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Osseous manifestations of sarcoidosis

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Abstract

Sarcoidosis is a systemic multisystem inflammatory disease of unknown etiology. The disease is characterized by formation of non-caseating granulomas. The most common presentation is bilateral hilar lymphadenopathy and lung infiltration, but the disease is very heterogeneous, with an unpredictable clinical course. Musculoskeletal manifestations are common. Bone involvement is less frequent, and usually occurs in patients with chronic multisystem course of the disease. They are most commonly found in the phalanges of hands and feet, and are usually bilateral. The skull, long bones, ribs, pelvis, and axial skeleton may also be affected.

Osseous involvement may be asymptomatic but in some cases can cause a severe disability.

Imaging techniques are important for diagnosis. Radiological investigations revealed sclerotic or destructive lesions (involving also joints), cystic and punched out lesions and cortical abnormalities. Biopsy is required for differential diagnosis with respect to malignancy. Treatment is a part of systemic therapy and is not needed in all cases. Glucocorticoids and TNF-α antagonists are used for management.

Key words: sarcoidosis, bone, skeletal manifestations.

Introduction

Sarcoidosis is a systemic inflammatory disease of unknown cause. The disease is characterized by multisystem accumulation of non-caseating granulomas. It usually presents with pulmonary infiltrations and bilateral hilar lymphadenopathy but may affect various organs.

Sarcoidosis is also known as Besnier-Boeck-Schaumann disease to commemorate the physicians who reported for the first time characteristic cutaneous and systemic features of the disease [1]. The first known description of a patient suffering from sarcoidosis is, however, attributed to Jonathan Hutchinson and appeared in print in 1869 [2–4].

Epidemiology and pathogenesis

Sarcoidosis occurs all over the world. Epidemiological data are known only partially. Prevalence of the disease is 4.7–64.0 in 100,000, and annual incidence is 1.0–35.5 in 100,000 [5]. Annual incidence in Poland is 10 in 100,000 [6]. It affects both sexes and the female to male ratio is 1 : 1.46 [5]. Most patients are aged 20–45 years, although recently an increase in new onset of sarcoidosis in people older than 60, especially women, has been reported [6]. The disease in more common in northern Europe as well as in African-American individuals within the USA.

The cause of sarcoidosis remains unknown. Several reports link onset of the disease to environmental factors affecting individuals with genetic susceptibility. It is possible that there is more than one causative factor, and a few sets of factors may result in development of the disease. Such factors as killed or partly degraded pathogens, including mycobacteria and propionibacteria, are suggested as triggers of the immune response.

Other factors, small metallic particles, tattoos dyes and others have also been suggested [5]. Sarcoidal reaction to the dyes at the site of tattooing and tattooing as a precipitating factor have been reported in a number of case reports. It is believed that is may result from chronic antigenic stimulation, especially in predisposed individuals [7].

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Th1, Th15 and Treg cells are believed to be involved in altered immune regulation in patients with sarcoidosis. Macrophages in the patients have antigen-presenting capacity. This phenomenon is associated with expression and function of MHC class II molecules and molecules of costimulatory signals. Macrophages are transformed into epithelioid cells. These cells together with giant cells are the main components of non-necrotizing granulomas which trap non-degradable remnants of causative agents. Granulomas are a form of inflammatory response of the body.

