

Sarcoidosis presenting with large vessel vasculitis and osteosclerosis-related bone and joint pain

K.A. Kirou¹
H.E. Bateman²
M. Bansal³
R. Schneider⁴
G.A. Fantini⁵
S.A. Paget¹

¹Division of Rheumatology, Hospital for Special Surgery and Weill Medical College of Cornell University, New York; ²Division of Rheumatology, UMDNJ-RWJ Medical School, New Jersey; ³Department of Pathology, ⁴Department of Radiology, Hospital for Special Surgery and Weill Medical College of Cornell University; ⁵Division of Vascular Surgery, New York Hospital and Weill Medical College of Cornell University, New York, USA.

Kyriakos A. Kirou, MD, Assistant Professor; Helen E. Bateman, MD, Assistant Professor; Stephen A. Paget, MD, Professor and Head of Rheumatology; Manjula Bansal, MD, Associate Professor; Robert Schneider, MD, Associate Professor; Gary A. Fantini, MD, Associate Professor.

Please address correspondence and reprint requests to: Kyriakos A. Kirou, MD, Hospital for Special Surgery, 535 East 70 Street, New York, NY 10021, USA. E-mail: kirouk@hss.edu

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2000.

Key words: Sarcoidosis, osteosclerosis, arthralgia, vasculitis, magnetic resonance imaging, thrombocytopenia.

ABSTRACT

A 34-year-old African-American female diagnosed earlier with idiopathic thrombocytopenic purpura (ITP), lymphadenopathy, splenomegaly, uveitis, and pulmonary nodules, developed a subclavian artery aneurysm, and generalized annular osteosclerotic lesions with disabling arthralgias. Biopsies from bone and lymph node revealed non-caseating granulomas and no evidence of malignancy or infection, confirming the clinical impression of sarcoidosis.

Introduction

Sarcoidosis is a granulomatous inflammatory disorder of unknown etiology with multi-organ involvement and often protean clinical manifestations (1). Among the rheumatologic features of the disease, acute sarcoid arthritis is the most common. It usually presents as a triad along with erythema nodosum and bilateral hilar adenopathy (Löfgren's syndrome) and typically follows a benign course (2-5). Chronic sarcoid arthritis occurs either as a result of an adjacent bone lesion or as granulomatous synovitis and osteolytic bone lesions of the digits (2-5). In contrast to the above, we describe here a case of chronic sarcoidosis with unusual rheumatologic manifestations, namely, large vessel vasculitis and disabling arthralgias in association with osteosclerotic bone lesions.

Case report

This 35-year-old African-American female presented in 1989 with chest pains, epistaxis, and splenomegaly. Idiopathic thrombocytopenic purpura (ITP) was diagnosed and treated successfully with glucocorticoids (GC) and i.v. anti-Rh₀ (D) immune globulin.

In 1994 she developed exertional dyspnea, chest pains, fatigue, weight loss, and right eye uveitis. A chest computed tomography (CT), in September 1995, demonstrated right paratracheal adenopathy, diffuse, small pulmonary nodules, and increased size of the right hilum. In February 1996, evaluation of a pulsating mass in her right supraclavicular area by chest CT and aortography revealed a subclavian arterial aneurysm and no evidence of occlusive dis-

ease. The patient denied a history of fevers, limb claudication, exposure to syphilis, tuberculosis or HIV. Active right eye granulomatous uveitis, mild splenomegaly, and generalized lymphadenopathy were noted but there were no abnormalities in arm and leg pulses and pressures. Laboratory studies revealed diffuse hypergammaglobulinemia and a high Westergren erythrocyte sedimentation rate (ESR) of 61 mm/hour. The patient was anergic. Antinuclear antibodies, rheumatoid factor, VDRL, and serologic tests for viral hepatitis and HIV were negative. Angiotensin converting enzyme (ACE) level was normal. Subclavian aneurysm surgery was performed. Pathology revealed marked intimal thickening with myxoid stroma, extensive patchy destruction of the elastic lamina in the tunica media, thickening of the adventitia, vasa vasorum with thickened walls and perivascular lymphocytic infiltrate (in rare vessels), and no atheromatous plaques: findings consistent with healed arteritis (6,7). Concurrent cervical lymph node biopsy showed noncaseating granulomas (NCGs). On both specimens, special stains and cultures for spirochetes, acid-fast bacilli, and fungi were negative. She was discharged on GC with a diagnosis of sarcoidosis.

