

## Case Report

# Leucocytosis in a Case of Sarcoidosis with Pleural Involvement – An Unknown Association

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## Abstract

A case of biopsy-proven sarcoidosis with pleural and lung parenchymal involvement is reported. The resolution of neutrophilia and other disease manifestations with azathioprine points towards sarcoidosis being the probable cause.

GG, 45 years old male, presented with fever and right-sided chest pain with biochemical features of granulomatous hepatitis and apparently unexplained leucocytosis. Azathioprine 100 mg daily was started; he improved dramatically within 3 weeks with disappearance of pain and normalization of alkaline phosphatase and leucocytosis

All clinical, biochemical and hematological parameters improved subsequently. There were no significant side effects and the patient is doing well after more than three years on azathioprine

The resolution of neutrophilia on treatment of sarcoidosis suggests a causal relationship. However, further follow-up is essential to screen for future hematological abnormalities.

## Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Pleural and pleuro-parenchymal involvement, though relatively rare, are described.<sup>1</sup> Gupta et al looked for hematological abnormalities in a consecutive series of sarcoid patients.<sup>2</sup> Leucopenia was relatively rare in Indian patients but lymphopenia, anaemia and raised ESR were common. Leucocytosis, however, is not described in sarcoidosis. Hepatic involvement, commonly granulomatous hepatitis characterized by disproportionately elevated alkaline phosphatase levels, is also known. We report a case of sarcoidosis with lung, pleural, and hepatic involvement with leucocytosis that responded only to immunosuppressive therapy with azathioprine.

## Case Report

GG, 45 years old male, presented in June '04 with moderate intermittent fever of 2 weeks duration with pain in the right lower chest and hypochondrium clinically suggesting a possible right lower lobe consolidation with pleural reaction. Chest radiography (Figure 1) revealed a right basal pneumonitis with pleural effusion. Leucocytosis (>20000), with around over 80% neutrophils and progressively raised alkaline phosphatase (6 to 12 times normal) was found on repeated examinations over next two weeks. Pleural aspiration revealed straw colored fluid which was found exudate with mononuclear cell predominance (over 90%). The fluid on aerobic culture revealed no growth and no AFB was detected in smear or culture examinations. Blood culture for aerobic organisms was negative and so also the bone marrow biopsy culture; the marrow was found hypercellular. Ultrasonography of the upper abdomen was unremarkable except for mild pleural effusion. The patient was treated symptomatically with antibiotics (including

meropenem and teicoplanin) and other drugs over three weeks without any clinical, hematological or biochemical response. A high-resolution computed tomography (HRCT) scan of the chest revealed scanty pleural effusion with areas of patchy pleural-based thickening along with areas of organization with interstitial thickening of the underlying parenchyma (Figure 2). Open pleural and lung biopsy yielded epithelioid granulomata without caseation and the subsequent culture failed to yield any organism including acid-fast bacilli (AFB). The patient responded partially to empirical treatment with rifampicin, isoniazid, ethambutol, pyrazinamide with prednisolone. However, he worsened within a few days with relapse of fever and the old pain and radiological deterioration following the tapering of prednisolone from 40 to 20mg/day after using for 10 days. The total white blood cell (WBC) count and serum alkaline phosphatase remained consistently high. Subsequently, he was started on methotrexate 15 mg weekly and prednisolone 40 mg daily that was tapered by 10 mg per week. The pain subsided, the leucocytosis and raised alkaline phosphatase resolved; there was significant radiographic clearing (Figure 3). However, he lost follow-up and after a few months to present again in June '05 with acute dyspnea and fever associated with type I respiratory failure. He was admitted, evaluated, diagnosed and treated successfully for lower respiratory tract infection with intravenous antibiotics. However, the fever persisted as low grade and the serum alkaline phosphatase level turned high again. Post-recovery, Azathioprine 100 mg daily was started; he improved dramatically within 3 weeks with disappearance of pain and normalization of alkaline phosphatase and leucocytosis. He lost follow up after a few months although reportedly he continued azathioprine till February 2009. Again, the patient had a relapse of symptoms in April-May with fever, right lower chest pain, leucocytosis and early rising trend of serum alkaline phosphatase. He failed to respond to antibiotics and the serum procalcitonin level remained normal. A relapse of the disease was thought and upon insistence for resuming the old treatment, azathioprine was restarted again (100 mg daily) to which he responded in two weeks time. The patient comes for follow up

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Fig. 1 : Chest radiograph in June, 2004 showing right basal pneumonitis with pleural effusion