Table I. Differential diagnosis of sarcoidosis

A. Systemic and organ-specific manifestations of sarcoidosis
Lymphoproliferative diseases
Sarcoid-like reaction to malignancy
Infectious diseases, including:
tuberculosis
atypical mycobacterial infections
brucellosis
coccidioidomycosis and other fungal diseases
leishmaniosis
Silicosis
Pneumoconiosis
Beryllium hypersensitivity
Talc or zirconium exposure
Drug-induced granulomatosis
Interstitial lung disease
Autoimmune disorders
Blau syndrome and other autoinflammatory syndromes
Common variable immune deficiency
B. Musculoskeletal manifestations of sarcoidosis
Bone metastasis
Multiple myeloma
Osseous hemangiomas
Enchondromas (Ollier disease, Maffucci syndrome)
Paget's disease
Osteopetrosis
Osteopoikilosis (including Buschke-Ollendorff syndrome)
Hyperparathyroidism and other bone metabolic disorders
Vitamin D-resistant rickets (X-linked hypophosphatemia)
Mastocytosis
Bone tuberculosis
Brucellosis with joint and bone involvement
Coccidioidomycosis with musculoskeletal involvement (desert rheumatism)
Inflammatory spondyloarthropathy
Muscular metastases
Muscular infarction (including that resulting from diabetes mellitus)
Inflammatory myopathy including regional forms

Clinical presentation and diagnosis

Sarcoidosis may affect various organs resulting in a heterogeneous clinical picture of the disease. Pulmonary manifestation occurs in 87–97% of the patients. It is associated with persistent cough and chest radiographs revealed bilateral intrathoracic hilar lymphadenopathy or diffuse micronodular pulmonary infiltrations. On computed tomography, typical nodules with irregular margin and satellite micronodules are detectable, and this finding is known as the galaxy sign.

Other common manifestations include skin (papules, nodules, lupus pernio), occurring in about 15–18% of the patients. Th eye is involved in 10–30% of patients (uveitis, retinal vascular changes, and lacrimal gland enlargement). More uncommon are manifestations associated with the affected liver (20–30%), spleen (10%), heart (2–5%), nervous system (both central and peripheral, about 5%) and the upper respiratory tract (about 2%) and gastrointestinal tract (about 1%) [5].

Diagnosis of sarcoidosis in a number of cases is difficult. On one hand, it is focused on analysis of clinical symptoms and signs, application of imaging techniques and evidencing of non-caseating granulomas. On the other hand, alternative disease which may cause similar alterations should be excluded, as shown in Table I.

It is important to remember that pathological findings are very important for diagnosis but are not pathognomonic. About 40% of tuberculous granulomas are non-caseating, while one-fifth of sarcoidosis granulomas have some sign of caseation [8]. Biomarkers are helpful but they do not have 100% sensitivity. Activity of serum angiotensin-converting enzyme need correction for a genetic polymorphism that affects serum enzyme level and its diagnostic usefulness is controversial [5].

A better option is determination of chitotriosidase. Other markers which are used include interleukin-2 receptor, neopterin, lysozyme, KL-6 (Krebs von den Lungen-6), and amyloid A. These markers are less usable in diagnosis but more applicable in monitoring of the disease [5].

Musculoskeletal manifestations of sarcoidosis

Musculoskeletal manifestations of sarcoidosis are relatively common. It is estimated that they occur in 25–30% of patients, but their severity is very variable [9].

In a significant portion of patients rheumatic manifestations are minor, constitute a part of the complex clinical picture of the disease or are overseen in routine evaluation or attributed to another comorbidity, e.g. osteoarthritis. On the other hand, in some patients articular, muscular or osseous involvement is prominent and severe, and the rheumatologist may be the first doctor who sees the patient with sarcoidosis [10].

Arthralgia and arthritis

Chronic arthritis is usually a part of the multiorgan form of sarcoidosis. It is commonly associated with skin manifestations. Arthritis occurs in a form of oligoarthritis affecting the large joints. Tenosynovitis and periarticular soft tissue mild inflammation are more frequently found than true synovitis. Tenosynovitis is localized mostly within the wrist or ankle joint, and is symmetrical. Various other joints can be involved. Many of the patients suffer from bilateral ankle and talocrural joints' inflammation.

Other joints commonly involved include the knees and elbows as well as metacarpophalangeal joints. The inflammation is rather mild. Moderate to mild inflammatory alterations are revealed in synovial fluid or synovial biopsy, although these methods are not considered as diagnostically important. In some cases, differential diagnosis with articular tuberculosis including Poncet's disease is needed [11].

