Osseous disease in patients with pulmonary sarcoidosis and musculoskeletal symptoms

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Little is known about the clinical manifestations and correlates of osseous sarcoidosis and few data exist to guide pulmonologists in their evaluation of patients for possible osseous involvement. To determine the relationship between pulmonary and osseous sarcoidosis, and to develop an algorithm for use by pulmonologists in assessing patients with suspected osseous sarcoidosis, we conducted a retrospective, case control study of patients with pulmonary sarcoidosis and musculoskeletal complaints who were evaluated for osseous disease. All patients underwent a standard evaluation to include physical examination, chest radiograph (CXR), spirometry (PFTs), bone scintigraphy and plain radiographs of the hands and feet. Patients completed a health assessment questionnaire and serum angiotenisin converting enzyme, erythrocyte sedimentation rate, and C-reactive protein were measured. Patients eventually diagnosed with osseous sarcoidosis were compared to those lacking osseous involvement.

Osseous involvement in patients with pulmonary sarcoidosis and musculoskeletal symptoms was common and seen in 38.9% of subjects. Patients with osseous sarcoidosis were more likely to concomitantly suffer from cutaneous sarcoidosis and to have elevated ACE levels and ESRs. No measure of pulmonary involvement (CXR stage, PFTs or symptoms) differentiated patients with osseous sarcoidosis from those without this condition. In cases of osseous sarcoidosis, bone scintigraphy identified a mean of four sites of osseous involvement, some of which would have been missed with the use of plain radiographs limited to the hands and feet. Patients completed a health assessment questionnaire and serum angiotenisin converting enzyme, erythrocyte sedimentation rate, and C-reactive protein were measured. Patients eventually diagnosed with osseous sarcoidosis were compared to those lacking osseous involvement.

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Key words: bone; sarcoidosis, scintigraphy.

Introduction

Sarcoidosis is a multi-system disease of unknown etiology that predominantly affect the lungs and intrathoracic lymph nodes. Non-nectotizing granulomas are the pathological hallmark of sarcoidosis and disorders in T-cell function play a role in the pathogenesis of this decease. In approximately 5% of patients, sarcoidosis involves the bones (1). Small bones of the hands and feet are most often affected, but any bone may be involved (2,3). Osseous sarcoidosis may result in bone resorption and bone destruction. Osteoporosis may also complicate sarcoidosis either as a result of corticosteroid therapy or secondary to direct granulomatous inflammation (4). The development of osseous sarcoidosis is felt to portend persistent systemic disease (5).

Although osseous sarcoidosis is rarely encountered in the absence of cutaneous lesions and is associated with the presence of chronic, multisystem disease, little specific data exist regarding the relationship between osseous sarcoidosis and pulmonary sarcoidosis (1,5). Specifically, the extent of pulmonary involvement in patients with osseous sarcoidosis is unclear and most prior studies have been limited because of their design and sample size.

Since pulmonologists frequently serve as the primary physicians for patients with sarcoidosis, they may be called upon to evaluate patients suffering from sarcoidosis for...
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Methods

PATIENTS AND EVALUATION

Prospectively collected data on all patients consecutively evaluated at our institution (a university affiliated, territory care medical centre) for osseous sarcoidosis between March 1996 and March 1998 were reviewed. Patients were seen in a multimodality clinic with both the pulmonary and rheumatology services. Six of the patients in the study were active-duty U.S. Army soldiers. All patients had a histological diagnosis of sarcoidosis based on a biopsy demonstrating non-necrotizing granulomas with special stains revealing no evidence of either fungal or mycobacterial infection. The evaluation for osseous sarcoidosis was prompted when the patient reported musculoskeletal symptoms as the chief complaint. Specifically, when queried regarding symptoms on our clinic’s intake survey, subjects selected ‘musculoskeletal symptoms’ first. The form asks patients to list their complaints in order of importance. The physician performing the initial evaluation then confirmed that musculoskeletal symptoms were, in fact, the patient’s main concern. For all subjects, the evaluation included: a complete physical examination, pulmonary function testing (PFTs) with measurement of the diffusion of carbon monoxide (DLCO), a chest radiograph (CXR), a Technetium-99 radiolabeled bone scan and plain radiographs of the hands and feet. Patients also had radiographs taken of other bones which demonstrated abnormal radiotracer uptake.

