CONCISE REPORT

Rapid multifocal chondrolysis after liver transplantation in four patients

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Background: Favourable clinical outcomes achieved with liver transplantation may be jeopardised by corticosteroid-induced osteoarticular complications, such as osteoporosis or aseptic osteonecrosis.

Case report: A previously unreported joint complication in liver transplant recipients is described.

Methods: Retrospective study of liver transplant recipients in whom destructive joint disease developed, identified among 330 symptomatic patients out of a total of 1260 managed over a 15 year period (November 1984-January 2000) in a university based liver transplantation centre.

Results: In four patients (23–56 years), rapid chondrolysis developed 2–12 years after transplantation in more than three weightbearing or non-weightbearing joints free of radiological features of avascular osteonecrosis, evidence of infection, or defined inflammatory arthritis. Pathological examination of five hip joints and one knee joint found no evidence of infection or inflammation. Six joint replacement procedures were performed successfully in three patients.

Conclusion: Clinicians managing liver transplant recipients, and perhaps recipients of other organs, should be aware that rapid chondrolysis may develop. The pathogenesis of this rare complication is unclear.

L iver transplant recipients are at risk for osteoarticular complications, including osteoporotic vertebral fractures and aseptic avascular osteonecrosis (AVN).[1] To our knowledge, rapid chondrolysis unrelated to infection or inflammation has not been described in organ transplant recipients. Among 1260 liver transplant recipients followed up at the Paul Brousse Teaching Hospital over a 15 year period (November 1984-January 2000), 4/330 presenting with musculoskeletal complaints experienced rapid and extensive chondrolysis in several joints within a few years after transplantation. We describe the features of this joint complication and discuss possible underlying mechanisms.

CASE REPORTS
Case 1
A 54 year old woman underwent liver transplantation (LT) in 1988 for primary biliary cirrhosis. In October 1990 she reported mechanical pain in both hips. Radiographs disclosed moderate superolateral joint space narrowing in both hips, without dysplasia. Interestingly, the hips were normal on a plain abdominal film obtained before transplantation. Serial radiographs showed complete joint space obliteration over 18 months on the right and 14 months on the left. Magnetic resonance imaging showed no features of AVN, subchondral fractures, effusion, or synovitis. Laboratory tests were negative for evidence of inflammation or infection. A radiographic skeletal survey disclosed joint space narrowing

in both medial femorotibial compartments. The patient died in 1995 from liver failure while she was waiting for joint replacement surgery.

Case 2
This 25 year old man with hepatitis B related cirrhosis received a liver transplant in 1985 then required re-transplantation in 1986. In December 1993, he reported an 8 month history of mechanical pain in his left hip. Radiographs showed complete joint space obliteration at the left hip without osteosclerosis or osteophytes and nearly complete joint space obliteration at the right hip. No joint abnormalities were visible on plain abdominal films obtained in 1992. A magnetic resonance imaging study did not show AVN, effusion, or synovitis but showed a small irregular subchondral low T_1 weighted signal with similar high T_2 weighted images in the right hip joint, and only a low T_1 weighted triangle shape signal in the left hip joint. Laboratory tests for inflammation or infection were negative or normal. Radiographs showed no features of ankylosing spondylitis or calcium pyrophosphate dihydrate (CPPD) deposition disease. Total hip replacement (THR) was performed on the left side in June 1994 and on the right side 6 months later. No evidence of synovial inflammation was seen upon gross examination of the operative specimen. Microscopically, the capsule and synovium were fibrous, and the femoral head showed active osteoarthritic (OA) lesions with no AVN or microcrystal deposits; however, the trabecular bone displayed a marked osteoporotic pattern. In 1997, he started experiencing pain in his right shoulder; abnormalities similar to those at the hips were found, with severe narrowing of the right glenohumeral joint space and mild inferior osteophytosis but no evidence of AVN.

