

Clinical features and treatment of bone sarcoidosis

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Abstract

Sarcoidosis is a multi-system granulomatous disease that exhibits extremely heterogeneous manifestations. Although the lungs are the most commonly involved organs the extension of the granulomatous inflammation may also affect the bones. Almost any bone can be involved; curiously, the small bones of the hands and feet are most frequently affected. Diagnosis and recognition of osseous sarcoidosis is straight forward if typical bone lesions occur in a patient with multi-system disease; however, a solitary bone lesion almost always requires a bone biopsy to firmly establish the diagnosis. Corticosteroids, antimalarials, and immunosuppressive drugs (methotexate, azathioprine, cyclophosphamide) may control pain, reduce swelling, and subdue granulomatous inflammation, but on the whole, therapy is disappointing.

Keywords

Sarcoidosis, granuloma, bone cysts.

Introduction

More than a century ago Jonathan Hutchinson, a surgeon-dermatologist, described the first case of sarcoidosis at King's College Hospital in London (Figure 1). Although for the better part of the twentieth century the disease has remained confined to the domain of the chest physician, its multi-system nature has been widely recognized.^{1, 2, 3} Now, in the twenty-first century clinicians of different disciplines, radiologists, pathologists, immunologists, biochemists, rheumatologists and geneticists huddle together to find the cause of sarcoidosis. Although the clinical and radiological features of pulmonary sarcoidosis are relatively easy to recognize, the diagnosis is often delayed or completely missed because of its resemblance to tuberculosis, berylliosis, fungal infections, and collagen vascular disease particularly in those patients who suffer from extrapulmonary involvement. The following description combines the pathogenesis, clinical features, biochemical changes, and immunological features of osseous forms of sarcoidosis and provides an outline for the diagnosis and the management of bone sarcoidosis.

Historical Note

Karl Kreibich, born on May 20, 1869 in Prague, graduated in 1894 at the German Medical Faculty in Prague. He went to Vienna to work for six years in the Dermatology Clinic run by Moritz Kaposi. In 1903, soon after the introduction of x-ray Kreibich requested an x-ray examination of the hands of a patient with sarcoidosis. He found multiple radiolucencies situated particularly in the distal ends of second phalanges; a pattern considered classical to this day. In 1904 he examined 60 histological sections of lupus pernio in search for tubercle bacilli; he found none. In 1906, he returned to Prague and was made Professor of Dermatology and then the head of Dermatology Clinic. A few years later he concluded that lupus pernio, the hallmark of chronic sarcoidosis, and associated bone lesions



Figure 1. Jonathan Hutchinson by Spy

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represented a distinct granulomatous process not related to tuberculosis. Kreibich died in Prague on December 30, 1932. During his life time he published over 200 scientific papers.⁴

Granuloma of Sarcoidosis

The lesion of sarcoidosis is a well-defined round or oval granuloma made up of compact, radially arranged epithelioid cells with pale nuclei (Figure 2). The typical giant cell of the sarcoid granuloma is of the Langhans' type in which the nuclei are arranged in an arc or a circular pattern around a central granular zone; however, foreign body giant cells are also common. Lymphocytes are seen at the periphery; caseation is absent; fibrinoid necrosis occurs occasionally, particularly in areas where several granulomas have coalesced; and asteroid and Schaumann inclusion bodies are not infrequently observed. Monoclonal antibody techniques and indirect immunofluorescence methods have uncovered the dynamic relationship between the various components of the granuloma and the putative causative agent. The centre of the granuloma is composed of macrophage-derived cells and CD4 helper lymphocytes, whereas the periphery of the granuloma has a large number of antigen-presenting interdigitating macrophages and CD8 suppressor lymphocytes. The lymphokines from the inflammatory cells recruit blood-borne monocytes, prevent macrophage migration, and keep the chronic inflammatory reaction alive and efficient. It is probable that this arrangement of interdigitating suppressor cells on the periphery and the helper cell collection in the center provides an efficient perimeter defence to a persistent, poorly degradable "antigen" of low potency. This architectural arrangement is a feature of tuberculoid leprosy and miliary tuberculosis where an efficient immune system keeps the bacillary load to a minimum; in lepromatous leprosy, on the other hand, the arrangement of the immune cells is disorganized and haphazard, and bacteria abound.⁵

