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Bone marrow involvement in sarcoidosis: an elusive extrapulmonary manifestation

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ABSTRACT
Sarcoidosis is a granulomatous disease with various extrapulmonary manifestations. We describe a 51-year-old African American woman with a history of cutaneous sarcoidosis admitted with bicytopenia. Suspicion for systemic sarcoidosis was established after contrast-enhanced computerized tomography of the chest, abdomen and pelvis showed a pulmonary nodule, diffuse lymphadenopathy and hepatosplenomegaly. Cytopenias in sarcoidosis, when present, may reflect bone marrow infiltration. Hence, biopsy was obtained and bone marrow sarcoidosis was diagnosed. This manifestation, in spite of ethnic and gender predilection, is rarely seen. As with other forms of sarcoidosis, treatment comprises of corticosteroids.

Abbreviations: ANCA: Antineutrophil cytoplasmic antibody; BM: Bone marrow; BMS: Bone marrow sarcoidosis; CT: Computerized tomography; HIV: Human immunodeficiency virus; HLA: Human leukocyte antigen; MRI: Magnetic resonance imaging

1. Introduction
Sarcoidosis is a systemic disease characterized by non-caseating epithelioid granulomas [1]. Since its first description in 1899 by Caesar Boeck, a Norwegian dermatologist, its variable clinical presentation has involved multiple medical subspecialties [2]. It is thought to be the result of immune responses to various ubiquitous environmental triggers [3,4]. In the USA, the annual incidence is estimated to be 10 per 100,000 population [5]. Peak age is between 20 and 39 years, with all races and ethnic groups being at risk [6].

In more than 90% of patients sarcoidosis involves the lungs [7]. Extrapulmonary manifestations can be subtle but contribute to significant morbidity [8,9]. Among these, bone marrow sarcoidosis (BMS) has been much less reported. We describe a case of sarcoidosis with biopsy-proven lung and bone marrow (BM) involvement.

2. Case report
A 51-year-old African American woman with past medical history of biopsy-proven cutaneous sarcoidosis and nicotine dependence, presented with a 2 week history of insidious onset bilateral below knee burning pain, consistent with paresthesias and without other neurological symptoms. Low grade fever, hyporexia with an unintentional 30 pound weight loss over 2 years and chronic dry cough were also reported. Vital signs were normal. Physical examination revealed clubbing, non-tender hepatosplenomegaly and multiple violaceous to brownish indurated papules and plaques over the face, neck, back and extremities. Laboratory parameters were significant for leukopenia (2.7 [4.4–10.7 x 10E9 cells/L]) with neutrophilia (68.3 [44–73%]), lymphopenia (14.7 [20–43%]) and monocytosis (14.7 [5–13%]), borderline normocytic normochromic anemia (11.9 [12–15.6 g/dL]), elevated alkaline phosphatase (674 [38–126 U/L]), hyperlactatemia (3.8 [0.7–2.1 mmol/L]), hypokalemia (3.2 [3.5–5.1 mmol/L]) and hypoalbuminemia (2.3 [3.4–5 g/dL]). Inflammatory markers were also elevated, including erythrocyte sedimentation rate (113 [0–30 mm/h]) and C-reactive protein (1.86 [<0.3 mg/dL]). Peripheral blood smear showed decreased leukocytes and erythrocytes, normal appearing segmented neutrophils, reactive lymphocytes and absolute lymphopenia without blasts. Chest X-ray showed prominent interstitial markings.

Further hematological studies revealed low iron (35 [50–170 μg/dL]), iron saturation (19 [20–50%]), transferrin (148 [250–380 mg/dL]) and total iron binding capacity (185 [240–450 mg/dL]) but normal ferritin (135 [10–291 ng/mL]). Serum folate (6.6 [3.1–17.5 ng/mL]), vitamin B12 (482 [211–911 pg/mL]) and copper (137 [72–166 μg/dL]) levels were normal. Angiotensin converting enzyme (147 [14–82 U/L] and immunoglobulin...
G (1855 [700–1600 mg/dL]) were raised. Other tests included human immunodeficiency virus (HIV) p24 antigen and HIV-1/2 antibody, QuantiFERON-TB Gold, Monospot, anti-myeloperoxidase and anti-proteinase 3 antibody, p-antineutrophil cytoplasmic antibody (ANCA) and c-ANCA and were unremarkable. Cerebrospinal fluid studies were normal. Contrast-enhanced computerized tomography (CT) of chest, abdomen and pelvis revealed diffuse lymphadenopathy along the esophagus, adjacent to the gastroesophageal junction and pancreatic tail, as well as in the periaortic and pericaval retroperitoneal regions. In addition to hepatosplenomegaly, a right upper lobe spiculated pulmonary nodule was described. Radiological findings were suggestive of a lymphoma or bronchogenic malignancy, though sarcoidosis remained a possibility.

BM aspirate and core biopsy showed multiple non-caseating granulomas and was otherwise normocellular with trilineage hematopoiesis (Figure 1). Flow cytometric immunophenotypic analysis found no evidence of T- or B-cell lymphoma or acute leukemia. Fluorescence in-situ hybridization was negative for myelodysplastic syndrome or chronic lymphocytic leukemia. CT-guided core biopsy of the right upper lobe pulmonary nodule also showed non-caseating granulomas (Figure 2). Ziehl-Neelsen, Gomori methenamine silver and Wade-Fite staining of both biopsies were negative.

