Crystal deposition in hyperparathyroidism

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The relationship between hyperparathyroidism and articular calcification is well established. It is based firstly on the finding of a high incidence of chondrocalcinosis in patients with hyperparathyroidism (18 per cent. of 91 cases: Dodds and Steinbach, 1968); and secondly on the appreciable numbers of cases of hyperparathyroidism found amongst large series of patients with chondrocalcinosis (McCarty, 1966, quoted a figure of up to 7·5 per cent.).

There is also evidence of a significant though less clear-cut relationship between hyperparathyroidism and hyperuricaemia and gout. Mintz, Canary, Carreon, and Kyle (1961) observed hyperuricaemia in four out of eight patients with hyperparathyroidism; and Scott, Dixon, and Bywaters (1964) found eleven cases of hyperuricaemia (five with actual clinical gout) among twelve patients with hyperparathyroidism. Although renal impairment may have contributed to the hyperuricaemia in some cases, it seemed likely that the hyperparathyroidism *per se* was the underlying cause in several others.

It follows, therefore, that a patient with hyperparathyroidism is at risk of developing crystal-induced synovitis from either urate or calcium pyrophosphate or both; and there have been isolated reports of the recovery of appropriate crystals from the joint aspirate during episodes of acute synovitis (Jackson and Harris, 1965; Serre, Simon, Thevanet, and Barjon, 1966).

However, a search of the literature has failed to reveal any combined morbid anatomical-crystallographic studies on patients with hyperparathyroidism who in life suffered from both urate and calcium pyrophosphate synovitis and who subsequently came to *post mortem*. It is to correct this omission that we report this clinico-pathological study.

Case report

A 64-year-old ice-cream vendor of Italian extraction was admitted to Guy's Hospital in July, 1969, complaining of painful swollen hands. He had previously first presented to the same hospital in 1961 with acute gout of the left great toe, an affliction that had troubled him since

1947. He reported that his brother also suffered from gout, the only one of his seven siblings to do so.

Examination

At his first attendance he was noted to be obese and normotensive; the heart was clinically normal. Plasma uric acid was 9 mg./100 ml., but renal function was normal.

Progress

He commenced long-term therapy with probenecid, but it is doubtful that he continued to take the tablets regularly. During the following 8 years he was occasionally seen in the out-patients department and then complained of recurrent episodes of acute synovitis. It is known that from 1966 he experienced exertional dyspnoea and in 1968 had an episode of pain and swelling in the right hand.

Admission

On July 29, 1969, he was readmitted to hospital as an emergency in congestive cardiac failure. He was found to have an acute polyarthritis of the metacarpophalangeal joints of both hands which were red, swollen, and tender. The murmurs of mitral stenosis and regurgitation were present. He was hyperuricaemic (plasma uric acid 7·8 mg./100 ml.) and showed normal renal function (Cr^{51} EDTA—GFR 69 ml./min.). X rays revealed calcification in the region of the mitral valve (Fig. 1) and

FIG. 1 *Lateral radiograph of chest, showing calcification in region of mitral valve.*

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widespread chondrocalcinosis articularis (Fig. 2a-f). The radiological appearances of the left great toe suggested gout (Fig. 3, overleaf).

Plasma calcium levels were persistently elevated to between 11.1 and 12 mg./100 ml. Phosphate excretion index was +0.294. On the basis of these investigations

hyperparathyroidism was diagnosed but operation was not possible because of his cardiac condition. In September he developed an acute synovitis of the right knee that was shown to be due to calcium pyrophosphate crystals.

He died in October of unremitting cardiac failure.

FIG. 2 *Articular calcification seen radiologically*
 (a) *Menisci of knee*
 (b) *Articular cartilage of knee*
 (c) *Symphysis pubis and in left hip joint*

2 (d) *Triangular cartilage of wrist joint*

2 (e) *Metacarpophalangeal joints*

2 (f) *Achilles tendon.*

FIG. 3 Radiological appearance of both first metatarsophalangeal joints consistent with urate gout.

POST MORTEM EXAMINATION

The autopsy revealed a single calcified plaque (2×0.5 cm.; Fig. 4) on the lower surface of the posterior mitral valve cusp which stenosed the valve orifice to a narrow crescent. The anterior cusp and the chordae tendinae attached to both cusps were normal. Pulmonary oedema was present and the right ventricle was hypertrophied (0.8 cm. thick).