Cases of osseous sarcoidosis were defined by either 1. a bone biopsy revealing non-necrotizing granulomas or by 2. characteristic radiographical features consistent with osseous sarcoidosis. The decision to pursue a bone biopsy was left to the discretion of the patient’s primary physician. If the diagnosis of osseous involvement was made by radiographs alone, abnormalities had to be seen in more than one bone. Characteristic radiographical features included: osteosclerosis, osteolysis, trabecular reticulations and bone cysts. Similar criteria for a diagnosis of osseous sarcoidosis without a bone biopsy have been employed in prior studies (5,10,11). Patients who failed to meet either case definition served as controls. Control patients were followed for at least 6 months to insure that they did not develop osseous sarcoidosis.

Stage by CXR was also determined with Stage I representing bilateral hilar lymphadenopathy (BHL) alone, Stage II defined as BHL with interstitial infiltrates and Stage III characterized as interstitial infiltrates alone. All subjects completed a health assessment questionnaire which included a 10 cm visual analog scale (VAS) to measure both pain and overall health status. This questionnaire was completed at the initial evaluation and prior to further testing. Higher scores on the VAS were associated with worse pain and a worse health status. The PFTs and DLCO were interpreted in accordance with the guidelines of the American Thoracic Society (6). Normal values were derived from Crapo et al. and corrections for race were made in accordance with published guidelines (7,8). Values for lung volumes and expiratory flow rates were considered abnormal if they fell outside the 95% confidence interval for the predicted values. Both the plain radiographs of the bones and the bone scans were reviewed by bone radiologists blinded to the patient’s clinical status.

In addition to the variables noted above, cases and controls were compared with respect to: demographic variables (age, gender and race); the interval (years) between the initial diagnosis of sarcoidosis and the evaluation for osseous sarcoidosis; serological markers of inflammation; and the extent of pulmonary symptoms. The presence of other extrapulmonary involvement (cutaneous, ocular and neurological) was also determined. Specifically, the serum angiotensin converting enzyme (ACE) level, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Pulmonary symptoms of interest included dyspnea, chest pain and cough. For pulmonary symptoms, patients completed a standard questionnaire inquiring as to whether they suffered from dyspnea, chest pain and/or cough. We considered both lupus pernio and plaque-like lesions that showed non-necrotizing granulomas on biopsy as evidence of cutaneous sarcoidosis.

Continuous variables were compared using the Student’s t-test. The chi-square was used to analyse categorical variables except when the expected values were small. In those cases, a Fisher’s exact test was employed. All tests were two-sided and unpaired. A P value of less than 0.05 was assumed to represent statistical significance. SPSS 6.0 (Chicago, IL, U.S.A.) was used to complete statistical analyses. Ninety-five per cent confidence intervals (95% CIs) are reported where appropriate.

Results

The study cohort included 18 patients. Seven patients were diagnosed with osseous sarcoidosis (38.9%; 95% CI: 18.3–63.9%). Two of these patients underwent bone biopsy that revealed non-necrotizing granulomas with no evidence of mycobacterial or fungal infection. The remaining five patients with osseous involvement were diagnosed via plain radiographs. In patients lacking osseous sarcoidosis, the diagnoses for the musculoskeletal complaints were as follows: over-use syndrome (n = 4), osteoarthritis (n = 2), dactylitis (n = 2) and non-specific arthralgias (n = 3).

As shown in Table 1, the demographic compositions of the two cohorts were comparable. The mean age of the patients with osseous sarcoidosis was 41.4 ± 8.5 years as
compared to 45.0 ± 11.7 years in the control subjects ($P = 0.12$). Only 28.6% of the cases were females compared to 54.5% of the controls, but this difference was not statistically significant ($P = 0.28$). A majority of patients in each cohort were African-American and there was no difference in the racial composition of the two groups ($P = 0.60$). The interval between the initial diagnosis of sarcoidosis and the evaluation for osseous sarcoidosis did not differ between the two groups (6.3 years for cases vs. 5.1 years for control; $P = 0.51$). Patients with osseous sarcoidosis were significantly more likely to suffer from cutaneous sarcoidosis ($P = 0.002$). All patients with osseous sarcoidosis had cutaneous lesions while only two of the 11 controls had skin involvement. There was no difference in the prevalence of either ocular or neurological involvement. As a screening test for osseous sarcoidosis, the presence of cutaneous sarcoidosis had a sensitivity and specificity of 100.0% and 81.8%, respectively. The positive and negative predictive values were 77.8% and 100.0%, respectively.