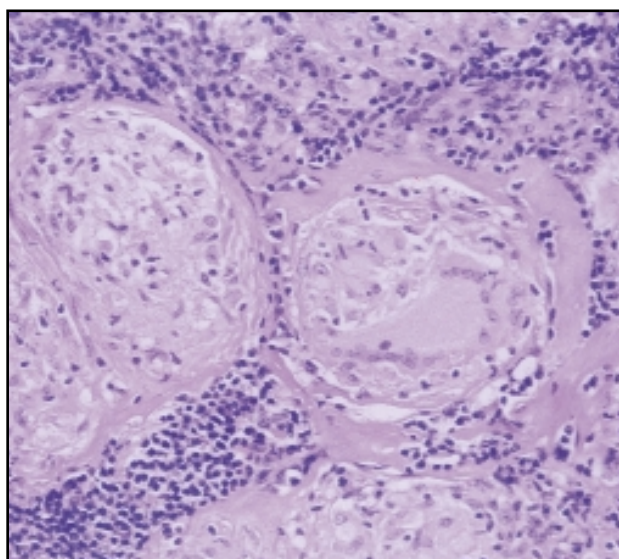


Figure 2. Noncaseating granuloma with a Langhans' type giant cell in a lung biopsy specimen (HE X 120)

Natural History of a Sarcoidosis Granuloma

If a granuloma does not resolve spontaneously or after adequate therapy, it becomes converted into an avascular, almost acellular connective tissue. Granulomas that persist longer than a year or two show peripheral hyalinization and fibrosis resulting in tissue scarring. The mechanisms regulating the development of fibrosis are not well understood. The alveolar macrophage, however, appears to play an important role by producing a number of active mediators, including a macrophage-derived fibroblast growth factor that activates fibroblasts, fibronectin, interleukin 1, and biologically active factor VII. The role of lymphocyte products such as interleukin 2 and gamma-interferon is unclear. Prostaglandins (PGE₂) modulate fibroblast growth. Neutrophils may be involved in the pathogenesis of fibrosis. The cells are recruited from the blood by a macrophage-derived factor. These lung neutrophils may participate in the development of fibrosis either by producing superoxide anion or by influencing the local concentration of immune complexes.⁶

The Multisystem Nature of Sarcoidosis

Because of its diverse manifestations, sarcoidosis presents to clinicians of many different specialties. Clinical manifestations depend on the race, duration of the illness, site and extent of tissue involvement, and activity of the granulomatous process.

Nonspecific Constitutional Manifestations

About a third of patients with sarcoidosis complain of such nonspecific symptoms as fever, fatigue, and weight loss. Fever is generally mild, but temperature elevations to 103 to 104°F are not unusual. Weight loss is generally limited to 5-15 lb during the 10-12 weeks prior to presentation; however, we have seen patients with sarcoidosis who had lost 50 lbs or more before the diagnosis was established. Occasionally, night sweats occur. The constitutional symptoms occur more frequently in African American patients in the USA and Asians from the Indian subcontinent than in Caucasians.

Lungs

Asymptomatic Pulmonary Sarcoidosis

At Sarcoidosis Clinics at Los Angeles County Hospital, and the Ambulatory Health Care Center at Keck School of Medicine of University of Southern California, about 20% of the patients with sarcoidosis are detected at routine chest radiography. The percentage is higher in European clinics. Most of these patients are asymptomatic; a few, on careful questioning, may complain of vague retrosternal discomfort.