FIG. 4 Calcified plaque on lower surface of posterior mitral valve cusp.

There was a right superior parathyroid adenoma measuring $2.5 \times 0.8 \times 0.5$ cm. Its histology, which was characteristic (Fig. 5a and b, opposite), may be compared with the structure of one of the normal parathyroids (Fig. 5c, opposite).

All joints examined showed encrustation on the joint surfaces with amorphous white mineral (Fig. 6) and deposition of similar material within the intra-articular cartilages and adjacent ligaments.

Chemical analyses showed 45 mg. of calcium and 2.7 mg. of uric acid per gramme of medial right knee ligament and 27.2 mg. of calcium with 3.1 mg. of uric acid per gramme of right sterno-clavicular ligament. In addition to these deposits, there were a tophus adjacent to the first left metatarsophalangeal joint and a calcified dural plaque that measured 7×3 cm.

FIG. 6 Macroscopic appearance of parathyroids and thyroid glands; articular surface of lower surface of patella; calcified plaque on mitral valve.

FIG. 5 (a) *Histology of adenoma of right superior parathyroid gland, showing well-marked acinar formation (low power)*

(b) *Parathyroid adenoma (high power).*

(c) *One of the normal parathyroid glands (low power).*

Both kidneys were congested and contained several small cortical cysts. Histology showed patchy fibrosis and some aggregates of mononuclear cells related, for the most part, to the cysts. There were also a number of intratubular casts.

Post mortem x rays of the dense calcific deposit on one mitral valve cusp and of the finely deposited calcium in a meniscus and two portions of articular cartilage are shown in Fig. 7 (overleaf).

X-RAY DIFFRACTION

X-ray diffraction studies were carried out on the various mineral deposits and the powder patterns were compared with standard pictures.

In Fig. 8 (overleaf), for example, the uppermost pattern is a standard of sodium acid urate and the lowest a mixture of the monoclinic and triclinic forms of calcium pyrophosphate. The intermediate pattern, obtained from mineral deposit in the first left metatarsophalangeal joint, shows a superimposition of the pattern for sodium acid urate upon

those for the two forms of calcium pyrophosphate.

The x-ray diffraction findings are shown in the Table (overleaf). In many sites calcium pyrophosphate was identified and, as is usually the case, the triclinic form predominated over the monoclinic form. Only in the dural plaque was the monoclinic form found in isolation. This is a most unusual finding and as is reported below the polaroscopic appearances for this lesion differed from the rest.

Urate was identified in many joints in addition to calcium pyrophosphate. It is of interest that the tophus contained recognizable calcium pyrophosphate dihydrate as well as abundant urate. The calcified plaque of the mitral valve was shown to consist of carbonate-apatite.

POLARIZING MICROSCOPY

The finding of both urate and calcium pyrophosphate in many joints led us to examine the histological preparation in more detail by the use of compensated polarizing microscopy, to study the

FIG. 7 Post-mortem radiograph of calcified mitral plaque (top left), meniscus (bottom left), and two specimens of articular cartilage (right).

FIG. 8 X-ray powder photographs taken with $\text{CuK}\alpha$ radiation: (A) Approximately equal amounts of monoclinic and triclinic forms of calcium pyrophosphate dihydrate (B) Sample of deposit from left metatarsophalangeal joint (C) Sodium acid urate monohydrate.

disposition of these two types of crystalline material in the tissues and in particular in the articular cartilage. A sensitive tint (first order red) compensator was used in all cases.

Low-power examination of the cartilage from the sternoclavicular joint (Fig. 9a) showed numerous crystalline deposits that varied from the small superficial accumulations seen on the left of the figure to larger and more deeply situated foci visible on the right. Extensive areas of intervening cartilage were free of crystal deposition.

With higher magnification it was possible to identify individual crystals by their sign of birefringence, since urate crystals are negatively birefringent and calcium pyrophosphate dihydrate show weak positive birefringence. Crystals of both kinds can be seen in close proximity to one another (Fig. 9b).

Some pockets (Fig. 9c) show a predominance of urate, while in others (Fig. 9d) the major component is calcium pyrophosphate.

