

# The puzzle of lymphoma among the granulomatous disorders

Sir,

A 40-year-old man presented to us with the low-grade intermittent fever, streaky hemoptysis, and cough for 2 months. His chest X-ray showed bilateral hilar adenopathy [Figure 1] and computed tomography (CT) of the thorax showed bilateral peribronchovascular nodules [Figure 2].

Differentials of tuberculosis, lymphoma, and sarcoidosis were considered. The total leukocyte count was  $4.9 \times 10^9/L$ , hemoglobin was 11.3 g/dL, and the platelet count was 112,000/uL. His lactate dehydrogenase was 539.2 U/L. Purified protein derivative was negative, and the serum angiotensin-converting enzyme (ACE) level was 51 U/L. Bronchoscopy showed mucosal irregularity of the bronchial tree bilaterally. Transbronchial lung biopsy (TBLB) was performed from the right upper lobe. Endobronchial ultrasound (EBUS) showed enlarged station 7, 11 L, 11R, 4 L, and 4R lymph nodes. They were 12 mm  $\times$  15 mm in size, discrete, and homogenous in appearance. EBUS-transbronchial needle aspiration slides and cell blocks from the lymph node showed reactive lymphoid cells and a few histiocytic aggregates. TBLB and endobronchial biopsies showed epithelioid cell granulomas. Evaluation for tuberculosis was negative.

A diagnosis of Stage 2 sarcoidosis was made, and he was started on oral steroid, as he was symptomatic with intermittent fever and persistent cough. His symptoms improved and there was also radiological improvement. ACE level was reduced to 19 U/L. After 5 months, while on tapering doses of steroids, he developed a low-grade intermittent fever with chills, streaky hemoptysis, and abdominal discomfort. Repeat testing showed a drop in the white blood cell (WBC) count to  $3400/mm^3$  and hemoglobin to 9.1 g%. Bone marrow aspiration and biopsy were done, which was reported as hypercellular marrow with trilineage hematopoiesis, and there were no abnormal cells observed. CT of the thorax and the abdomen were done which showed gross hepatosplenomegaly and multiple ill-defined hypodense lesions in both the liver and spleen. Mediastinal lymph nodes were further enlarged and nonnecrotic. Excision biopsy of the right supraclavicular lymph node was done and the histopathological study showed Classical Hodgkin's lymphoma with mixed cellularity type. Initial TBLB and

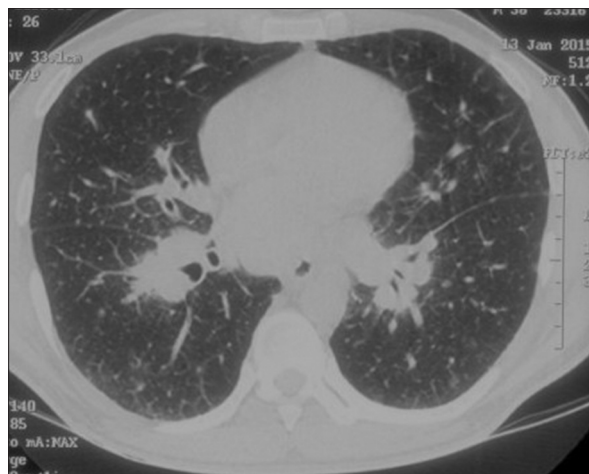
EBUS-fine-needle aspiration cytology (FNAC) slides and cell block were reviewed again, and there was nothing suggestive of lymphoma. Hence, this was a case where the diagnosis of lymphoma was made in the patient who was on the treatment for sarcoidosis.