The patient returned to our arthritis clinic in February 1997 with a 6-month history of severe left groin pain, and milder symptoms in the right elbow and right knee, despite 5 mg of prednisone daily. Examination revealed deep focal tenderness at symptomatic periarticular sites without either joint line tenderness or joint swelling. The patient was unable to actively move her left hip due to pain but passive motion was relatively spared. Her platelet count had decreased to 77 X 10⁹/L, and ESR was now 91 mm/h. Serum alkaline phosphatase, calcium, phosphorus were normal, as was the 24 hr urinary calcium. No monoclonal gammaglobulins were detected on serum and urine protein electrophoreses. Plain radiographs revealed multiple sclerotic lesions of variable sizes (many with lucent centers), in the pelvis (Fig. 1A), vertebrae, ribs, skull, and long bones, sparing only the hands and feet. On bone scintigraphy with ⁹⁹Tc^m-methylene di-

phosphonate, only a few of the sclerotic lesions could be detected. Magnetic resonance imaging (MRI) of the pelvis and knee demonstrated prominent bone lesions illustrated in Figures 1B and 1C. Soft tissue signal hyperintensities on fat-suppressed MRI images of the pelvis were also noted. These were seen in the left hip adductor muscles near their insertion onto the pubic bone, in the iliac origin of the right gluteus maximus muscle and in the left iliopsoas bursa, all adjacent to similarly hyperintense bone lesions. Iliac bone biopsy showed a NCG and fibrosis among the sclerotic bone trabeculae (Fig. 2). NCGs were also seen on bone marrow aspirations done on other occasions. However, biopsy from the MRI hyperintense area of the right gluteus maximus muscle was negative for NCGs.

Her symptoms improved somewhat with 60 mg of prednisone, and she was discharged on that dose, with a subsequent slow taper. Later, other joints became symptomatic including her hips, wrists, knees, ankles, left shoulder, and lower back. During flares of the disease one or more of these joints became very painful (requiring narcotic analgesics) in an asymmetric, oligoarticular pattern that almost always included the left hip. Non-steroidal antiinflammatory drugs were avoided because of the thrombocytopenia and oral GC doses as high as 70 mg of prednisone could not control her symptoms during these flares, necessitating pulse therapy (i.v. methylprednisolone 1 g daily for 1-3 days).

Several second-line or immunosuppressive agents were tried. Hydroxychloroquine, cyclosporine A (2.5 mg/Kg daily), and methotrexate (MTX, up to 40 mg subcutaneously weekly) were ineffective. Most recently, oral combination therapy with daily azathioprine 100 mg, leflunomide 20 mg, and GC provided adequate control of her symptoms and the benefit has been sustained over several months, even after leflunomide discontinuation and tapering of GC to 5 mg of prednisone.

Discussion

Since there are no pathognomonic clinical or laboratory findings of sarcoidosis, the presence of NCG on tissue bi-

opsy and the exclusion of other granulomatous diseases are necessary for diagnosis (1). The clinical features and pathologic findings in our patient were

consistent with chronic sarcoidosis and alternative diagnoses were excluded by appropriate pathologic, microbiologic, and serologic studies.