Respiratory Symptoms

Over a third of patients with sarcoidosis complain of dyspnea, cough, chest pain, and tightness of the chest. The cough is usually dry. Haemoptysis is rare and occurs in patients with extensive fibrosis with cavitation and aspergilloma. Chest pain is generally confined to the retrosternal area. Occasionally the pain can be severe and indistinguishable from cardiac pain. At least in one reported patient the pain became intensified after drinking alcohol.⁷

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Chest Radiographic Abnormalities (Figure 3)

The following radiographic staging system is commonly used:

- Stage 0 Normal chest X-ray
- Stage I Bilateral hilar lymphadenopathy without pulmonary infiltrates
- Stage II Bilateral hilar lymphadenopathy with pulmonary infiltrates
- Stage III Pulmonary infiltrates without hilar adenopathy
- Stage IV End-stage fibrosis, bullae, honeycombing and cavities

Lung Function Abnormalities

Extensive physiological studies in the past emphasized functional changes characteristic of "restrictive impairment" in patients with sarcoidosis. Vital capacity, residual volume, and total lung capacity are reduced. The loss of diffusing capacity remains perhaps the most common abnormality in sarcoidosis. The diffusing capacity is reduced even in patients with hilar adenopathy without any associated parenchymal infiltrates on chest x-ray film. The gas exchange

abnormalities are frequent. The obstruction of airways - large and small - is common, particularly in African - American patients and may result from any one or more of the following three factors: endobronchial granulomas and bronchiolitis; fibrosis and disruption of the supporting structure around the airways; and release of chemical mediators, complement products, and anaphylotoxins from activated alveolar macrophages. The presence of airways obstruction may indicate persistent and extensive disease.

Bone Involvement in Sarcoidosis

Frequency:

The frequency of bone involvement varies from 3 to 13% (Table 1) depending on the primary interest of the author and the source and composition of the clinical and radiological material under review.⁸ In a British study of 237 patients with both clinical and histological evidence of multi-system sarcoidosis, radiographs of bones, principally hands and feet were done in 180 patients. Bone involvement was noted in 19 (11%) patients.⁹ An entirely different conclusion was arrived in an interesting