Patients with osseous sarcoidosis were similar to control subjects in terms of the pulmonary variables we examined. As shown in Table 2, all patients with osseous involvement had Stage I CXRs as compared to 81.8% of controls ($P = 0.49$). Of the two control subjects who did not have Stage I CXRs, both had interstitial infiltrates alone (Stage III). Table 2 also demonstrates that neither spirometry nor the DLCO separated cases from controls. The proportion of patients with abnormal lung volumes and expiratory flow rates did not differ between the two groups (42.9% for cases vs. 36.3% for controls, $P = 0.99$) and the distribution of pulmonary symptoms was comparable between patients with osseous sarcoidosis and those without osseous disease. Three of the seven patients (42.9%) with osseous involvement reported pulmonary symptoms compared to three of the eleven (27.3%) control subjects ($P = 0.63$). The frequency of the various pulmonary complaints is shown in Table 2.

Non-pulmonary symptoms further failed to segregate cases from controls. Based on the VAS to measure pain, patients with osseous sarcoidosis had a mean score of 5.7 ± 2.8 compared to 4.9 ± 2.6 in patients without osseous disease ($P = 0.61$). The health assessment scores also did not separate the two groups.

Unlike the demographic and pulmonary variables, certain serum markers of inflammation differentiated patients with osseous disease from those without osseous involvement. For example, the mean serum ACE level in cases was 90.1 IU/l vs. 28.5 IU/l in control ($P = 0.04$). The ESR was greater in patients with osseous disease (36.9 mm/h vs. 14.9 mm/h) than in controls ($P = 0.03$). There was no significant difference in the CRP between the two study groups.

With regard to radiological studies, bone scintigraphy identified an average of 4 ± 1.6 sites with abnormal tracer activity in patients with osseous sarcoidosis. In four of the seven patients (57.1%) with osseous sarcoidosis, bone scintigraphy revealed sites of osseous disease that would have been missed with only plain radiographs of the hands and feet. Without the use of Tc-99 bone scan, two cases of osseous sarcoidosis (28.6%) would not have been detected. The most common sites of osseous sarcoidosis (in descending frequency) were as follows: hands, feet, ankles, femur, tibia and skull. In all but one case, the site of pain as reported by the patient correlated with the location(s) of bone involvement identified radiographically.

**Discussion**

In this case control study of patients with pulmonary sarcoidosis who reported musculoskeletal symptoms, we found that osseous sarcoidosis occurred frequently. Pulmonary disease in patients with osseous sarcoidosis appears limited in that most patients have neither parenchymal involvement nor abnormal PFTs. Our findings are important in that they suggest a clinically helpful algorithm for use in cases of suspected osseous sarcoidosis. It is important to note that it is often clinically useful to objectively verify the diagnosis of osseous disease in sarcoidosis. Confirmation of the diagnosis will provide an

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<th>Table 1. Clinical variables</th>
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<tr>
<td>Osseous sarcoidosis $(n=7)$</td>
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<tr>
<td>Age (mean ± sd)</td>
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<tr>
<td>Gender (% female)</td>
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<tr>
<td>% African-American</td>
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<tr>
<td>Interval (years) between initial diagnosis of sarcoidosis and diagnosis of osseous sarcoidosis (mean ± sd)</td>
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<td>% of patients with cutaneous sarcoidosis</td>
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N.S.: not statistically significant; sd: standard deviation.
Radiograph; D

Spirometric data is reported as mean ± standard deviation; no statistically significant differences were noted. CXR: chest radiograph; DLCO diffusion of carbon monoxide; FEV1: forced expiratory volume in 1 sec; FVC: forced vital capacity.

exploration for the patient’s complaints, have prognostic implications, and present an objective marker of disease activity to follow.

The results of this study are consistent with the conclusions of others who have examined the significance of osseous sarcoidosis. Numerous case reports have documented that pulmonary manifestations are common in osseous sarcoidosis and have confirmed that cutaneous sarcoidosis, particularly lupus pernio, may be strongly associated with osseous disease (1,9). In the largest series of osseous sarcoidosis cases reported (n = 29), Neville et al. reported that 86% of patients had abnormal chest radiographs (5). They also found chronic skin lesions in 66% of these patients (5).

