Extrapulmonary Sarcoidosis with Concurrent Smouldering Multiple Myeloma Transforming into Plasma cell myeloma: Case Report of an Unusual Association

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Received: 5 January 2024

Accepted: 21 January 2024

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DOI 10.5001/omj.2026.18

Abstract

Sarcoidosis is a benign, chronic granulomatous disease of unknown aetiology. A causal association between sarcoidosis and many hematologic malignancies has been suggested in the literature. The simultaneous existence of sarcoidosis and lymphoproliferative malignancies (sarcoidosis-lymphoma syndrome) has been well-documented. Very rarely, a link between sarcoidosis and multiple myeloma has been observed, with only a handful of them involving smouldering multiple myeloma. Herein, an unusual case of disseminated sarcoidosis simultaneously diagnosed with concurrent smouldering multiple myeloma which later transformed into plasma cell myeloma is presented in this report.

Keywords: Bone Marrow; Concurrent Presentation; Lymphoproliferative Malignancy; Extrapulmonary Sarcoidosis; Smouldering Multiple Myeloma; Plasma Cell Myeloma.

Introduction

Sarcoidosis is a highly diverse chronic systemic granulomatous illness of idiopathic origin, hypothesized to be produced by an abnormal antigen-specific immune response mounted by T-cells in response to an unidentified environmental trigger in vulnerable hosts. Non-necrotizing granulomas, the histopathological hallmark, are classically devoid of a lymphocyte collarette and composed of a central organised collection of CD4+ T-helper lymphocytes, histiocytes, and epithelioid giant cells, surrounded by a ring of epithelioid-shaped activated fibroblasts.[1,2] This multi-organ disease can practically affect any and every organ in the body much like tuberculosis, its close masquerade.[3] The lungs and lymph nodes are virtually always inflicted, with the other commonly affected organs being liver, skin, spleen, heart, and eyes, followed by the musculoskeletal system less frequently. The increased risk of lymphoproliferative malignancies associated with sarcoidosis is a concept referred to as 'sarcoidosis-lymphoma syndrome' and has been explored in several studies, the first of which was published in 1986 by Brincker. However, there is a dearth of case reports describing the relationship of extrapulmonary sarcoidosis with plasma cell dyscrasias in particular.[4,5] Multiple myeloma is a haematological malignancy arising from the abnormal monoclonal proliferation within the bone marrow of malignant plasma cells.[6] This case report describes a case of disseminated sarcoidosis simultaneously diagnosed with smouldering multiple myeloma as per the International Myeloma Working Group (IMWG) diagnostic criteria which later evolved into multiple myeloma.[7]

Case Report

A 65-year old male, presented to the medicine OPD with history of intermittent fever, diffuse abdominal pain, weight loss, and melena, with no past/contact history of tuberculosis. Examination revealed hepatomegaly (14 cm span), splenomegaly (4 cm below costal margin), and free fluid in the abdomen, with no lymphadenopathy. Rest

of the systemic examination was unremarkable. Routine laboratory investigations and second tier investigations to rule out infective process were done **(**Table 1).

USG abdomen revealed hepatosplenomegaly, upper gastrointestinal endoscopy showed oesophageal varices and portal gastropathy, suggestive of portal hypertension. CECT-abdomen also illustrated few wedge-shaped hypodense lesions in spleen, likely to be infarcts. Although chest skiagraphy was normal, CECT-chest showed minimal bilateral pleural effusion, fibroatelectatic opacities in left upper lobe, with few subcentimetric paratracheal and subcarinal lymph nodes. Bone marrow (BM) examination was performed as part of the clinical evaluation for the pyrexia of unknown origin, based on the reports of which further biochemical work-up for sarcoidosis and monoclonal gammopathy was done (Table 1).