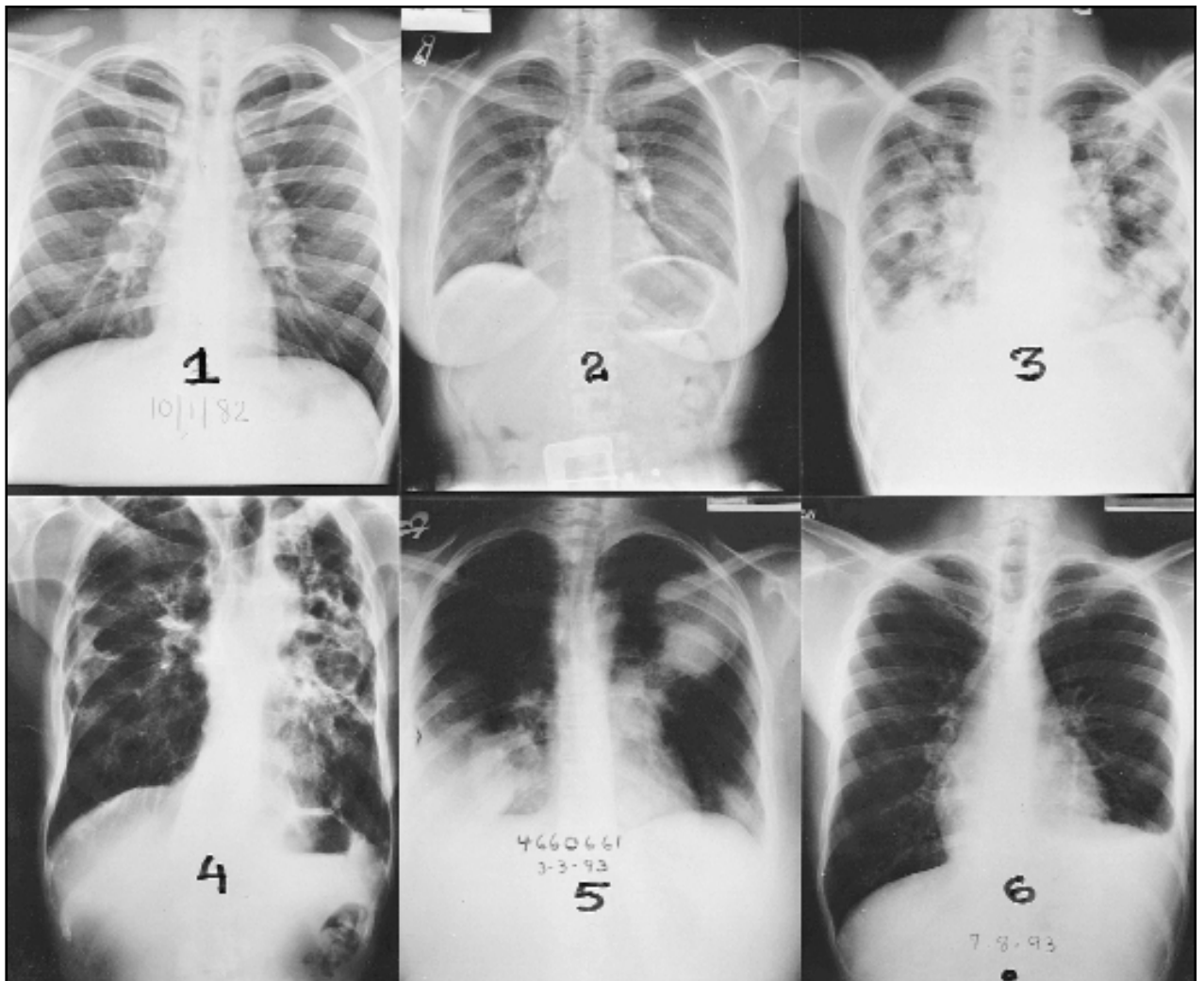


Figure 3. Chest radiographic features of sarcoidosis:

1. Bilateral Hilar lymphadenopathy, 2 Bilateral Hilar Calcifications, 3 Bilateral Hilar and paratracheal adenopathy with parenchymal nodules, 4, Extensive fibrosis and bullous lung disease, 5 Multiple parenchymal masses, and 6 Unilateral pleural effusion on the left side.

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City	Number of Patients		Bone Lesions	
	With Sarcoidosis	With bone X-Rays	No.	%
London	537	475	19	4
New York	311	139	13	9
Paris	329	165	6	4.5
Los Angeles	150	60	3	4
Tokyo	282	282	5	2
Reading	425	425	5	1
Lisbon	89	89	12	13
Edinburgh	502	502	6	1.2
Novi Sad	285	225	25	11
Geneva	121	121	4	3
Total	3,031	2,483	98	3

Table 1. Frequency of Bone Lesions in Large Series of Patients with Sarcoidosis from 10 Cities*

*Data from James DG, Neville E, Siltzbach LE, *et al.* A worldwide review of sarcoidosis. *Ann NY Acad Sci* 278: 321, 1976.

study by Baltzer *et al* who obtained x-rays of both hands in 338 patients of sarcoidosis and 342 control subjects. The radiolucent cystic areas were seen in 17 (15%) of the patients and in 27 (7.8%) of controls. The authors concluded that cystic bone lesions in sarcoidosis were rare and the incidence was not higher than in the normal controls. They also found no correlation between bone cysts and skin lesions.¹⁰ It appears that the most of their patients were young and not had the disease long enough to develop bone lesions. In a series reported by James and Williams, 66% of patients with bone cysts were women, most of them were in the fourth or fifth decade. Bone lesions are more frequent in black patients.^{11, 12} (Figure 4)

Types of Bone Lesions

Sarcoidosis bone lesions are characterised by their bilateral distribution; the site of origin (cortical, preservation of the periosteum); location (hands and feet); position (usually the ends of the affected bones); and the shape (cystic or lacelike with minimal disturbance in the nearby soft tissues). In sarcoid bone lesions the cortical

