

Bone marrow involvement in sarcoidosis: an elusive extrapulmonary manifestation

J. Isaac Peña-García ^a, Sana Shaikh^b, Bhishma Barakoti^b, Christos Papageorgiou^c and Alexandre Lacasse^b

^aGeriatric Research Education and Clinical Center, Miami VA/Jackson Memorial Hospital, Miami, FL, USA; ^bDepartment of Internal Medicine, SSM St. Mary's Hospital - St. Louis, St. Louis, MO, USA; ^cSSM Health Cancer Care, SSM St. Mary's Hospital - St. Louis, St. Louis, MO, USA

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

ARTICLE HISTORY

Received 14 November 2018
Accepted 25 January 2019

KEYWORDS

Bone marrow sarcoidosis; sarcoidosis; bone marrow biopsy; cytopenias; extrapulmonary sarcoidosis

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 × 10⁹ 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 mg/dL]), elevated aspartate aminotransferase (64 [5–40 U/L]), 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 neurosarcoidosis, 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 fire-fighting, 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].

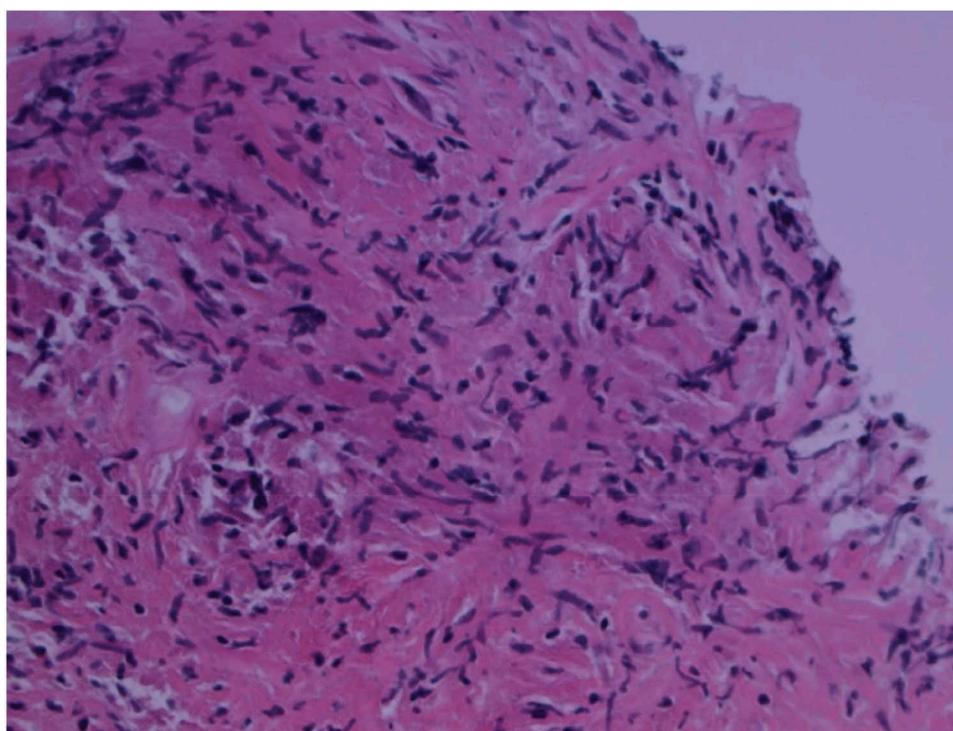


Figure 1. Right retrocaval lymph node biopsy showing granulomatous formation and giant cells with minute areas of necrosis.