Other forms of infectious arthritis (including viral) should be taken into consideration. In patients with oligoarthritis and particularly monoarthritis such conditions as gout, other crystal-induced disease (calcium pyrophosphate or hydroxyapatite) or the peripheral form of inflammatory spondyloarthropathy should be excluded [12].

Deforming arthritis known as Jaccoud's arthropathy is very rare in patients with sarcoidosis. A few case reports has been published and in some patients deformations are not associated with inflammatory erosions. Löfgren's syndrome is a triad of symmetric hilar adenopathy, erythema nodosum and arthritis. It is a relatively common manifestation of sarcoidosis but joint pain is frequently overseen in the patients.

Symptoms of Löfgren's syndrome are self-limited in most of the cases. A few patients need medication, usually in the form of a small dose of glucocorticoid administration. Relapses are also not frequent. It is believed that Löfgren's syndrome occurs mostly during spring, and occurs in patients with some specific genetic background [9]. Analysis of the clinical profile of sarcoidosis patients presenting with Löfgren's syndrome versus non-Löfgren's syndrome revealed that those with non-Löfgren's syndrome were older, more commonly male and in a more advanced radiological stage of the disease. They more frequently required medication. Patients with Löfgren's syndrome developed more frequently fever and about 1/6 of them suffered from isolated periarticular ankle inflammation [13].

Symptoms and signs of Löfgren's syndrome require extensive differential diagnostics although recognition of the syndrome is relatively easy. Exclusion of other causes of hilar adenopathy should include screening for tuberculosis histoplasmosis, fungal infections, malignancy or benign tumors.

Involvement of joints of the axial skeleton has been reported but is rare and often asymptomatic. It may mimic spondyloarthropathy and sacroiliitis is described in some cases [14, 15]. On the other hand, a possible association of sarcoidosis and inflammatory spondyloarthropathy has been suggested [16].

An interesting finding was described by Sigaux et al. [17]. They investigated 64 patients (49 women) with sarcoidosis and chronic back pain and revealed that 29/64 had been diagnosed of spondyloarthropathy. Sacroiliitis was found in 13/64. They suggested higher incidence of spondyloarthropathy in patients with sarcoidosis. One of possible difficulty in diagnosis of spondyloarthropathy in patients with sarcoidosis is marrow edematous lesions [18]. These alterations can mimic the so-called pre-radiographic stage of spondyloarthropathy [19].

Myopathy

Sarcoid myopathy can occur in various forms, including acute, chronic and nodular myopathy. Muscular involvement is suggested to occur in a half of all patients with sarcoidosis but is symptomatic in less than 3% of them [12].

Acute sarcoid myopathy is a rare form of muscular involvement. It can be found in the early stage of the disease in younger patients, and is characterized by rapid onset of proximal weakness associated with myalgia. Serum creative kinase level is enhanced and electromyographic evaluation reveals muscular impairment. Diagnosis is made on the basis of muscle biopsy and detection of non-caseating granulomas surrounded with dense lymphocytic infiltrations [12].

Chronic sarcoid myopathy is the most common form of muscular involvement in sarcoidosis. Chronic myopathy is seen mostly in females aged 50–60. The myopathy develops insidiously and is characterized by symmetrical proximal muscle weakness. Serum muscular enzyme activity remains normal or only slightly elevated. Diagnosis may be facilitated with detection of muscle atrophy with magnetic resonance imaging or 18F-fludeoxyglucose positron-emission tomography. Confirmation is made with muscle biopsy revealing granulomas as well as endomysial and perivascular inflammatory infiltrations.

Painful symmetrical nodules located typically within the limbs are a characteristic feature of nodular sarcoid myopathy. The nodules are placed between muscle bundles without directly affecting the muscle fibers. Imaging techniques are useful in detection of the nodules. The central portion of the nodule can contain inflammatory infiltrations and granulomas.