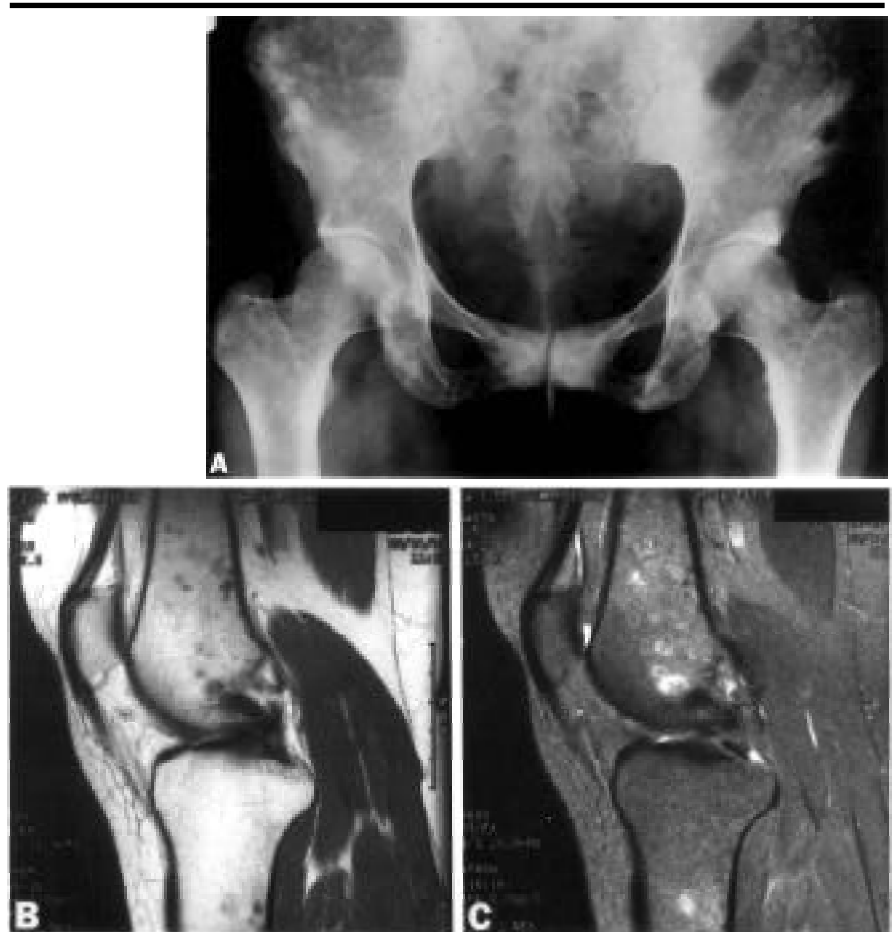


Fig. 1. (A) Plain radiograph of pelvis reveals multiple sclerotic lesions of variable sizes (few mm - 2 cm). Many have lucent centers. MRI of right knee with imaging at proton density (B) and fat suppressed proton density sequences (C). Many lesions have a low signal in B and acquire a high signal peripherally in C. Others show decreased signals on both images.

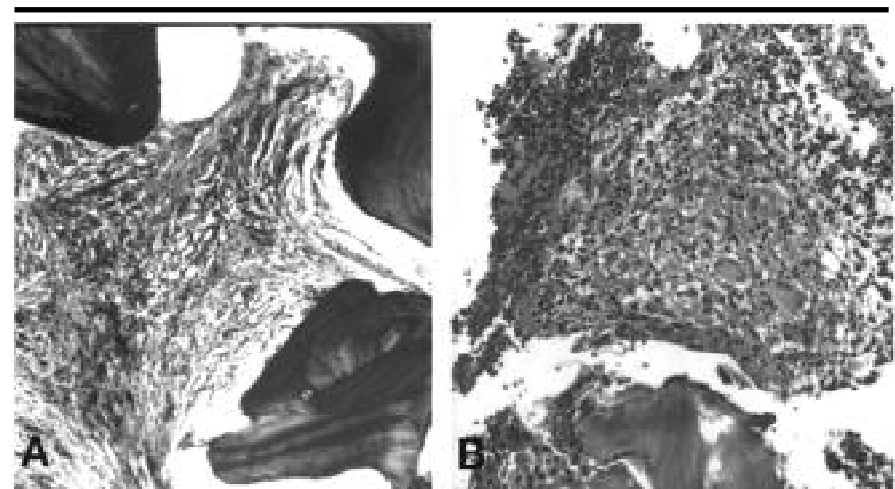


Fig. 2. Photomicrographs of pelvic bone show extensive bone marrow fibrosis with chronic inflammatory infiltrate (A) and a rare noncaseating granuloma consisting of giant cells, histiocytes, and lymphocytes (B). Special stains for bacteria, fungi, and acid fast bacilli were negative. H & E x125.

Thrombocytopenia in sarcoidosis is infrequent and can be due to hypersplenism, bone marrow infiltration by NCGs, or autoantibodies (8). Our patient's high number of bone marrow megakaryocytes, and her response to anti-Rh₀ (D) argued in favor of an immune etiology. Although, typically, vasculitis in sarcoidosis occurs in the lung (necrotizing sarcoid granulomatosis; 9), the disease, rarely, is also associated with a granulomatous vasculitis of extrapulmonary blood vessels of all sizes (10-13). When large vessels are involved in sarcoidosis the clinical picture resembles that of Takayasu's arteritis (TA) (12, 13). In our case, the subclavian artery pathology findings suggested "healed vasculitis" (6, 7), a condition that probably represents the sequelae of preceding active inflammation and has been associated with aneurysmal formation secondary to tunica media destruction (6). Although syphilis and other infectious vasculitides were easily excluded with appropriate laboratory tests, idiopathic large vessel vasculitides (mainly TA and temporal arteritis) could have produced the same arterial histology changes. However, both the clinical picture and the coexistence of documented granulomatous inflammation in the lymph nodes, uveal tract, and bone, suggested sarcoidosis as the unifying diagnosis.

Only a few cases of osteosclerosis occurring in the setting of sarcoidosis have been reported in the literature (reviewed in ref. 14). The lesions primarily affected the axial skeleton and were often associated with low back, pelvic, or neck pain, depending on their localization (14-17). Peripheral joint symptoms were not observed, perhaps because of less extensive bone involvement compared to our case. Moreover the present case differed from previous reports of sarcoid osteosclerosis in that, despite similarities in bone scan and MRI characteristics (14-17), on plain radiography the lesions

were annular with osteosclerotic rims and not uniformly dense (Fig. 1A). Presumably lesions that were hypointense on all MRI sequences were old sclerotic lesions, and those that enhanced peripherally on fat-suppressed proton density images most likely indicated an inflammatory response to NCGs (Figs. 1B, 1C) (15). Other causes of multifocal osteosclerotic lesions such as osteoblastic metastases, mastocytosis, hemangiomas or lymphoma were excluded on the basis of pathologic and microbiologic studies.