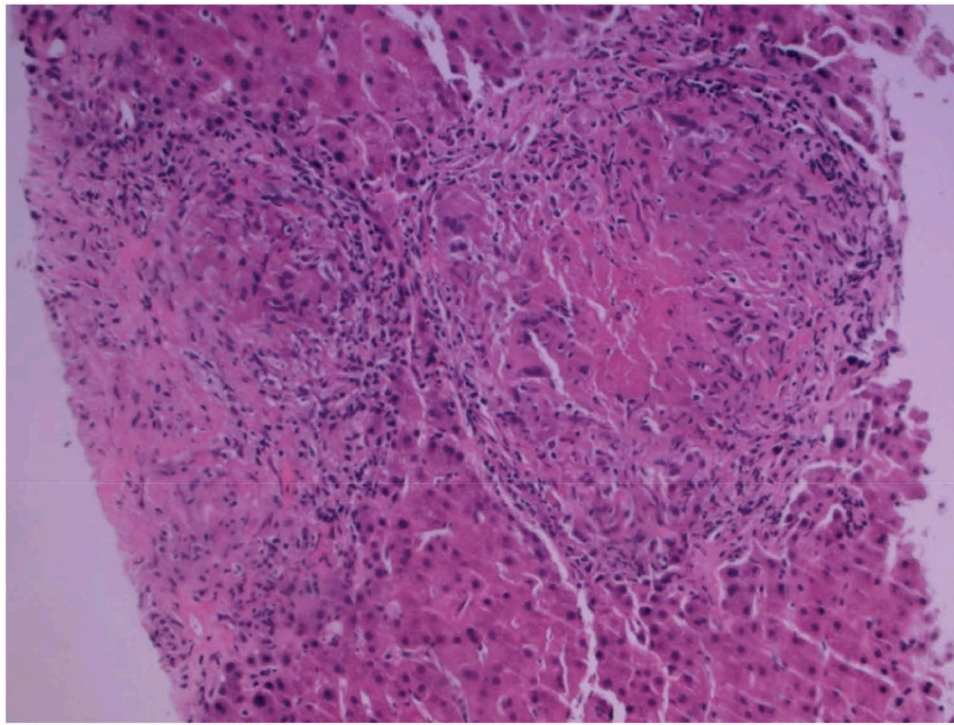


Figure 2. Liver biopsy showing two well-circumscribed nodules characterized by abundant histiocytes and no necrosis.

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

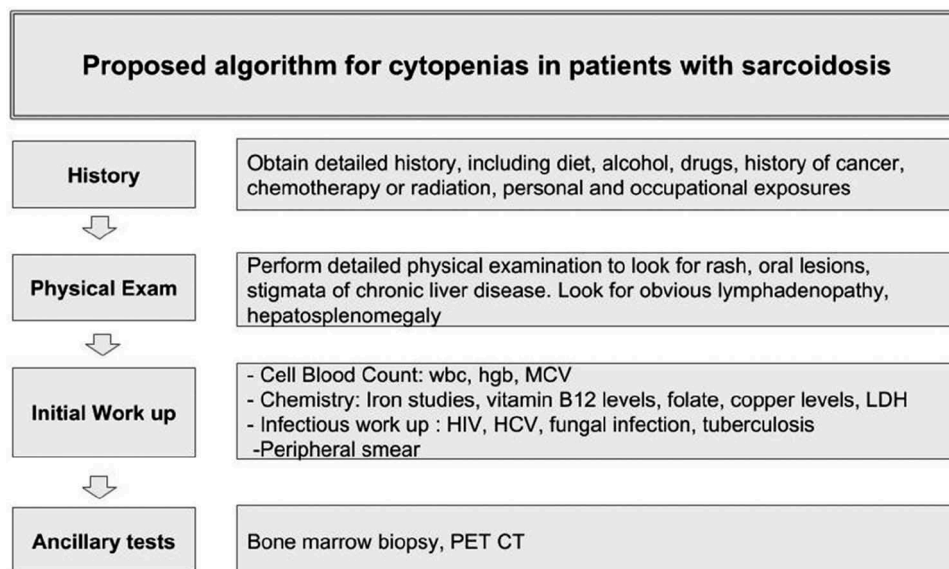


Figure 3. Proposed approach to patient with sarcoidosis presenting with cytopenias [3,7,9,31,40,46].

[56]. 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.