Case 3
A 21 year old woman with autoimmune cirrhosis received three liver transplants, in 1988, 1991, and 1995, respectively. In 1992 she sought advice for mechanical pain in both knees with an effusion in the right knee. Aspiration recovered non-inflammatory fluid with 280 leucocytes/mm^3, no monosodium urate or CPPD crystals, and no apatite-like material by alizarin red staining. Radiographs of the hips and knees were normal. In March 1997 she reported severe pain in both hips and knees. Repeat radiographs disclosed superolateral polar joint space narrowing in both hips without evidence of AVN but with moderate osteophytosis on the right (fig 1). A Tc^{99m} bone scan showed increased uptake in both hips, shoulders, and tibial plateaus. Routine laboratory tests were unremarkable. Complete joint space obliteration occurred within 14 months in both hips. A radiographic skeletal survey showed severe joint space narrowing of the medial compartments of

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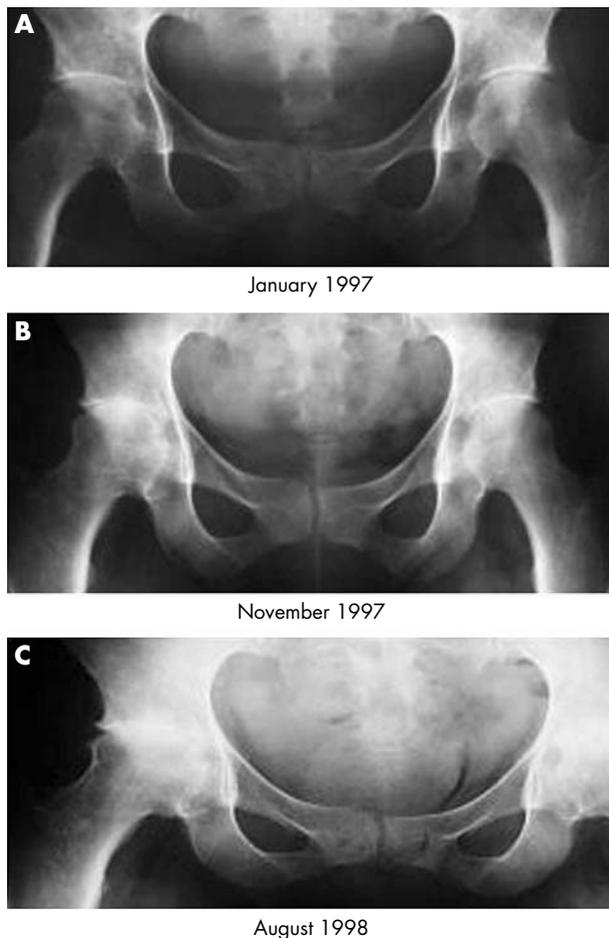
January 1997

November 1997

August 1998

Figure 1 Plain radiographs of the hips (patient 3: (A) January 1997; (B) November 1997; (C) August 1998). Gradual narrowing of the joint space of the right hip, then of the left hip over a 19 month period.

both knees and of the glenohumeral joints (fig 2). THR was done on the left side in December 1998 and on the right side 1 year later. Pathological examination showed fibrosis of the capsule and mild hyperplasia of the synovium. The cartilage had almost completely disappeared in the loadbearing area,

and the subchondral bone was thin. No evidence of infection or of a definite inflammatory process was found. In November 2000, total knee replacement was performed on the left; the surgical specimens showed gross degenerative lesions of the hyaline cartilage with fissuring and laminar dissection as seen in laminar inflammatory hip disease.

Case 4

A 30 year old female patient with sclerosing cholangitis received a liver transplant in 1986. In February 1998 she reported use related pain in the left knee, where there was a small effusion. A radiograph of the pelvis was normal, but incipient joint space narrowing was visible in the medial compartment of the left knee. In May 1999 she had pain in both knees and ankles with marked motion range limitation, most notably in the right hip. Radiographs showed severe joint space narrowing in the right hip and medial compartment of the left knee, as well as marked involvement of both tibiotalar joints. Bone scan showed increased uptake in these four joints. Laboratory tests were unremarkable. THR was done on the right side in January 2001. Pathological examination showed OA lesions. The surface cartilage varied in thickness and showed several fissures; moderate osteoporosis was present in the underlying trabecular bone.

DISCUSSION

Multifocal rapid chondrolysis occurred in these four patients 2–12 years after LT, with three to six weightbearing or nonweightbearing joints affected in each patient (table 1). All four patients met the radiological criteria for rapid chondrolysis defined for the hip[2]: 50% or greater decrease in joint space width within 1 year; total joint space obliteration within 1–3 years; global superior polar narrowing, with or without superolateral or medial predominance, and absence of additional abnormalities other than moderate osteophytosis.