It is important to remember about glucocorticoid-induced myopathy. This condition results from a glucocorticoid excess, and can be misdiagnosed with sarcoidal myopathy in patients receiving glucocorticoid for management of sarcoidosis.

The myopathy is caused by muscular atrophy due to decrease in protein synthesis. The atrophy affects fast-twitch glycolytic muscle fibers, i.e. type II fibers, predominantly IIb subclass. Myopathy is usually a result of chronic glucocorticoid medication. The acute form of the myopathy is very rare.

There are no specific symptoms or signs; thus the definite diagnosis is difficult. Moreover, sarcoidal myopathy may coexist with glucocorticoid-induced myopathy as well. Painless or mildly painful weakness that develops insidiously and progresses slowly is the main symptom. Discontinuation of corticoid management with administration of other non-steroidal agent usually leads to restoration of muscular strength and facilitate diagnosis.

Bone involvement

Epidemiology

Osseous sarcoidosis is a rare manifestation of the disease. Its prevalence remains unknown. Most of the patients remain asymptomatic. Radiological evaluation is limited to some parts of the body and is performed for other reasons than detection of bone involvement. Thus, the majority of osseous sarcoidosis is discovered incidentally rather than due to symptoms suggesting bone alterations. Most of the papers referred to the report of Neville et al. [20] suggesting than 1–15% of patients suffering from sarcoidosis have osseous involvement. Similar prevalence, i.e. 3–13%, was reported by James et al. [21].

On the other hand, Sparks et al. [22] reported only 20 cases of osseous involvement detected in 2013 patients with sarcoidosis identified between 1994 and 2013 at Brigham and Women's Hospital in Boston Massachusetts. Therefore, prevalence was 1.5% only.

Relatively low prevalence of bone involvement is consistent with the earlier report of Baughman et al. [23], who found osseous sarcoidosis in 0.5% of all patients with sarcoidosis. Low prevalence is suggested to result from underdiagnosis, especially as more than half of bone involvement remains asymptomatic [20].

Site of bone involvement

All the skeleton may be a place for development of osseous sarcoidosis. There are contrary data on common sites of osseous involvement. Lytic lesions described as bone cysts occur in the phalangeal heads of the hands and feet. It has been suggested that bone cysts are more common in black people [24]. Various locations of sarcoidosis within the bone have different presentations, including apple core pattern in the finger [25], and different X-ray pictures in the long bones [26–29]. In some patients, bone lesions are described as having a "moth-eaten" pattern involving the cortex of the phalanges and accompanied by soft tissue swelling. Hands are involved in about 15% of the patients [30].

Sclerotic lesions are seen in the spine. They should be differentiated from metastases. Similar lesions are seen in the pelvis. Sparks et al. [22] reported spine and/or pelvis as a site of sarcoidosis lesions in 90% of patients with osseous manifestations. Zhou et al. [30] found the spine and pelvis as a site of sarcoid bone lesions in 68.8% and 35.9%, respectively. Spine involvement can be associated with spinal cord compression [31]. The patients are usually referred to neurological departments.

Skull lesions may have different character and can be a significant difficulty for diagnosis. A skull base mass lesion due to sarcoidosis was mimicking malignancy and a lytic lesion needs to be differentiated from other bone disorders [32]. A pediatric case of rapid-onset thoracic myelopathy due to a sarcoid lesion was reported in 9-year-old otherwise healthy girl [33].

