Clinical impact of bone and calcium metabolism changes in sarcoidosis

Gianfranco Rizzato

History

BONE CHANGES

Even before the introduction of X-rays, Besnier had noted the association of swelling of the fingers with lupus pernio. In 1904 Karl Kreibich, later Professor of Dermatology in Prague but at that time working in Vienna, described four patients with cystic changes in the bones of the hand in connection with lupus pernio and gave an excellent radiographic reproduction of the hands in one and sarcoid histology of the skin in another. Other reports showing bone involvement by sarcoidosis were published soon thereafter. In 1919 Schaumann was the first to emphasise the location of the specific granuloma in the marrow. The first detailed accounts of the radiology were those of Fleischer and Jungling who demonstrated that radiological involvement is more frequent in the bones of the hands and feet than in the long bones, vertebrae, or skull. James in 1959 was the first to recognise that bone involvement occurs very rarely in the absence of skin lesions but is common in patients with persistent disease, especially with lupus pernio and other skin lesions. The first study on trabecular osteoporosis in 49 untreated patients was possible only when computed tomography became available; our group has shown that a mild trabecular bone loss may appear only in chronic sarcoidosis. This feature had never been noted before because simple radiographic studies are not sensitive enough to show a mild osteoporosis and because there is rarely an indication for biopsy of the bone affected by sarcoidosis. Our findings have been confirmed by two other groups.

Corticosteroids may, of course, cause osteoporosis which is spontaneously reversible, at least in young people, if the treatment can be discontinued for at least six months.

CALCIUM METABOLISM CHANGES

Hypercalcaemia in sarcoidosis was first demonstrated in 1939. The next milestone was the discovery in 1979 that increased serum concentrations of 1,25-dihydroxy-vitamin D3 (calcitriol; 1,25(OH)2D3) are associated with the hypercalcaemia in sarcoidosis. Two years later it became clear that the site for overproduction of calcitriol must be extrarenal since hypercalcaemia and raised calcitriol levels were observed in an anephric patient with sarcoidosis. The puzzle was finally solved in 1983 with the report that cultured alveolar macrophages in sarcoidosis are able to produce calcitriol.

Epidemiology

Bone involvement is reported to be from 1% to 34% depending on the primary interest of the author and whether a radiological evaluation of the bones has been performed, though the recognition of this problem has increased since the introduction of computed tomographic (CT) scanning. In an untreated group of patients we have found that, when sarcoidosis was known for at least 20 months, vertebral cancellous mineral content was lower than normal (>1 SD below normal—that is, Z score < -1) in seven of 14 men, in four of six young women, and in three of five postmenopausal women. Thus, over 50% of patients with chronic sarcoidosis had osteopenia. Hypercalciuria is found more frequently. Taking an upper limit of urinary calcium excretion rate of 300 mg/24 hours, it was found in 77 (40%) of 192 patients in London. Renal calculi have been found in about 10% of patients with chronic sarcoidosis, with a prevalence ranging from 1.3% to 14%. In rare cases (2.2% in one retrospective study, 3.6% in one prospective study) they may be the presenting feature of the disease. Moreover, there may be asymptomatic renal stones at presentation in a further 2.7%.

Pathogenesis of extrarenal synthesis of 1,25(OH)2D3: a compensatory mechanism mounted by the immune system?

The structure of the 1,25(OH)2D3 that was synthesised by the sarcoïd alveolar macrophages was confirmed by mass spectroanalysis. Production of 1,25(OH)2D3 in the system was enhanced in a dose-dependent fashion by γ-interferon. Ιγ Interferon is produced spontaneously by activated lymphocytes and alveolar macrophages in active sarcoidosis. These findings provide evidence that γ-interferon plays a major role in the pathogenesis of extrarenal synthesis of 1,25(OH)2D3.