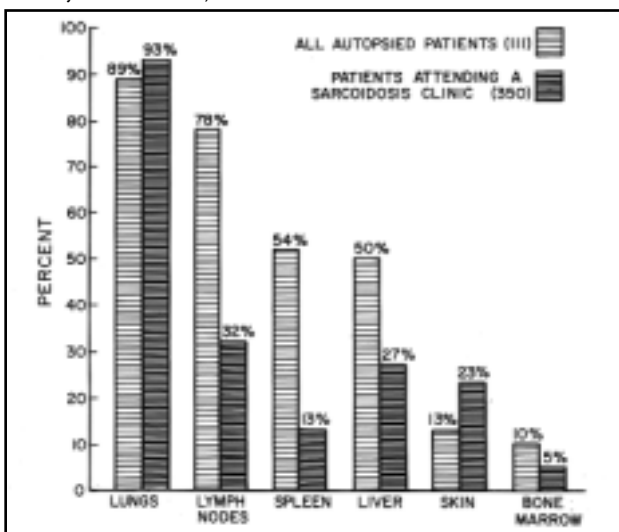


Figure 4. Incidence of bone sarcoidosis

borders of the bones are well preserved. Articular disease is usually manifested by soft tissue swelling, and effusions. In advanced cases, as subchondral lesions extend into joint spaces, the adjacent joints may be involved. Calcification is absent. The questions regarding the causation and localization of bone lesions in sarcoidosis remain unanswered. Since the lesions occur mostly in non-weight bearing bones (hands), they show features of increased bone resorption rather than bone production. Insufficient osteogenesis in relation to osteolysis results in decrease of total bone mass and hence in decrease of bone density. The osteoporosis is evident radiologically by thin cortices, and sharp, widely spaced, often palisading trabeculae. (Figure 5a & b)

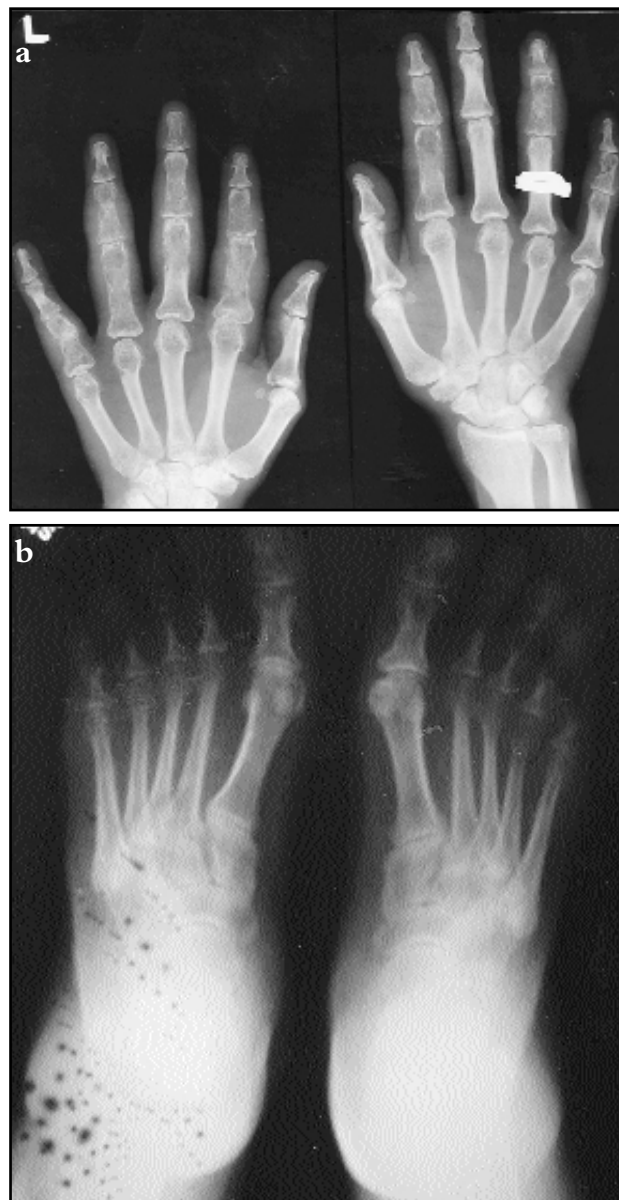


Figure 5. (a) Bone Sarcoidosis presenting as multiple bilateral focal cystic lesions in the phalanges with associated soft tissue swelling. Other areas of less discrete lesions demonstrating rarefaction and a “lacy” appearance of the marrow trabeculae. Although both hands are involved, the distribution is random with some phalanges involved, others spared. Note the preservation of joint spaces. (b) Bone cysts in the feet