Calcium and vitamin D disturbances in sarcoidosis

Calcium phosphate homeostasis is a tightly regulated set of mechanisms of the human body. One of the important regulating factors is calcitriol, i.e. $1,25(OH)_2D_3$. Calcitriol is a derivate synthesized from cholecalciferol and ergocalciferol ingested in the diet. Sun exposure is responsible for synthesis of cholecalciferol in the lower layers of the skin. Hydroxylation of cholecalciferol to calcifediol (25-hydroxycholecalciferol or $25(OH)D_3$) takes place in the liver. Calcifediol is measured in serum to evaluate the vitamin D status. Calcitriol is produced in the proximal renal tubules in the process of 1α-hydroxylation of $25(OH)D_3$. Hydroxylation is stimulated by parathormone. In pregnant women hydroxylation takes place in the placenta. In patients suffering from sarcoidosis, conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ occurs in activated macrophages of the granuloma tissue.

The excess of calcitriol causes enhanced calcium and phosphate resorption in the intestine, increased

resorption of calcium in the kidneys and altered calcium metabolism is bones. These phenomena may result in hypercalcemia. An increased plasma level of calcium is found in 10–17% of patients with sarcoidosis. Some studies suggested that hypercalciuria is detected in 62% of patients with sarcoidosis but in 10–20% only calcium output is very high [34, 35]. Other studies indicated occurrence of hypercalcemia and hypercalciuria in 10% and 30% of the patients, respectively [36].

It was shown that urinary calcium output correlated with chitotriosidase activity in serum, an important biomarker of the disease activity [37]. Hypercalciuria is associated with polyuria due to inhibition of sodium-potassium ATPase. It may result in dehydration as well as formation of renal stones despite polyuria. Calcitriol also has activity other than control of calcium-phosphorus homeostasis.

Calcitriol affects immune and inflammatory response of the body. It influences secretion of some cytokines and stimulates proliferation of the monocytes and their differentiation to epithelial cells. It was shown that secretion of calcitriol from macrophages is more independent from controlling mechanisms than production of this activated form of vitamin D in other tissues. Macrophages have no alternative metabolic pathway activated under conditions of hypercalcemia, i.e. synthesis of $24,25(OH)_2D_3$ instead of calcitriol. Thus, it is possible that hypercalcemia in patients with sarcoidosis is associated with a normal plasma level of calcitriol. Moreover, in sarcoidosis patients administration of vitamin D_2 is associated with increase in serum level of both $25(OH)D_3$ and $1,25(OH)_2D_3$, while in healthy individuals an enhanced level of $25(OH)D_3$ is observed only [35].

Calcitriol beside a number of immune effects can lead to suppression of parathyroid hormone and activation of release of calcium from the bones. The latter finding seems to be contradictory, given that sufficient levels of serum calcitriol generally prevent overall loss of calcium from bone. It is believed that the increased levels of serum calcium resulting from calcitriol-stimulated intestinal uptake cause bone to take up more calcium than it loses by hormonal stimulation of osteoclasts. Calcitriol is used for management of osteoporosis but its overproduction can decrease bone mineralization and promote fragility as well. It is of interest that serum alkaline phosphatase activity remains within the normal range in the majority of sarcoidosis patients with bone involvement [34, 35].

Mineral bone density is decreased in patients with sarcoidosis [38] although some reports indicated lack of changes in bone mineral density in the patients [39]. The main cause is medication with glucocorticoids. Endogenous overproduction of calcitriol can be accompanied by vitamin D deficiency [40, 41]. Kiani et al. [42] reported a negative correlation between vitamin D deficiency and pulmonary functional state in patients with sarcoidosis. Supplementation with calcium and vitamin D should be performed with great caution [43]. Saha et al. [44] reported a rare case of sarcoidosis of the parathyroid gland presenting with hypercalcemia.

Detection of osseous involvement in patients with sarcoidosis

Imaging techniques are the main method of detection of osseous sarcoidosis. There are no data on sensitivity of the imaging methods in detection of osseous sarcoidosis. Differential diagnosis is difficult. The most important is differentiation of disseminated (or solid) sarcoidosis lesions with metastases. Biopsy is considered as a gold standard. 18F-fludeoxyglucose positron-emission tomography is suggested as a valuable method for detection of osseous manifestations that cannot be visualized in radiography or computed tomography [45, 46].