Alveolar macrophages recovered by bronchoalveolar lavage from patients with sarcoidosis possess 1α-hydroxylase activity and are able to metabolise 1,25(OH)2D3 from 25-hydroxy-vitamin D3. Substrate specificity and enzyme affinity for 25-hydroxy-vitamin D3 are similar to those reported for the renal enzyme. Whereas synthesis of 1,25(OH)2D3 by the pulmonary alveolar macrophages and mammalian kidney show some similarities, 25(OH)D-1α-hydroxylase from the sarcoïd macrophages...
Pathogenesis of abnormal calcium metabolism

Regardless of the potential role of 1,25(OH)\(_2\)D\(_3\) in the modulation of inflammation, it is evident that granulomas provide a non-renal source of 1,25(OH)\(_2\)D\(_3\). This has been demonstrated in diseased lymph nodes and in alveolar macrophages. This hyperproduction may result in increased intestinal absorption of calcium, as shown by balance studies and measurement of calcium absorption with radiolabelled calcium. Consequently hypercalcaemia, hypercalciuria, nephrocalcinosis and renal stones may occur, while serum immunoreactive parathyroid hormone is either suppressed or in the low to normal range. Hypercalcaemia usually develops only when the calcium burden coming from the increased intestinal absorption is very high, or when there is some degree of renal insufficiency. Hypercalcaemia varies directly with calcium intake and can be prevented or corrected by dietary restriction of calcium. Exposure to sunlight or to ultraviolet light may be deleterious because of the induction of skin overproduction of vitamin D. For the same reason a seasonal incidence of hypercalcaemia may be seen in summer in patients with sarcoidosis.

The story, however, is not so simple because increases in urinary hydroxyproline levels, an index of bone resorption, occur in sarcoidosis which means that some of the excess urinary calcium may originate from the skeleton. In addition, high levels of 1,25(OH)\(_2\)D\(_3\) may stimulate osteoclastic activity and bone resorption.

Clinical impact

Hypercalcaemia and hypercalciuria are usually asymptomatic but the toxic effects of calcium on renal tubules may produce symptoms of polyuria, volume depletion, and polydipsia. Nephrogenic diabetes insipidus and other tubular defects (wasting of potassium, magnesium, phosphate, glucose and amino acids, metabolic acidosis or alkalosis) are described, but their occurrence is very rare. Depending on its duration and severity, hypercalcaemia may lead, rarely, to acute renal failure, or more frequently to chronic changes in interstitial calcium deposition, and interstitial fibrosis with possible chronic renal insufficiency. Acute hypercalcaemia may result in renal tubule necrosis from intracellular calcium overload and tubule obstruction by calcium precipitates. Nephrocalcinosis occurs in fewer than 5% of patients with sarcoidosis but in more than 50% of patients with renal insufficiency, and is the major cause of chronic renal failure in sarcoidosis. It is found more often in renal biopsy samples or at necropsy than in radiographs. Renal calculi have already been described in this report (see above). Nephrolithiasis may in turn impair renal function by obstructing the urinary tract with resulting hydrenephrosis and need for invasive procedures such as lithotripsy, endoscopic treatment, percutaneous intervention or surgical removal.

Radiological evaluation of the skeleton is not included in the work up of the disease as presented in the ATS/ERS/WASOG guidelines at the last Congress of the World Association for Sarcoidosis and Other Granulomatous Disorders held in Essen, Germany in September 1997. Nevertheless, it may show that the small bones of the hands and feet are affected frequently, especially the middle and distal phalanges. Scattered osteosclerotic changes may also be noted in the skull, long bones, ribs or elsewhere, and may be an occasional finding of a total body scan with gallium-67 (fig 1). Cyst-like lesions of various sizes may also be present occasionally. However, skeletal involvement may be assessed best by bone scintigraphy.

Treatment

Hypercalcaemia, hypercalciuria and calcemic nephropathy may be prevented by a low calcium diet, adequate hydration, and minimisation of exposure to light. Milk, cheese, calcium-containing antacids, and vitamin D should be avoided. Corticosteroids are the mainstay of treatment for more severe hypercalcaemia occurring despite these preventive...
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vegetables, tomatoes, and fruit).63

rich foods (nuts, pepper, chocolate, dark green

40 mg/24 hours, to limit their intake of oxalate-

two litres per day, and, when oxaluria is above

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the renal stones in patients with sarcoidosis are

known. In our experience most of the
renal stones in patients with sarcoidosis are