Although our patient's joint symptoms occurred in the setting of chronic sarcoidosis, her presentation differed from the typical case of chronic sarcoid arthritis in that there were no objective findings of arthritis, by either clinical examination or MRI. Instead, based on radiological studies, there was evidence of periarticular inflammation and it was postulated that the pain and tenderness were most likely originating from the periarticular bone lesions and adjacent inflamed entheses and bursae. Her arthralgias were unusually disabling and refractory to oral GC. They responded well to pulse MP therapy, yet GC-induced remissions were short-lived, in accordance with a recent study (18). Low dose MTX has been promising in chronic GC-refractory musculoskeletal sarcoidosis (2), but was not effective in our patient. In contrast, combination therapy that included initially oral GC, azathioprine, and leflunomide and subsequently only the first two agents, appeared to be helpful and might represent an additional option for the management of sarcoidosis cases with refractory musculoskeletal symptoms.

References

1. NEWMAN LS, ROSE CS, MAIER LA: Sarcoidosis. *N Engl J Med* 1997; 336: 1224-34
2. PETERSSON T: Rheumatic features of sarcoidosis. *Curr Opin Rheumatol* 1998;10:73-8.

3. SARTORIS DJ, RESNICK D, RESNIK C, YAGHMAI I: Musculoskeletal manifestations of sarcoidosis. *Semin Roentgenol* 1985; 20: 376-86.
4. GUMPEL JM, JOHNS CJ, SHULMAN LE: The joint disease of sarcoidosis. *Ann Rheum Dis* 1967; 26: 194-204.
5. JAMES DG, NEVILLE E, CARSTAIRS LS: Bone and joint sarcoidosis. *Semin Arthritis Rheum* 1976; 6: 53-81.
6. ROSE AG, SINCLAIR-SMITH CC: Takayasu's arteritis. A study of 16 autopsy cases. *Arch Pathol Lab Med* 1980; 104: 231-7.
7. MCDONNELL PJ, MOORE GW, MILLER NR, HUTCHINS GM, GREEN WR: Temporal arteritis. A clinicopathologic study. *Ophthalmology* 1986; 93: 518-30.
8. LAWRENCE HJ, GREENBERG BR: Autoimmune thrombocytopenia in sarcoidosis. *Am J Med* 1985; 79: 761-4.
9. CHURG A: Vasculitis in sarcoidosis. In CHURG A and CHURG J (Eds.): *Systemic Vasculitides*. New York, Igaku-Shoin 1991: 299-304.
10. KWONG T, VALDERRAMA E, PALEY C, ILOWITE N: Systemic necrotizing vasculitis associated with childhood sarcoidosis. *Semin Arthritis Rheum* 1994; 23: 399-395.
11. PETRI M, BARR E, CHO K, FARMER E: Overlap of granulomatous vasculitis and sarcoidosis: presentation with uveitis, eosinophilia, leg ulcers, sinusitis, and past foot drop. *J Rheumatol* 1988; 15: 1171-3.
12. SCHAPIRO JM, SHPITZER S, PINKHAS J, SIDI Y, ARBER N: Sarcoidosis as the initial manifestation of Takayasu's arteritis. *J Med* 1994; 25: 121-8.
13. ROSE CD, EICHENFIELD AH, GOLDSMITH DP, ATHREYA BH: Early onset sarcoidosis with aortitis - "juvenile systemic granulomatosis?" *J Rheumatol* 1977; 102-6.
14. FRANCO M, PASSERON C, TIEULIE N, VERDIER J-F, BENISVY D: Long term radiographic follow-up in a patient with osteosclerotic sarcoidosis of the spine and pelvis. *Rev Rhum (Engl Ed)* 1998; 65: 586-90.
15. GOLZARIAN J, MATOS C, GOLSTEIN M, STALLENBERG B, DEPIERREUX M, STRUYVEN J: Case report: osteosclerotic sarcoidosis of spine and pelvis: Plain film and magnetic resonance imaging findings. *Br J Radiol* 1994; 67: 401-4.
16. VINNICOMBE S, HERON C, WANSBROUGH-JONES M: Case of the month. Dense bones. *Br J Radiol* 1992, 65: 1049-50.
17. JELINEK JS, MARK AS, BARTH WF: Sclerotic lesions of the cervical spine in sarcoidosis. *Skeletal Radiol* 1998, 27: 702-4.
18. GOTTLIEB JE, ISRAEL HL, STEINER RM, TRIOLO J, PATRICK H: Outcome in sarcoidosis. The relationship of relapse to corticosteroid therapy. *Chest* 1997; 111: 623-31.