In brief, the main findings with 18F-fludeoxyglucose positron-emission tomography in musculoskeletal involvements of sarcoidosis patients are increased 18F-fludeoxyglucose uptake around joints, in bones and muscles as well as the so-called tiger man sign. The tiger man sign is an appearance in 18F-fludeoxyglucose positron-emission tomography resulting from hypermetabolic hilar and mediastinal lymphadenopathy, and intense uptake by the muscles [47].

It is important to remember that some forms of sarcoidosis or sarcoidosis-like lesions are associated with malignancy. Kusaba et al. [48] described a case of sarcoidosis as a paraneoplastic syndrome due to multiple myeloma. Osseous lesions were found in the spine and were accompanied by ocular and nodular involvement. Similar cases are summarized by Tiago Serra et al. [49]. Association of sarcoidosis with lymphoma has been sporadically reported as well. A case of sarcoidosis related to medication with nivolumab was described [50]; however, it was possible that the primary malignancy, i.e. melanoma, was a cause of sarcoidosis-like lesions.

Imaging techniques are crucial in diagnosis but the sarcoidosis lesions are characterized by a variety of pictures. It is especially seen in long bones and spine involvement [45]. 18F-fludeoxyglucose positron-emission tomography is also very useful in monitoring the effectiveness of the treatment [51].

Treatment

There is no cure for sarcoidosis and therapy is oriented at preventing or limiting organ damage by suppres-

sion of the granulomatous process as well as relieving symptoms of the disease. It is well known that a significant part of the patients have spontaneous remission and do not require medication. Some patients with sarcoid osseous involvement have asymptomatic and non-progressive disease and also do not require treatment.

In general it is estimated that between 20% and 70% of all patients need systemic therapy. Bone involvement occurs mostly in advanced, chronic multiorgan forms of the disease. Despite lack of symptoms directly associated with bone involvement, most of the patients should be treated. Similarly, all symptomatic osseous involvements are indications for specific treatment even when the patient has no other manifestations.

Systemic corticosteroids are considered as standard medication. There are no firm guidelines for dosage and period of the treatment. In most cases, the initial dose of 20–40 mg of prednisone daily is followed after 6–12 weeks with dose reduction. Higher doses are recommended in some life-threatening situations. Corticosteroids in bone are suggested to reduce soft tissue edema and granuloma formation [52]. They have no beneficial effect on the bone tissue although reduction of the granulomatous tissue ameliorated calcitriol synthesis.

Articular and muscular involvement is a firm suggestion to add early steroid-sparing agents, mostly methotrexate [53]. Other medications, including leflunomide, azathioprine, cyclophosphamide or mycophenolate mofetil, are also used for management.

The mechanism of action of the drugs is believed to be associated with reduction of the granulomatous process. TNF-α is considered as the main factor stimulating development of the granuloma. All drugs have been suggested to affect TNF-α. TNF-α antagonists that directly diminish the cytokine are also used in medication [54].

Conclusions

Sarcoidosis is still a very enigmatic disease with a number of clinical presentations. Bones are a "silent" location of granulomas. About a half of the patients have some, usually mild symptoms only.

The main practical problem is differentiation of granuloma sarcoid lesions with metastases to the bone. Imaging techniques are insufficient for final diagnosis. They are key methods in detection and localization of the lesions. Biopsy and pathological evaluation of specimens is practically the only reliable method of differential diagnosis [55, 56].

Application of glucocorticoids, a method of choice in the treatment of sarcoidosis, should be administered with caution to patients with osseous sarcoidosis. Glucocorticoids enhance osteoporosis, and application of vitamin D and calcium is not always appropriate in the patients due to dysregulation of metabolism by the products of the granulomatous tissue.

Consultation with an experienced rheumatologist is always recommended in patients with sarcoidosis suspected of bone involvement.

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