Clinical features and treatment of bone sarcoidosis *Papers*

James and Williams classified bone lesions based on their series of 29 patients followed for more than 40 years. 19 (66%) were woman and 18 (62%) presented in the fourth and fifth decades. Bone changes were present in the hands and feet in 26 patients, in the nasal bone in 3, and in the hard palate and the temporal bone in 1 each. Of course, it should be realized that radiology is a rough and imprecise reflection of early bone lesions; only the gross changes are clear. Since bone lesions may remain asymptomatic and are discovered incidentally in many cases, the exact nature, distribution, and progression of lesions remain unknown.¹³

I. Lytic Lesions

Also called 'bone cysts' but the term is a misnomer. These lesions are either minute cortical defects in phalangeal heads or larger rounded punched out lesions involving cortex and medulla, most frequently of the middle and proximal phalanges. It likely reflects an osteoporotic process producing tunnelling that is more local and destructive. The peripheral lesions simulate marginal erosions. Metacarpal heads are less frequently involved. Nasal bone lesions are always small, and may appear lytic defects on the background of osteoporosis.

II. Permeative Lesions

"Tunnelling" of the cortex of the shaft of the phalanx, followed by remodelling of the cortical and trabecular architecture results in a reticular pattern. The concave phalangeal shafts become tubular. The lesions are usually accompanied by soft tissue swelling.

III. Destructive Lesions

In an advanced sclerotic phase the bone may develop multiple fractures of devitalized cortex resulting in a sequestrum. Joint destruction when occurs is localized to the subchondral areas of the bone. Fractures are rare, but may occur if extensive lytic lesions are present. (Figure 6)



Figure 6. Destructive sarcoid lesions of the bone

IV. Periosteal Reaction

Periosteitis is uncommon; a case with hypertrophic osteoarthropathy has been reported.¹⁴

V. Digital Clubbing

Clubbing of the digits, as demonstrated by precise measurement with a micrometer, occurs more frequently than generally realized especially in stages II and III. Clubbing may sometimes be painful.¹⁵

VI.

The nasal bones are involved particularly in patients with lupus pernio.¹⁶ Skull, pelvis, ribs, sternum, and the distal ends of long bones are rarely affected.¹⁷ Although bone lesions are often asymptomatic, in many cases the affected part may be tender and painful. Stiffness of the digits, finger deformities, and soft tissue swelling overlying the bone cysts are frequent and often precede the radiological diagnosis.

VII. Vertebral Sarcoidosis

Vertebral Sarcoidosis is a rare condition. (Figure 7a, b). A needle or open biopsy is required to establish the diagnosis. Occasionally, sclerotic changes in vertebrae may mimic metastatic disease¹⁸⁻²⁰.

VIII. Calcaneal Sarcoidosis

The heel pain can occur in sarcoidosis but often the X-ray of the foot is normal. Occasionally, a calcaneal spur may be seen. Heel pain may also occur in other systemic illnesses including rheumatoid arthritis, sickle cell anemia, Paget's disease, acromegaly, and diabetes mellitus²¹.

VII. Why is the Bone involved in Sarcoidosis?

The reasons why bone lesions occur in sarcoidosis are not clear. The following hypotheses have been put forward²².

- A. The high levels of 1,25(OH)2D3, frequent in sarcoidosis, may stimulate osteoclastic activity and bone resorption. The therapeutic use of vitamin D in senile, postmenopausal, or glucocorticoid-induced osteoporosis is associated with enhanced bone resorption. However, in the study of Meyrier *et al*, the serum levels of 1,25(OH)2D3 were elevated in both patients with and without resorption, suggesting that other factors other than vitamin D must contribute to bone resorption²³.
- B. In a patient by Fallon *et al*, photon absorption densitometry showed osteopaenia, while a bone biopsy disclosed peritrabecular granulomas and osteoclastic resorption. Thus it is possible that granulomas induce a local osteoclastic reaction²⁴.
- C. In multiple myeloma an osteoclastic activating factor (OAF) is produced by normal activated lymphocytes. It is the source of bone erosion and hypercalcemia. Meyrier *et al* have postulated that the sarcoid granuloma might be the source of an OAF inducing bone resorption.