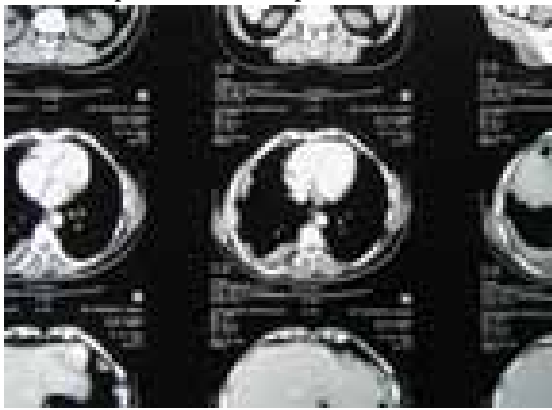


Fig. 2 : Chest CT done in July, 2004

irregularly and when last seen on January 2010, he has been doing well on the same dose of azathioprine as 100 mg per day. The latest chest X-ray in 2010 shows no pleural effusion with minimum parenchymal densities (Figure 4).

## Discussion

Our patient in concern had multisystem involvement of sarcoidosis affecting the pleura and lung parenchyma (without hilar adenopathy), the liver and the bone marrow causing unexplained leucocytosis. Pleural effusion in sarcoidosis, though relatively rare (0-5%), is well known<sup>1,3</sup> and lung involvement (around 90 %) is very common. The hepatic involvement is usually marked biochemically by raised alkaline phosphatase and histologically by granulomatous hepatitis from sarcoid involvement. Several uncommon manifestations have been recorded in a prospective survey for such manifestations in 240 biopsy proved patients of sarcoidosis to find pleural involvement in 7 (3.33%) with no documentation of leucocytosis.<sup>4</sup> Pleural involvement may be painful or asymptomatic, and is usually associated with extensive parenchymal disease and frequently with extrapulmonary disease.<sup>3</sup> Although suspected clinically, the diagnosis is confirmed by finding non-caseating granulomata on histology with exclusion of tuberculosis and fungal disease by culture. Pleural effusion in a patient of histologically proven sarcoidosis is usually attributed exclusively to Sarcoidosis.<sup>5</sup>

Hepatic involvement in this patient is obvious from the abnormal liver function tests. The disproportionate rise of



Fig. 3 : Chest radiograph in Aug, 2005



Fig. 4 : Chest radiograph done in Jan, 2010 showing significant radiographic clearing

alkaline phosphatase resolved concomitantly with the disease only on methotrexate and later on azathioprine administration.

The neutrophilia was confusing, especially when it did not respond to antibiotics including carbapenem and teicoplanin alongside no organism being cultured from blood and pleural fluid. The resolution of neutrophilia and other disease manifestations with azathioprine points towards sarcoidosis being the probable cause.

Bone marrow involvement in sarcoidosis usually causes neutropenia, anemia and lymphopenia.<sup>5</sup> Neutrophilic leucocytosis is unknown in uncomplicated sarcoidosis. However there are two case reports of sarcoidosis with neutrophilia that preceded chronic myelomonocytic leukemia.<sup>5</sup> We have followed up the patient till January, 2010 and on continuation of the medicine (azathioprine 100 mg daily) till date (with a break in between to cause relapse), he remained well without any significant symptoms and drug related toxicity. It is difficult to perceive at present especially after a follow up of over five years that that any leukemic illness exists in a smoldering fashion in this particular patient but it is difficult to explain a febrile relapse

pleural and hepatic involvement.

Sarcoidosis has traditionally been treated with steroids but several other agents such as methotrexate, cyclophosphamide, chlorambucil, thalidomide, pentoxifylline, chloroquine, hydroxychloroquine and infliximab have been tried, especially where systemic steroids are contraindicated.<sup>6</sup> Methotrexate is commonly used as a steroid-sparer in symptomatic and refractory sarcoidosis. Inadequate response to methotrexate resulted in azathioprine use; another effective drug in difficult Sarcoidosis.<sup>6</sup> All clinical, biochemical and hematological parameters improved subsequently. There were no significant side effects and the patient is doing well after more than three years on azathioprine. The resolution of neutrophilia on treatment of sarcoidosis suggests a causal relationship. However, further follow-up is essential to screen for future hematological abnormalities. Therapy was unnecessarily deferred due to lack of confidence in accepting sarcoidosis as the diagnosis, particularly due to multisystem involvement in a patient from a region with

high prevalence of tuberculosis.

## References

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