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EDITORIAL

APATITE ASSOCIATED ARTHRITIS

MASSIVE deposition of crystals of hydroxyapatite (HA) in connective tissues is well recognized in supraspinatus tendinitis (1), the calcinosis associated with scleroderma (2) or dermatomyositis (3) and the periarthritis that occurs in patients with renal failure undergoing chronic dialysis (4, 5). HA deposition has also been identified in acromegalic arthropathy (6), ochronosis (7), myositis ossificans (8), Paget's disease (9), tumoral calcinosis (10), intervertebral disc calcification (11) and heterotopic ossification after joint replacement (12). In addition, periarticular deposition of HA may be associated with metabolic diseases such as diabetes mellitus, hypothyroidism (13) and secondary hyperparathyroidism (14), or it may occur as a local complication of corticosteroid injections into the small joints of the hands (15). Synovial deposition of apatite has been seen during therapy with high-dose vitamin D (16).

In 1976, Dieppe and his colleagues (17) first identified microcrystals of HA in the synovial fluid of five patients with osteoarthrosis of the knees using analytical electron microscopy. This was soon confirmed by others (18) and apatite crystals were identified in joint effusions of patients with otherwise unexplained acute arthritis, sometimes in association with calcific periarthritis (19). More recent investigations have suggested that crystals are common in osteoarthritic synovial fluids. In a study of 100 OA patients, Schumacher (20) found that in 60% the effusions contained either calcium pyrophosphate dihydrate (CPPD) or HA crystals. Of these, 30% were apatite, 27% were CPPD and 43% had both. HA crystals were detected in 8/32 effusions from patients with RA, where they appeared to be related to the development of secondary OA (21). In a controlled study (22) Dieppe found microcrystals of HA in nine out of 34 OA synovial fluids and in none out of 25 RA fluids. The presence of crystals in OA synovial fluid appears to be related to the severity of the radiographic changes but not necessarily to inflammatory episodes.

Where then is the origin of these crystals and are they involved in the pathogenesis of OA? Using transmission electron microscopy Ali (23) identified microcrystals of HA, which are normally confined to the calcifying epiphyseal cartilage, within matrix vesicles in the mid-zone of osteoarthritic cartilage. More recently he has also identified cuboid crystals of Whitlockite in the superficial zone of the articular cartilage and needle-shaped crystals of HA on the surface of OA cartilage (24). These findings, together with the increase in matrix vesicles and alkaline phosphatase activity in the cartilage (23), have led him to the belief that an abnormality of calcification may be involved in the aetiology of OA. Ali's studies have, however, been largely uncontrolled, and recent work in Edinburgh (25) has revealed similar cuboidal crystals, provisionally identified as HA, in the superficial zone of ageing but otherwise normal articular cartilage obtained from the femoral heads of women undergoing hip arthroplasty following subcapital fractures.

Recent reviews of experimental work strongly suggest that inorganic pyrophosphate (26) and proteoglycan aggregates (27) may be key factors in inhibiting apatite mineralization in normal cartilage. Much of the evidence suggests that HA deposition is a consequence, rather than a cause of osteoarthrosis, and that it may also occur in normal ageing cartilage and in many other connective tissues following a variety of pathological insults. In these circumstances HA crystal deposition may be associated with release from inhibition of mineralization, following pyrophosphate hydrolysis to phosphate (26), breakdown of proteoglycan aggregates (27) or an influx of calcium-binding glycoproteins (28).

In this journal Dieppe *et al.* (29) describe a group of 12 elderly patients with a dis-

tinctive type of destructive arthropathy predominantly affecting the shoulders and knees. Eleven of the twelve were women and clinical features included pain on use, rapid progression to joint instability and large cool effusions with viscous synovial fluid and low cell counts despite the presence of a lot of apatite-containing particles. One of the patients had acromegaly, a condition known to be associated with HA deposition (6), and there was a preceding history of calcific periarthritis in three. Other preceding conditions included seropositive RA in one, a mild seronegative inflammatory polyarthritis in one, generalized nodal OA in one and a single patient with mild hypercalcaemia. CPPD crystals were also identified in five of the cases, but the clinical and radiological findings were quite unlike the destructive form of chronic CPPD arthropathy (30) which is usually associated with active inflammatory changes and striking hypertrophy of bone. In these patients the radiographs showed marked attrition of bone and cartilage, with a paucity of proliferative changes.

Similar patients were first described in France as cases of 'L'épaule senile hémorrhagique' (31) and three of the eight patients previously reported by Dieppe (32) as having 'mixed crystal deposition disease' had identical clinical and radiological features. These patients with 'apatite associated destructive arthritis' strongly resemble McCarty's four patients with 'Milwaukee shoulder' (33), although the synovial proliferation and osteochondromatosis which were a feature of the American cases were not seen. The Bristol group did not assay the synovial fluid for collagenase or neutral protease activities, which were so strikingly elevated in the patients with 'Milwaukee shoulder' (34).

Although the age, sex distribution, clinical presentations and radiological findings appear to be very distinctive and similar in the French, American and British cases, the numbers of patients reported to date are still too few for one to be certain whether this is indeed a distinct new disease entity or an unusual end-point of a number of joint disorders.

Certainly, the clinical and pathological findings in the Bristol cases do not support the notion that this is a crystal 'induced' disease. Urate and CPPD crystals are frequently found in non-inflammed asymptomatic joints from patients with gout (35) and chondrocalcinosis (36). Perhaps monosodium urate (MSU), CPPD and HA crystals are all 'necessary but not sufficient' prerequisites for symptomatic disease, and perhaps one should regard all these crystal deposition disorders as crystal *associated* diseases?

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