ORCID

J. Isaac Peña-García  <http://orcid.org/0000-0003-0551-4564>

References

- [1] Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee. *Am J Respir Crit Care Med.* 1999 Feb;160(2):736–755.
- [2] Yee AM. Sarcoidosis: rheumatology perspective. *Best Pract Res Clin Rheumatol.* 2016;30(2):334–356.
- [3] Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med.* 2007;357(21):2153–2165.
- [4] Chen ES, Moller DR. Etiology of sarcoidosis. *Clin Chest Med.* 2008;29(3):365–377.
- [5] Ungprasert P, Carmona EM, Utz JP, et al. Epidemiology of sarcoidosis 1946–2013: a population-based study. *Mayo Clin Proc.* 2016;91(2):183–188.
- [6] Rybicki BA, Major M, Jr PJ, et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol.* 1997;145(3):234–241.
- [7] Valeyre D, Prasse A, Nunes H, et al. Sarcoidosis. *Lancet.* 2014;383(9923):1155–1167.
- [8] Al-Kofahi K, Korsten P, Ascoli C, et al. Management of extrapulmonary sarcoidosis: challenges and solutions. *Ther Clin Risk Manag.* 2016;12:1623–1634.
- [9] Rizzato G, Palmieri G, Agrati AM, et al. The organ-specific extrapulmonary presentation of sarcoidosis: a frequent occurrence but a challenge to an early diagnosis. A 3-year-long prospective observational study. *Sarcoidosis Vasc Diffuse Lung Dis.* 2004;21(2):119–126.
- [10] Shadid S, Ter Maaten JC. Sarcoidosis—a great mimicker. *J Intern Med.* 2002;251(2):174–176.
- [11] Cozier YC, Berman JS, Palmer JR, et al. Sarcoidosis in black women in the USA: data from the black women’s health study. *Chest.* 2011;139(1):144–150.
- [12] Morimoto T, Azuma A, Abe S, et al. Epidemiology of sarcoidosis in Japan. *Eur Resp J.* 2008;31(2):372–329.
- [13] Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev.* 1983;5:124–156.
- [14] Rybicki BA, Amend KL, Maliarik MJ, et al. Photocopier exposure and risk of sarcoidosis in African-American sibs. *Sarcoidosis Vasc Diffuse Lung Dis.* 2004;21:49–55.
- [15] Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med.* 2004;170:1324–1330.
- [16] Kucera GP, Rybicki BA, Kirkey KL, et al. Occupational risk factors for sarcoidosis in African-American siblings. *Chest.* 2003;123:1527–1535.