The specimen of ligament from the knee joint shown in Fig. 9e contains a mixture of the two kinds of crystals.

The section from the calcified dural plaque (which contained calcium pyrophosphate in the monoclinic form only) showed a Maltese cross-like appearance denoting a spherical structure (Fig. 9f).

A few mineral deposits in the kidney (Fig. 9g) were related to the tubules and contained both urate and calcium pyrophosphate crystals. It is of interest to recall that Scott and others (1964) prophetically postulated that hyperuricaemia in hyperparathyroidism might be due to a tubular defect consequent on calcium deposition. A number of renal tubular casts were shown to contain urate crystals (Fig. 9h).

FIG. 9 Sections viewed under polarized light, using a first order red (or quarter wave plate) compensator. Slow positive wave of compensator goes from lower left to upper right corners (arrows):
 (a) Cartilage from sternoclavicular joint (low power)
 (b) Same, showing crystals of both positive (calcium pyrophosphate) and negative (urate) birefringence adjacent to one another (high power)
 (c) Another field from sterno-clavicular cartilage, showing preponderance of negatively birefringent crystals (urate)
 (d) Another field, showing preponderance of positively birefringent crystals (calcium pyrophosphate)
 (e) Medial knee ligament, showing a mixture of the two kinds of crystals
 (f) Calcified dural plaque, showing Maltese-cross appearance, suggesting a spherical structure (calcium pyrophosphate dihydrate monoclinic form only)
 (g) Deposit of both kinds of crystals in relation to a renal tubule
 (h) Renal tubular casts containing negatively birefringent (urate) crystals.

Table X-ray diffraction study

Tissue	Joint	Sodium acid urate	Calcium pyrophosphate dihydrate	Apatite
Articular cartilage	1st right MTP	+	—	—
Articular cartilage	1st left MTP	+	Trace	—
Articular cartilage	Sterno-clavicular	—	+	Trace
Meniscus	Knee	+	+	—
Medial knee ligament		—	+	—
'Tophus'	Adjacent 1st left MTP	++	+	—
Mitral valve		—	—	+
Dural plaque		—	+(Monoclinic form only)	—
Kidney		—	—	+

Discussion

This report confirms the previous x-ray diffraction study of Lagier, Baud, and Buchs (1966) that articular calcification in primary hyperparathyroidism takes the form of calcium pyrophosphate dihydrate. They found *all* extra-articular calcification in the form of apatite (together with Whitlockite in tuberculous or parasitic disease). In the patient considered in this report, calcium pyrophosphate was found additionally both in the dural plaque and as scattered crystals in the renal parenchyma. In the

former case, as in the case of the various articular structures, the crystals were identified by both polarizing microscopy and x-ray diffraction.

However, the major interest of this case is not so much in the finding of both urate and calcium pyrophosphate crystals in various articular structures, which might have been predicted, but rather in the intimate relationship shown to exist between the two types of crystals in the discrete pockets in the cartilage where they both appear.

Very little is known concerning local factors that determine the specific site of deposition in cartilage of urate in the presence of hyperuricaemia and of calcium pyrophosphate in the presence of hypercalcaemia. The suggestions that emerge from the intimate relationship between the two types of crystal deposited in the tissues of this patient are, on the one hand, that factors determining the local precipitation of crystals may be similar for each type of crystal and, on the other hand, that the prior precipitation of one kind of crystal may alter the local environment within the cartilage and so favour the precipitation of the other form of crystal.

Summary

This clinicopathological case report concerns a 64-year-old man who in life suffered from attacks of both urate and calcium pyrophosphate synovitis. Hyperparathyroidism was diagnosed but he succumbed to the effects of a calcific mitral valvulitis before operative treatment could be undertaken. At autopsy a large parathyroid adenoma was found. All joints examined showed a chalky encrustation of the cartilage which was demonstrated by x-ray diffraction to contain both sodium acid urate and a mixture of the triclinic and monoclinic forms of calcium pyrophosphate dihydrate. A tophaceous deposit adjacent to one big toe joint showed calcium pyrophosphate dihydrate in addition to sodium acid urate. The calcified material in the heart valve was identified as carbonate apatite.

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