had the opportunity to study a patient in whom severe destruction of both knee joints necessitated arthrodesis of one of them. Clinical and pathological material is presented in an attempt to throw some light on the pathogenesis of the condition.

CASE REPORT

A man aged forty-six presented in 1966 in renal failure from proliferative glomerulonephritis. In 1965 he had had an episode of intestinal obstruction from Crohn's disease. There had been no joint symptoms associated with either the intestinal or renal complaint and the patient had not received steroids at any time.

Regular haemodialysis was begun to prepare the patient for renal transplantation, and in February 1967 he received a cadaver kidney. The recipient's own kidneys were not removed. Immediate immunosuppressive treatment consisted of prednisone 100 milligrams daily and azathioprine (Imuran) in a dose of 2.5 milligrams per kilogram of body weight. The dose of the latter remained the same throughout after the first few days. Prednisone dosage was

FIG. 1
Histogram of prednisone dosage after operation.

reduced during the first four weeks to 50 milligrams daily and continued at about this level for four months, with an increase to about 200 milligrams daily for a brief period to control one rejection episode (Table I, Fig. 1). Despite this, transplant function settled satisfactorily and by July 1967, six months after operation, blood urea was maintained at 30 milligrams per 100 millilitres.

Two months after the transplant, when the patient was receiving prednisone 50 milligrams daily and azathioprine 225 milligrams daily, he complained of pain in both knees. At that time examination did not reveal anything abnormal. In August 1967, seven months after the operation, bilateral effusions into the knees were noted. Aspiration was performed on several

TABLE I
DOSAGE OF PREDNISONE AND AZATHIOPRINE AFTER KIDNEY TRANSPLANT
ON FEBRUARY 2, 1967

Date	Prednisone (milligrams per day)	Azathioprine (milligrams per day)
February 2, 1967	100	250
February 3, 1967	100	125
February 4, 1967	75	65
February 11, 1967	70	225
February 14, 1967	65	225
February 17, 1967	60	225
February 20, 1967	55	225
February 23, 1967	50	225
April 11, 1967	200	225
April 14, 1967	175	225
April 16, 1967	150	225
April 18, 1967	125	225
April 20, 1967	100	225
April 22, 1967	75	225
April 24, 1967	50	225
May 16, 1967	45	225
May 30, 1967	40	225
June 27, 1967	35	225
July 13, 1967	30	225
August 4, 1967	25	225
December 5, 1967	20	225
January 23, 1968	15	225
February 13, 1968	12.5	225
March 12, 1968	10	225
May 14, 1968	7.5	225

occasions and steroids were injected into one or other knee on two occasions without apparent benefit.

The synovial fluid was straw-coloured and contained scanty red cells and polymorphonuclear leucocytes but no crystals or lipid material. Synovial fluid Rose-Waaler and latex tests were positive at titres up to 1:32 and 1:512 respectively, but these tests were consistently negative in the serum. Other relevant investigations at the time of the onset of arthritis were:

FIG. 2

FIG. 3

Antero-posterior and lateral radiographs of the knee.

FIG. 4

FIG. 5

FIG. 6

Figure 4—The appearance of the knee joint at operation. Figure 5—Coronal slices from the lower end of the femur seen from behind. There are pale areas of infarction, outlined by darker zones of demarcation. In the lateral condyle cartilage has been driven into the underlying necrotic bone. Figure 6—A slab radiograph of the lower end of the femur showing the surface of the medial condyle destroyed and an osteochondral fragment driven into the lateral condyle.

FIG. 7

FIG. 8

FIG. 9

Figure 7—Viable articular cartilage with necrotic subchondral bone below at the edge of an area of total infarction. The bone is entirely anucleate. (Haematoxylin and eosin, $\times 25$.) Figure 8—The three zones of infarction: above, viable marrow with thickened trabeculae, then the demarcating granulation tissue; and below, total infarction. (Haematoxylin and eosin, $\times 4$.) Figure 9—Outside the zone of demarcation there is extensive formation of new bone, both woven and lamellar, on the dead trabeculae. (Haematoxylin and eosin, $\times 25$.)

blood urea 30 milligrams/100 millilitres; uric acid 5.8 milligrams/100 millilitres; calcium 10.2 milligrams/100 millilitres; phosphates 3.9 milligrams/100 millilitres. Radiographs of the knees were normal and other joints showed no clinical or radiological abnormality.

There was progressive deterioration of the knees until in August 1968 the patient was unable to stand because of pain. On examination, bilateral effusions, painful limitation of movement and marked crepitus were found. Radiographs showed extensive joint damage (Figs. 2 and 3). Because of the severity of the symptoms, arthrodesis of the left knee was carried out in September 1968.

At operation the articular surfaces of the tibial and femoral condyles were found to be grossly disorganised (Fig. 4). Multiple loose osteochondral bodies were seen in the joint cavity and much of the joint surface was denuded of cartilage. The synovium was inflamed and proliferating.

After operation the patient was mobile with the left knee soundly arthrodesed. Operative treatment was considered for the right knee but was not undertaken because of deterioration of his general condition.

PATHOLOGY

The bone cut from the lower end of the femur and the upper end of the tibia showed extensive areas of necrosis of subchondral bone. Three zones could be distinguished: large pale necrotic areas which were demarcated by a narrow darker zone from the surrounding somewhat opaque marrow (Fig. 5). Large pieces of the joint surface had separated and there was a remarkable step-like depression in the lateral femoral condyle, into which an osteochondral fragment had been driven, in an area of bone infarction (Fig. 6).