- [17] Gorham ED, Garland CF, Garland FC, et al. Trends and occupational associations in incidence of hospitalized pulmonary sarcoidosis and other lung diseases in Navy personnel: a 27-year historical prospective study, 1975–2001. *Chest*. 2004;126:1431–1438.
- [18] Prezant DJ, Dhala A, Goldstein A, et al. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. *Chest*. 1999;116:1183–1193.
- [19] Barnard J, Rose C, Newman L, et al. Job and industry classifications associated with sarcoidosis in A Case-Control Etiologic Study of Sarcoidosis (ACCESS). *J Occup Environ Med*. 2005;47:226–234.
- [20] Brewerton DA, Cockburn C, James DC, et al. HLA antigens in sarcoidosis. *Clin Exp Immunol*. 1977;27:227–229.
- [21] Rossman MD, Thompson B, Frederick M, et al. HLA-DRB1*1101: a significant risk factor for sarcoidosis in blacks and whites. *Am J Hum Genet*. 2003;73:720–735.
- [22] Iannuzzi MC, Maliarik MJ, Poisson LM, et al. Sarcoidosis susceptibility and resistance HLA-DQB1 alleles in African Americans. *Am J Respir Crit Care Med*. 2003;167:1225–1231.
- [23] Voorter CE, Amicosante M, Berretta F, et al. HLA class II amino acid epitopes as susceptibility markers of sarcoidosis. *Tissue Antigens*. 2007;70:18–27.
- [24] Sato H, Grutters JC, Pantelidis P, et al. HLA-DQB1*0201: a marker for good prognosis in British and Dutch patients with sarcoidosis. *Am J Respir Cell Mol Biol*. 2002;27:406–412.
- [25] Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1885–1889.
- [26] Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the USA. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29(2):119–127.
- [27] Yachoui R, Parker BJ, Nguyen TT. Bone and bone marrow involvement in sarcoidosis. *Rheumatol Int*. 2015;35(11):1917–1924.
- [28] Mañá J, Rubio-Rivas M, Villalba N, et al. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis: cohort study of a 40-year clinical experience at a tertiary referral center in Barcelona, Spain. *Medicine (Baltimore)*. 2017;96(29):e7595.
- [29] Carrillo-Pérez DL, Apodaca-Chávez EI, Carrillo-Maravilla E, et al. Sarcoidosis: a single hospital-based study in a 24-year period. *Rev Invest Clin*. 2015;67(1):33–38.
- [30] Sharma OP. Sarcoidosis around the world. *Clin Chest Med*. 2008;29(3):357–363.
- [31] Judson M. The three tiers of screening for sarcoidosis organ involvement. *Respir Med*. 2016;113(1):42–49.
- [32] Yanardag H, Pamuk GE, Karayel T, et al. Bone marrow involvement in sarcoidosis: an analysis of 50 bone marrow samples. *Haematologia (Budap)*. 2002;32:419–425.
- [33] Akinsanya L, Hussain I, Awoniyi D, et al. Leucopenia as presentation of sarcoidosis. *Int J Health Sci (Qassim)*. 2008;2(1):109–112.
- [34] Sweiss NJ, Salloum R, Gandhi S, et al. Significant CD4, CD8, and CD19 lymphopenia in peripheral blood of sarcoidosis patients correlates with severe disease manifestations. *PLoS One*. 2010;5:e9088.
- [35] Browne PM, Sharma OP, Salkin D. Bone marrow sarcoidosis. *JAMA*. 1978;240(24):2654–2655.
- [36] Taylor HG, Berenberg JL. Bone marrow phagocytosis in sarcoidosis. *Arch Intern Med*. 1982;142(3):479–480.
- [37] Helbig G, Torba K, Pajak J, et al. Sarcoidosis with bone marrow involvement. *Pol Arch Med Wewn*. 2014;124(7–8):427–428.
- [38] Alahdab F. Expect the unexpected: unusual neurological presentation of bone marrow sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2014;18;31(1):67–70.
- [39] Bhargava V, Farhi DC. Bone marrow granulomas: clinicopathologic findings in 72 cases and review of the literature. *Hematol Pathol*. 1988;2:43–50.
- [40] Bodem CR, Hamory BH, Taylor HM, et al. Granulomatous bone marrow disease—a review of the literature and clinicopathologic analysis of 58 cases. *Medicine (Baltimore)*. 1983;62:372–383.
- [41] Pease GL. Granulomatous lesion in the bone marrow. *Blood*. 1956;11:720–734.
- [42] Vilalta-Castel E, Valdes-Sanchez MD, Guerra-Vales JM, et al. Significance of granulomas in bone marrow: a study of 40 cases. *Eur J Haematol*. 1988;41:12–16.
- [43] White RM, Johnston CL Jr. Granulomatous bone marrow disease in Virginia: study of 50 cases. *Va Med*. 1985;112:316–319.
- [44] Longcope WT, Freiman DG. A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from the Johns Hopkins hospital and massachusetts general hospital. *Medicine (Baltimore)*. 1952;31(1):1–132.
- [45] Brackers de Hugo L, Ffrench M, Broussolle C, et al. Granulomatous lesions in bone marrow: clinicopathologic findings and significance in a study of 48 cases. *Eur J Intern Med*. 2013;24:468–473.
- [46] Belfer MH, Stevens RW. Sarcoidosis: a primary care review. *Am Fam Physician*. 1998;58(9):2041–50, 2055–2056.
- [47] Ellman L. Bone marrow biopsy in the evaluation of lymphoma, carcinoma and granulomatous disorders. *Am J Med*. 1976;60(1):1–7.
- [48] Pavlovic-Popovic Z, Zaric B, Kosjerina Z, et al. Splenomegaly in sarcoidosis: frequency, treatment, prognosis, and long-term follow-up. *Srp Arh Celok Lek*. 2015;143:279–283.
- [49] Ungprasert P, Matteson EL. Neurosarcoidosis. *Rheum Dis Clin North Am*. 2017;43(4):593–606.
- [50] Gubatan J, Wang X, Louissaint A, et al. Hypercalcemia associated with isolated bone marrow sarcoidosis in a patient with underlying monoclonal gammopathy of undetermined significance: case report and review of literature. *Biomark Res*. 2016;15:4:18.
- [51] Sharma AM, Fried J, Sharma OP. Monoclonal gammopathy of undetermined significance in sarcoidosis. Two case reports. *Sarcoidosis*. 1992;9(1):70.
- [52] Slart RM, de Jong JW, Haeck PW, et al. Lytic skull lesions and symptomatic hypercalcaemia in bone marrow sarcoidosis. *J Intern Med*. 1999;246(1):117–120.
- [53] Del Mar Osma M, Francisco Jose O. Marrow non-casating granulomas: sarcoidosis. *Blood*. 2012;119(7):1622.
- [54] Vucinic VM. What is the future of methotrexate in sarcoidosis. A study and review. *Curr Opin Pulm Med*. 2002;8:470–476.
- [55] Conte G, Zugni F, Colleoni M, et al. Sarcoidosis with bone involvement mimicking metastatic disease at 18F-FDG PET/CT: problem solving by diffusion whole-body MRI. *Ecancermedicalscience*. 2015;9:537.
- [56] Nilsson K, Pahlson C, Lukinius A, et al. Presence of *Rickettsia helvetica* in granulomatous tissue from patients with sarcoidosis. *J Infect Dis*. 2002;185(8):1128–1138.