calcium oxalate. We advise patients to drink

sufficient water to keep the urine volume above

two litres per day, and, when oxaluria is above

40 mg/24 hours, to limit their intake of oxalate-

rich foods (nuts, pepper, chocolate, dark green

vegetables, tomato and fruit).63

Long term corticosteroid therapy may be

needed in sarcoidosis for many different
reasons. In such cases osteopenia is very

frequent and occurs in up to 70% of patients
when CT scanning is used.74 In sarcoidosis the

preventive therapy with calcium or vitamin D

may be contraindicated so that the options are

not so many; however, osteopenia may be

reduced in different ways. In a prospective

study on chronic patients needing long term
corticosteroid therapy we have shown that
bone loss and fractures were lower when using
deflazacort compared with prednisone,74 but
the study was not double blind and other studies
are needed to confirm such a result. In

another study we have shown that salmon calci-
tonin may be a good tool for preventing cor-
ticosteroid induced osteoporosis in patients
with sarcoidosis.75 Our results with calcitonin
were confirmed in a group of 103 patients (four
with sarcoidosis) needing long term cortico-
steroid therapy.66 Bisphosphonates are also
good antiresorptive agents and thus are useful
for preventing76 or treating77 corticosteroid-
induced osteoporosis. Only one study is under-
way on the use of alendronate in patients with
sarcoidosis and the preliminary results, which
are good, were presented at the recent WASOG
Congress held in Essen in September 1997.69
Oral calcium may be given to patients without
hypercalcemia, but calciuria needs careful
monitoring in this case. It is clear that we do
not have to accept bone loss and high fracture
rates as inevitable consequences of high dose
glucocorticoid therapy. The challenge now is to
make the assessment of the risk of osteoporosis
an integral part of the decision to commence
glucocorticoid therapy so that treatment may
be introduced before fractures occur. Such a
practice will alert substantial iatrogenic mor-

bidity in this already disabled group of

patients.70

For the rare patient who cannot be given
corticosteroids there are two other therapeutic
options for hypercalcemia: chloroquine and
ketaconazole. Both are inhibitors of 1α-
hydroxylase. Chloroquine and hydroxy-
chloroquine71 72 have potential retinal toxicity
which may limit their use, but this is not the

case if the dosage is limited to 250 mg/day. At
higher doses a close ophthalmological follow-
up is suggested in the long term. Ketaconazole
has been given in a dose of 800 mg/day for two
years to a 47 year old patient with hypercalcemia
with a good result (but with some decrease
in serum testosterone levels and libido).73 Two
other reports are less favourable because, using
the same dosage, renal function deteriorated in
two patients after four to six days of treatment74
and in one patient the drug had to be
discontinued after four months because of
hepatotoxic side effects.75 Oral phosphates are
another therapeutic option because they limit
intestinal calcium absorption.76

Diuretics may increase or decrease the

calcium concentration in plasma and urine
depending on the type of diuretic employed.77
Thiazide diuretics (hydrochlorothiazide, chlor-
talidone) decrease the renal excretion of Ca++
as a result of a direct action on the early distal
tubule, thereby increasing calcaemia. They are
contraindicated if the patient has hypercalcemia,
but may be an option to decrease hypercalcemia
in normocalcaemic patients if the serum
calcium levels are carefully monitored.

Whether or not hypercalcemia unaccompa-
nied by hypercalcaemia or renal stones requires
treatment is, however, an open question.
Lebacq et al78 have suggested administration
of 5 g cellulose phosphate daily by mouth, or
hydrochlorothiazide in a dose of 100 mg daily.
Amiloride also decreases excretion of Ca++.79
Our practice in the Milan Sarcoid Clinic is to
give to such patients a calciuria decreasing diu-
retic when two consecutive determinations of

Figure 1 Total body scan with gallium-67 showing uptake
due to an asymptomatic (and unsuspected) sarcoid bone
lesion of the skull.
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24 hour calcium is over 500 mg in spite of a low calcium diet. However, in spite of the rational basis, this practice remains poorly investigated and prospective studies are needed.

In contrast, loop diuretics (furosemide) enhance the excretion of Ca++. The calcitropic action of these agents is the basis for their use in symptomatic tubercular calcinosis. Spironolactone also increases Ca++ excretion through a direct effect on tubular transport.

4. Rizzato G. Sarcoidosis in Italy.
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