PET-CT done showed diffuse splenic and marrow hypermetabolism with fatty liver, portal hypertension, and splenomegaly, suggesting a diffuse infiltrative process in the BM, liver, and spleen. Liver trucut biopsy showed non-confluent naked granulomas, however, necrosis was found in one of them. The patient fulfilled the defining criteria of smouldering MM –serum monoclonal protein of >3g/dl and no myeloma defining events (hypercalcemia, anaemia, renal involvement, or bony lytic lesions). The anaemia in our patient was considered to be multifactorial secondary to BM sarcoidosis and/or melena due to portal hypertension. Hence, a final diagnosis of disseminated sarcoidosis with concurrent smouldering MM was rendered, following which he was put on steroid treatment, and advised 6 monthly follow-up. After initial response to therapy, patient deteriorated and a follow-up BMA after 8 months revealed features favouring transformation into multiple myeloma (MM), further confirmed with flowcytometry and BM biopsy (BMB). The repeat BMB showed no granulomas and complete transformation to MM. Flowcytometry displayed gene switchover from lambda to kappa light-chain, the incidence of which is mentioned in literature but is exceedingly rare and confers a very poor prognosis (Table 1). At 8 months of follow up, the patient succumbed to his illness.

Table 1: Results of laboratory tests.

TEST	RESULT
CBC	Hb-9.6 g/dl¶, TLC-24,710/mm^3, Plt-1.31 Lakh/mm^3
Peripheral smear	Neutrophilic leukocytosis with bicytopenia
Infection panel	HIV, HBsAg, Anti-HCV antibody, Rk-39 antigen, Brucella serology, Mantoux, Stool for occult blood - **NEGATIVE**
Inflammatory markers (ESR, Sr.ALP, Sr.Ferritin, Sr.d-dimer)	**Elevated**
BMA*	Hypercellular marrow with 4% atypical plasma cells, occasional ones showing bipolar cytoplasm, suggesting likelihood of a plasma cell dyscrasia (PCD).
BMB*	Cellular marrow with numerous noncaseating naked granulomas scattered interstitially with occasional asteroid bodies, with dense interstitial lymphoplasmacytic & histiocytic infiltrates in between the granulomas, suggestive of **disseminated sarcoidosis**; along with slight increase in atypical plasma cells showing CD38, CD138 positivity, and **lambda light-chain restriction**, consistent with **smouldering MM**. Disseminated fungal and mycobacterial infections were ruled out as Grocott-Gomori's methenamine silver and Ziehl-Neelsen stains were negative.
Sr ACE	66 μg/L (**elevated**) (Ref: <40 μg/L)
Sr calcium	8.7 mg/dL (**borderline low**) (Ref: 8.9-10.1 mg/dL)
A:G ratio	**Reversed**
SPEP: γ-globulin	**47% (elevated)**
M-protein	**4.3 g/dl (IgG monoclonal gammopathy)**
UPEP & immunotyping:	Monoclonal protein **-36%** of total urine protein
Ig SFLCA: κ free LC	32.7 mg/L (mildly elevated) (Ref: 3.3-19.4 mg/L)
λ free LC	145 mg/L **- λ restriction** (Ref: 5.6-26.6 mg/L)
κ:λ ratio	0.22 (Ref: 0.26-1.65)

BMA†	40% and 58% atypical plasma cells in BMA and BM imprint smears respectively; Impression- Known case of sarcoidosis with smouldering MM showing features favouring **transformation to plasma cell myeloma.**
BMB†	Owing to significantly increased plasma cells with CD38 and CD138 positivity, features are suggestive of a PCD, likely to be plasma cell myeloma in a known case of sarcoidosis with smouldering MM on repeat biopsy, with **no evidence of granulomatous lesions** (implying a good response of sarcoidosis to steroid therapy).
Flowcytometry (Sample:BMA†)	Features suggestive of multiple myeloma, with **kappa light-chain restriction** (CD38, CD138 – Positive; and CD19, CD56, CD27, CD81, CD200 - Negative).