Magnetic resonance imaging (MRI) of brain and lumbar spine did not show evidence of neurosarcoïdosis, cord compression or neural impingement. Nerve conduction studies were scheduled and the patient was discharged home on oral corticosteroids.

3. Discussion
The exact etiology of sarcoidosis is unknown [10]. It mimics other diseases and remains a histopathological diagnosis. Its annual incidence varies geographically, with Japanese men having the lowest and African American women having the highest one [11,12]. Environmental exposures, predisposing human leukocyte antigen (HLA) alleles and other genetic factors are all contributors [3,4]. Sarcoidosis has been associated with exposure to irritants, inorganic particles, insecticides and moldy environments [13–16]. Occupational studies have also linked it to firefighting, metalworking and service in the Navy, among others [16–19]. Numerous gene products have been implicated, such as HLA-B8 antigens, HLA-DRB1 and DQB1 alleles, HLA-DQ and HLA-DR, HLA-DQB1*0201 and HLA-DRB1*0301 [20–24].

Clinical presentation of sarcoidosis includes intrathoracic and extrathoracic manifestations. Extrathoracic manifestations vary depending on age, gender and ethnicity [25,26]. Of these, BMS has not been well characterized [27]. In a cohort study following 640 patients with sarcoidosis over 40 years, 95.8% of whom were Caucasians, none had BM involvement at the time of diagnosis and 0.3% had it at any time during follow up [28]. In contrast, 44% of the 736 patients in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study were African Americans, with BM involvement present in 3.9% of cases [25]. Other ethnic groups have shown different patterns. A study in Mexico revealed BM involvement in 23.4%, while studies conducted in China, Japan and India have not reported it [29,30].
Comprehensive history taking and physical examination remain important in the diagnosis of sarcoidosis. A complete blood count has been suggested as an adjunct to determine BM involvement [31]. The most common hematologic abnormality is anemia, including iron deficiency, hemolysis and anemia of chronic disease [2]. Anemia secondary to BM infiltration can be as high as 27% [32]. Traditionally anemia work up includes serum ferritin, but this may not be a reliable biomarker in patients with sarcoidosis given its association with inflammation and malignancy. Leukopenia alone may also be the initial presentation of sarcoidosis secondary to BM infiltration, hypersplenism or lymphocyte redistribution [33]. Although rarely reported, it can be a marker of severe disease [2,34]. In fact, higher incidences of anemia, leukopenia and extrapulmonary involvement have been seen in BMS [35,36]. A stepwise approach for diagnosis of cytopenias in sarcoidosis has been suggested (Figure 3). In the absence of hematologic derangements, establishing the diagnosis of BMS becomes challenging [37]. Our patient had anemia and leukopenia due to a combination of BM involvement and hypersplenism.

Estimated incidence of granulomas in BM biopsies is low (0.3–2.2%) [38–43]. Sarcoidosis accounts for up to 21% of these cases [40,44,45]. Clinical indications for obtaining a BM biopsy in sarcoidosis have not been clearly defined [46,47]. In our case, the history of cutaneous sarcoidosis, weight loss, generalized lymphadenopathy coupled with the bicytopenia were considered as strong indicators for BM analysis.

Several organ systems can be affected in sarcoidosis. Prevalence of splenomegaly is 26% and increases when other concomitant extrapulmonary lesions are present [48]. Neurologic complications in sarcoidosis can occur in 3–10% of cases, with cranial neuropathy and meningeal disease being the most commonly reported [49]. In BMS, neurological symptoms are infrequent and usually related to cord compression [38]. Lesions may be too small to be seen on imaging studies, which may explain reported paresthesias in our patient.

To the best of our knowledge, there are no randomized controlled trials comparing different therapeutic strategies for BMS [50]. Prednisone remains the mainstay of treatment. Adalimumab can be used when corticosteroids are contraindicated [51–53]. Methotrexate, the most widely studied corticosteroid-sparing treatment in sarcoidosis, has restricted use in patients with BMS due to its cytotoxicity [54].

4. Limitations

Four different categories showed some degree of limitation, namely disease progression, radiological studies, microbiology data and response to therapy. As a result of limited health care access and health literacy, the evolution from cutaneous to systemic sarcoidosis is unclear. In terms of imaging, positron emission tomography/computed tomography is highly sensitive in detecting granulomatous BM lesions [55]. It may help select appropriate candidates for a BM biopsy, but was not obtained for this patient. Cultures or stains for Rickettsial disease, reported to be contributory to granuloma formation in sarcoidosis, were not performed.
Unfortunately, patient was lost to follow up and treatment response remains unknown.

5. Conclusion

BMS represents an infrequent manifestation of extrapulmonary sarcoidosis and is more prevalent in women and African Americans. Unexplained cytopenias, although nonspecific, may be a solitary finding and thus clinicians should maintain a high index of suspicion. In order to establish diagnosis, more common etiologies such as vitamin deficiencies, anemia of chronic disease, hemolysis and hypersplenism need to be considered before proceeding with histopathological analysis. Therapy revolves around corticosteroids, nonetheless, promising drugs are under trial.

Disclosure statement

No potential conflict of interest was reported by the authors.

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