Another patient, a 34-year-old male, presented to us with a low-grade intermittent fever for 12 months and shortness of breath for 4 months. He also gave a history of skin lesions of 1.5 years duration which started as red papules and plaques and resolved over 1–2 months with hyperpigmentation. The complete blood count was normal except for the raised WBC count with lymphocytic predominance. Chest X-ray showed left mid- and lower-zone consolidation. Evaluation for the tuberculosis was negative. CT of the thorax showed bilateral lung consolidation and subcarinal lymph node enlargement. He underwent bronchoscopy with right-sided TBLB and EBUS-FNAC of the station 7 and 11R lymph nodes. EBUS-FNAC of the subcarinal lymph node showed occasional aggregate of epithelioid histiocytes, suggestive of granulomatous inflammation. TBLB showed chronic interstitial pneumonia with lymphohistiocytic infiltrates and occasional epithelioid histiocytes with interstitial fibrosis and Type II pneumocyte hyperplasia.

Serum ACE level was 67 U/L, and the Mantoux test was negative. Hence, a diagnosis of sarcoidosis seemed most



**Figure 1:** Chest X-ray showing bilateral hilar adenopathy



**Figure 2:** Computed tomography of the thorax showing bilateral peribronchovascular nodules

likely. Skin biopsy was done from the forearm lesion which showed CD30+ lymphoproliferative disease suggestive of anaplastic large-cell lymphoma. This was a case where lymphoma presented with features like that of sarcoidosis.

Lymphoma has always been a puzzle for the treating physicians throughout the years. It is a disease with variable presentations which can mimic and coexist with many other common diseases, including tuberculosis. Unless the clinical suspicion of lymphoma is high and one looks for it meticulously, the diagnosis of lymphoma may be missed, which can be fatal for the patient. “Very good” prognostic group according to the revised international prognostic index of lymphoma has a 4-year survival of 90%, which drops down to 50% in the “poor risk” group.<sup>[1]</sup> This throws the light on the need of diagnosing lymphoma at the earliest. In this letter, we were presenting two cases – one in which lymphoma was preceded by sarcoidosis and another one in which lymphoma presented with features like that of sarcoidosis.

There are case reports dating back to 1960s, where lymphoma coexisted with sarcoidosis or a diagnosis of sarcoidosis was made in whom later lymphoma was diagnosed. Brincker described 46 cases of sarcoid coexisting with malignant tumors based on the data from Danish cancer and the sarcoid registries.<sup>[2]</sup> It was Brincker who coined the term-“sarcoidosis lymphoma syndrome.” In a retrospective chart review of 21 patients done by Chalayer *et al.*, 14 patients had sarcoidosis before the diagnosis of lymphoma, five had coexisting sarcoidosis and lymphoma, and two had lymphoma before the diagnosis of sarcoidosis.<sup>[3]</sup>

Sarcoid-like granulomas are found in chronic inflammatory disease, chronic infections, and neoplastic diseases like lymphoma. Hence, a careful examination of the histology slide is required to rule out lymphoma.

There are two hypotheses on the sarcoidosis lymphoma syndrome. In sarcoidosis, there is an increase in CD4+ T-cells and reduction in CD8+ T-cells. CD4+ cells express activation markers interleukin-2 (IL-2) receptor and HLA-DR. They respond vigorously *in vitro* to mitogenic and antigenic stimulation and release IL-2 and interferon (ifn- $\alpha$ ). B-lymphocytes are generally unaffected. Raised circulating antibody levels and immune complexes could be due to the probable secondary B-cell stimulation. Increased antigenic presentation by the dendritic cells with release of IL-1, TNF- $\alpha$ , and oxidants and defective regulation by suppressor T cells might lead to the escape of a clone leading to lymphoid malignancy.<sup>[4]</sup> Another hypothesis is that clinical sarcoidosis, a generalized cell-mediated immune response to tumor antigens, might be a systemic counterpart of the localized sarcoid-like granulomas present within tumors or tumor-draining lymph nodes. According to this hypothesis, sarcoidosis is considered as a paraneoplastic syndrome.

If there is a high clinical suspicion of lymphoma, all the clinical, biochemical, and radiological findings are not correlating to another diagnosis of sarcoidosis or tuberculosis, or if there is inadequate response to the treatment, evidence for lymphoma should be actively looked for.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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