Microscopy confirmed the presence of extensive areas of complete necrosis of subchondral bone and marrow. Trabeculae in this area were of normal thickness. Overlying the dead bone was apparently viable cartilage (Fig. 7).

Between the dead bone and the surrounding marrow was a zone of demarcation consisting mostly of avascular collagen, stippled with calcification. There were occasional more vascular areas with a few chronic inflammatory cells, and a little patchy osteoclastic resorption. The original trabeculae, dead but uninterrupted, passed through the zone of demarcation (Fig. 8).

The viable marrow surrounding the necrotic areas was very abnormal, with many cells without nuclei, and smudged and necrotic fat cells. All through the marrow, close to the thin-walled blood vessels, there were collections of macrophages, some containing haemosiderin, others multinucleate and forming "oil cysts". Almost all the trabeculae in the cancellous bone included in the specimen were without nuclei and presumably dead (Fig. 9).

The synovial membrane showed hypertrophy of the villi and fibrosis, with hyperaemia and moderate diffuse infiltration of lymphocytes and in lesser numbers, histiocytes. Embedded in the superficial layers were small bony spicules with occasional collections of siderophages. Much of the surface was covered with fibrin, some of it undergoing partial organisation to form "melon seed" bodies.

The osteochondral fragments, whether loose or embedded in bone or synovium, showed intact articular cartilage which had proliferated to enclose a core of dead bone.

DISCUSSION

Skeletal disorders have been a particular problem after renal transplantation. Bravo, Herman and Smyth (1967) reported an incidence of 38 per cent in sixty long-term survivors. Four types of arthropathy, associated with calcium phosphate deposition, synovitis, hyperparathyroidism and avascular necrosis have been described (Editorial, *British Medical Journal* 1967).

Avascular necrosis is not uncommon, occurring in five of Bravo's sixty cases and ten of twenty-seven six-month survivors reported by Cruess, Blennerhassett, Macdonald, Maclean and Dossetor (1968). Symptoms began between two and twelve months after transplantation,

and at this stage radiographs were usually normal. Later, patchy subchondral demineralisation appeared and was followed by collapse and sclerosis, the end-result resembling avascular necrosis. Fragmentation of the joint surface was also noted in our case, with an appearance similar to osteochondritis dissecans.

Symptoms in previously reported cases have seldom been severe and the condition has usually responded to limitation of activity and weight-bearing. In one of the cases reported by Cruess *et al.* (1968) arthroplasty of the hip was necessary. Because surgery has seldom been needed, material has not been available for examination except at autopsy.

The pathological findings in our patient are similar to those reported in avascular necrosis complicating many other systemic disorders. The occurrence of these lesions in so wide a variety of conditions suggests a common pathogenic mechanism. The vasculature of the subchondral region of bone has two characteristics which may render it more vulnerable to emboli, firstly the small calibre of the vessels (Crock 1967) and secondly a lower perfusion pressure. The arterial pressure is highest at the centre of the shaft of the bone and falls towards the extremities (Stein, Morgan and Reynolds 1957), and experimentally a fall in perfusion pressure favours the arrest of emboli (Soloway, Robinson, Hufnagel and Huyser 1969). Intra-arterial injection of Lipiodol in rabbits has been shown to lead to accumulation of fat emboli in the subchondral region (Jones and Sakovich 1966).

There is clinical and experimental evidence that fat is deposited in the livers of patients on steroid therapy, and Jones, Engleman and Najarian (1965) have reported systemic fat embolism in a patient receiving large doses of steroids. Bravo *et al.* (1967) reported lipid-staining particles in the synovial fluid of three cases examined, but we were unable to confirm this finding in our case. Fisher, Bickel and Holley (1969) have demonstrated lipid material within the lumen of arterioles in the region of bone infarcts. In the advanced stage of joint destruction it is unlikely that such clear-cut evidence of the primary process will be found, but a greater awareness of the possibility of fat embolism may reveal more evidence in its support.

The occurrence of a proliferative synovitis and positive Rose-Waaler and latex tests has suggested that an immunological process may be involved. However, Bravo *et al.* (1967) found no relationship between the presence of antibodies and rheumatic manifestations, and the serum Rose-Waaler and latex tests are commonly positive after renal transplantation in patients with or without arthritis. Positive tests for rheumatoid factor in synovial fluid are not uncommon in conditions other than rheumatoid arthritis and appear to be a non-specific response to joint damage (Huskisson, Hart and Lacey 1970). There was no evidence from the history that our patient's arthritis was related to his original renal disease or to the abnormality of the small intestine.

Miles (1968) suggested a local action of steroids, the process initiated by a steroid atrophy of bone which could lead to small osteochondral fractures, collapse and fragmentation of the joint surface. We found neither radiological nor pathological evidence of bone thinning. Repeated intra-articular steroid injections are known to produce a similar picture (Bentley and Goodfellow 1969), but only one injection to each knee was given to our patient.

The pathology in this patient is suggestive of multiple bone infarcts, perhaps produced by fat embolism, although there was no direct evidence for this. In the absence of bone thinning, which would be characteristic of the effect of steroids, fat embolism seems likely. It is known that fat is deposited in the liver of such patients and that fat embolism can occur. Similar bone changes have been produced experimentally.

SUMMARY

1. Destructive changes in a knee joint, eventually requiring arthrodesis, are reported in a patient who had undergone renal transplantation.

2. The underlying pathology was avascular necrosis with separation of large osteochondral fragments.
3. The pathogenesis is discussed.

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