On the other hand, our study is unique and expands on their work in several significant ways. Firstly, we report spirometric data that reveals that PFTs fail to differentiate sarcoid patients with osseous disease from those without osseous involvement. Results of PFTs in these patients have not previously been examined systematically. Secondly, we demonstrate that objective outcome measures commonly used in patients with rheumatological disorders lack sufficient sensitivity to separate patients with osseous disease from those without bone activity. Both the extent and degree of pulmonary and rheumatic complaints failed to segregate patients with osseous sarcoidosis from those lacking bone disease. Interestingly, the pulmonary symptoms of patients with osseous disease were mild. The finding that the general pain scores were similar between cases and controls demonstrates the likely validity of our matching rather than a limited symptomatic impact of osseous sarcoidosis. The extent of pain reported by control subjects may reflect the impact of their symptoms on their daily activities. Thirdly, our use of serological markers of inflammation underscores that the serum ACE level and the ESR may be clinically useful in identifying patients with pulmonary sarcoidosis and musculoskeletal complaints who may concomitantly suffer from osseous sarcoidosis (10). Generally, the value of serum markers of inflammation in both the diagnosis and management of sarcoidosis is limited. For example, the serum ACE level has insufficient sensitivity for use as a diagnostic tool and, in some patients, does not correlate with disease activity. Our results, however, suggest a limited role for the serum ACE level and the ESR in prompting and evaluation for osseous sarcoidosis. Further study, though, is required to formally evaluate this hypothesis.

Most importantly, we focused on a subset of patients in whom osseous sarcoidosis was a clinical concern because of an antecedent history of sarcoidosis and because of the presence of musculoskeletal symptoms. In addition, each patient underwent a standard evaluation. Most prior studies focusing on osseous sarcoidosis have been limited because they have been small and because, simultaneously, they have failed to employ systematic protocols to evaluate subjects for osseous disease (11,12). For example, in an international study attempting to define the incidence of osseous disease in patients with sarcoidosis, only 81.9% of subject had bone radiographs (1). In the study by Neville et al., it is unclear if nuclear imaging studies were employed (5).

The optimal clinical approach to suspected osseous sarcoidosis has yet to be defined. Our findings, however, provide some guidance for clinicians. Pulmonologists suspecting osseous sarcoidosis should initially proceed to bone scintigraphy. Radiolabeled bone scans were useful in defining the extent of osseous disease and for determining sites requiring further evaluation with plain radiographs. In more than half of our cases, bone scans detected sites of activity which would otherwise have been overlooked. Two prior investigations utilizing bone scintigraphy in patients with suspected osseous sarcoidosis reported similar results (12,13). For example, Yaghami et al. found that bone scans identified approximately 30% more lesions than did plain radiographs (11). Normal bone scintigraphy, however, is insufficient to exclude osseous sarcoidosis. One patient in our study had a normal bone scan but plain radiographs revealed cysts in the digits of both hands. Therefore, in addition to bone scintigraphy, we recommend obtaining plain radiographs of both the hands and feet.

Our study has several limitations. Its retrospective nature exposes our study to some forms of bias (e.g. recall bias).
However, since we prospectively reviewed collected data and focused on endpoints with clear definitions, the impact of potential bias should be small. Additionally, only two of the seven cases underwent bone biopsy. As other conditions (e.g. mycobacterial infection) may mimic sarcoidosis on bone radiographs, it is possible that we may have misclassified patients as cases when, in fact, they had an alternative process to explain their abnormal bone radiographs. This, though, is unlikely. It would imply that our patients would have to suffer from two infrequent diseases simultaneously. Similarly, in other studies of sarcoidosis, the diagnosis of osseous disease has been based solely on radiographic imaging. In the study by Neville et al., only four (13.8%) patients underwent bone biopsy (5). The sample size of this study constrains our ability to draw definitive conclusions. That we failed to detect differences in certain variables between cases and controls may solely reflect the limited power of the study. The present study, however, improves on the literature in that the sample size was greater than most prior studies of this topic.

In summary, this study demonstrates that osseous involvement often complicates pulmonary sarcoidosis in patients with significant musculoskeletal symptoms. For such patients, pulmonologists should consider pursuing an evaluation for osseous sarcoidosis, particularly if the patient also has cutaneous manifestations of sarcoidosis. Clinical and demographic variables fail to readily identify patients with osseous sarcoidosis. Therefore, clinicians should employ objective radiological studies, including both bone scintigraphy and plain films of the hands and feet, for the evaluation of osseous sarcoidosis.

References