Several systemic or local diseases may result in severe joint destruction, including septic arthritis, inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, or familial Mediterranean fever), trauma, neurological disease, CPPD deposition disease, hydroxyapatite associated arthritis, ochronosis, haemochromatosis, and haemodialysis,[3 4] and AVN related OA.[5] In some cases, rapidly destructive joint disease occurs in the absence of identifiable causative factors. Thus, rapidly destructive OA of the hip can occur as an idiopathic condition, typically in women around 60 years of age, with

Figure 2 Plain radiographs of the shoulders (patient 3). Gradual obliteration of the glenohumeral joint space without evidence of rotator cuff damage.

Table 1 Clinical characteristics of four liver transplant recipients with rapid and multifocal chondrolysis

Characteristics	Case 1	Case 2	Case 3	Case 4
Age*/sex	54/F	25/M	21/F	30/F
Liver disease	Primary biliary cirrhosis	Hepatitis B related cirrhosis	Autoimmune cirrhosis	Primary sclerosing cholangitis
Immunosuppressive drugs	AZA, CyA, P	AZA, CyA, P	AZA, CyA, P	AZA, CyA, P
Time since liver transplant at joint symptom onset (years)	2	6	2	12
Steroid dose at joint symptom onset (mg/day)	13	8	7	2
Joints affected and time to complete chondrolysis	R hip/18 mo L hip/14 mo RL knees/20 mo	L hip/16 mo R hip/18 mo R GH	RL hips/14 mo RL knees/20 mo RL GH	L knee/14 mo RL ankles R hip/12 mo

*Age at time of transplantation.
AZA, azathioprine; CyA, ciclosporin A; P, prednisone; R, right; L, left; GH, glenohumeral joint.

overweight and joint overuse being predisposing factors.[6 7] In our patients, no evidence supporting any of these causes of chondrolysis was found by imaging studies or pathological examination. In particular, there were no radiological signs of AVN or insufficiency fractures of the femoral head. AVN was of special concern as it is extremely common among LT recipients, with, however, wide differences according to the nature and duration of the underlying liver disease.[8] None of our patients had evidence of hip dysplasia or a family history of OA.

Importantly, in addition to hip and knee chondrolysis, shoulder destruction occurred in two patients. The shoulder joint is rarely affected by destructive arthropathies. No history of acute episodes or radiological features suggesting rotator cuff damage or apatite related destructive arthropathy (''Milwaukee shoulder'')[9] was collected. Furthermore, this last condition occurs chiefly in elderly women. The involvement of both weightbearing and non-weightbearing joints in these patients supports a systemic cause for the chondrolysis.

Several non-steroidal anti-inflammatory drugs have been reported to accelerate joint destruction.[10] However, none of our patients took non-steroidal anti-inflammatory drugs after LT. Their only treatment was a conventional immunosuppressive regimen after transplantation, including azathioprine, ciclosporin A, and corticosteroids, which have no proven deleterious effects on cartilage.

As reported by Yamamoto and Bullough,[11] microfractures due to subchondral bone insufficiency in the femoral head related to corticosteroid-induced osteoporosis may lead to rapid chondrolysis. No microfractures were seen in our patients by imaging studies or by pathological examination of operative specimens, although mild osteopenia was noted in the femoral heads. Corticosteroid-induced bone loss may, however, act as a predisposing factor. Pathological findings were reminiscent of laminar inflammatory hip disease in one of our patients (case 3), who may have had a condition similar to acute idiopathic chondrolysis of adolescence, which has been ascribed to an autoimmune mechanism.[12] In this condition, however, the joint narrowing is usually concentric and is accompanied by acetabular protrusion,[13] which was not the case in any of our patients. Of interest, three out of four patients had autoimmune liver diseases but no definite inflammatory arthritis.

Thus, the unusual chondrolytic process in our patients remains unexplained. Conceivably, metalloproteinase (MMP) activation or an imbalance affecting intra-articular degradation/repair processes may be involved. Masuhara et al found that serum and plasma levels of MMP-3 and MMP-9 were significantly increased in patients with rapidly destructive hip OA.[14] Finally, a role for autoimmune liver diseases or side effects of immunosuppressive drugs cannot be ruled out. However, to the best of our knowledge, this pattern of accelerated joint destruction has not been described in association with other organ transplantations. The rapid and multifocal chondrolysis in our four patients was probably multifactorial. Further investigations of this condition are in order.

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There is no conflict of interest with this clinical study

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