None of the above hypotheses either singly or in unison have been shown to provide a satisfactory explanation to the presence bone lesions in sarcoidosis.

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IX. Differential Diagnosis

The recognition of typical punched out lesions is relatively easy if the patient presents with multisystem features of sarcoidosis. However, if the bone lesion occurs in the absence of the typical pulmonary and extrapulmonary features of sarcoidosis the diagnosis may be difficult. Many clinical disorders including tuberculosis, histoplasmosis, coccidioidomycosis, leprosy, brucellosis, syphilis, Wegener's granulomatosis, eosinophilic granuloma, multiple myeloma and lymphoma can cause bony lesions indistinguishable from those due to sarcoidosis. Nevertheless, in daily practice, only a few diseases need to be differentiated from sarcoidosis as far as the bone involvement is concerned (Table 2). In difficult situations a bone biopsy is needed to demonstrate the presence of noncaseating granuloma and exclude other conditions by appropriate laboratory tests and cultures.



X. Treatment

Osseous sarcoidosis responds poorly to corticosteroids as well as other drugs used in treating the illness²⁵. Corticosteroids often subdue the pain and ameliorate soft tissue swelling but do not completely normalize the bone abnormality. Furthermore, prolonged corticosteroid administration increases the risk of osteoporosis, fracture and avascular necrosis of the hip joint. Symptomatic relief may be obtained by colchicine, indomethacin, and other nonsteroidal antiinflammatory agents. Hydroxychloroquine and chloroquine have been found to be effective²⁶. Salmon calcitonin and alendronate are effective in preventing glucocorticoid induced bone-loss in sarcoidosis patients on long-term corticosteroids²⁷⁻²⁹.

XI. Conclusion

Bone involvement in sarcoidosis occurs in about 5% of the patients. Any bone can be involved, but the small bones of the hands or feet are most frequently affected. The typical sarcoid lesions can be discriminated from those due to tuberculosis, hyperparathyroidism, leprosy, enchondroma, and thalassemia. Treatment is often disappointing.

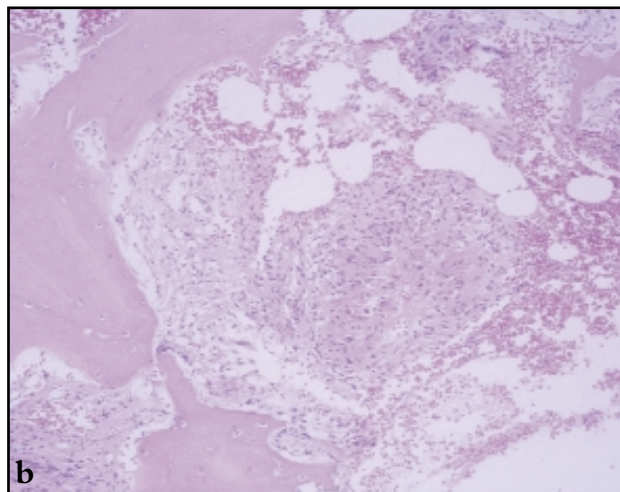


Figure 7. (a) Extensive rib and vertebral involvement; (b) A vertebral biopsy showing characteristic noncaseating granuloma.

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Features	Sarcoidosis	Hyperparathyroidism	Tuberculosis	Enchondroma	Thalassemia
Location	Typically phalanges	Radial aspect middle phalanges	Whole digit	Can be any bone but classically in phalanges	All bones
Soft tissue changes	May be presenting sign	Soft tissue calcification	Diffuse whole digit-also known as dactylitis	No	No
Joint destruction	Rarely- if subcortical erosion extend to articular surface	No	Yes	No	No
Appearance	Lacy or punched out erosions	Subperiosteal resorption Expansile-Brown tumors	Lacy with periosteal rxn and whole bone expansion	Expansile	Expansile with lacy trabeculae
Distribution	Random	Resorption-symmetric Brown tumors-random	One digit	Random	All bones

Table 2. Differential diagnosis of sarcoidosis bone lesions in hands

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