CBC- Complete blood count; ESR- Erythrocyte sedimentation rate; ALP- Alkaline phosphatase; A:G- Albumin-globulin; HIV- Human immunodeficiency virus; HBsAg- Hepatitis B surface antigen; HCV- Hepatitis C Virus; SPEP- Serum protein electrophoresis; UPEP- Urine protein electrophoresis; Ig SFLCA- Immunoglobulin serum free light chain assay; ACE- Angiotensin-converting enzyme; Ref- Reference range; BMA, BMB* - Bone marrow aspirate and bone marrow biopsy done at the time of initial diagnosis (November 2022); BMA†, BMB† - Bone marrow aspirate and bone marrow biopsy acquired during follow-up after 8 months (July 2023); ¶- The anaemia in our patient was considered to be multifactorial secondary to BM sarcoidosis and/or melena due to portal hypertension.*

Figure 1: **(a)** Initial BM aspirate smear showing slight increase in plasma cells, with few atypical plasma cells having unipolar (*black arrow*) and bipolar (*red arrow*) cytoplasm (*Wright Giemsa, ×1000*); **(b)** and **(c)** - Initial BM biopsy revealing non-caseating granulomas (*arrows*) devoid of a lymphocyte collarette found scattered throughout the marrow with varying degrees of interstitial lymphoplasmacytic infiltrates and fibrosis (*H & E, ×40 and ×400 respectively*).

Figure 2: Immunohistochemical studies performed on the initial BM biopsy revealed: **(a)** histiocytes showing immunoreactivity for CD38 (*×1000*), **(b)** B-cells surrounding the noncaseating granulomas showing CD20 expression (*×400*), **(c)** and the interstitium showing diffuse positivity for CD3 immunomarker (*×1000*).

Figure 3: **(a)** Follow-up BM aspirate revealed features favouring transformation to multiple myeloma (MM) with significantly increased plasma cells (*arrows*), **inset** shows few forms of atypical plasma cells (PC) including flame cells, binucleate, and multinucleate forms (*Wright Giemsa, ×400*); **(b)** Follow-up BM biopsy revealed no granulomas, while showing a complete progression to MM (*H & E, ×400*), inset: left- Russell bodies (intracytoplasmic inclusions) and Dutcher body (intranuclear inclusions), right- Immunohistochemistry: CD38, CD138 positive plasma cells showing kappa light chain restriction. **(c)** Flowcytometry (during follow-up) reveals the neoplastic plasma cells (*red population*) which are CD38, CD138, CD45+, and CD19-ve, displaying Kappa light-chain restriction, while the non-neoplastic plasma cells (*violet population*) are showing polyclonality.

Discussion

Sarcoidosis, a multisystem chronic inflammatory disorder of obscure cause, is histopathologically defined by a non-necrotizing granulomatous process consisting of sarcoid-type epithelioid granulomas associated with mononuclear cell infiltration and destruction of microarchitecture in any organ, most commonly the lung. It has a highly protean clinical presentation, from asymptomatic to grave complications like respiratory insufficiency, cardiac death, blindness, neurological impairment, etc.[8]

Epidemiological statistics emphasises the greater risk of malignancies like haematolymphoid and solid tumours in sarcoidosis, amongst which the association of sarcoidosis with multiple myeloma (MM), a plasma cell dyscrasia, is exceedingly uncommon.[3] The asymptomatic precancerous stage that invariably precedes MM is monoclonal gammopathy of undetermined significance (MGUS), while the clinical stage intermediate between MGUS and MM is smouldering multiple myeloma (SMM).[7] The incidence of clonal gene switchover from one light chain to another is extremely uncommon and is very sparsely cited in literature, and also portends a very poor prognosis.

As only a limited number of instances of sarcoidosis coexisting with MM have been described in existing literature, there is insufficient data to establish a causal link between the two conditions.[6] Although a veritable

explanation for this possible relation remains contentious despite extensive research, the following hypotheses have however been proposed. Since sarcoidosis is known to produce immune system abnormalities like reduced cytotoxic T-lymphocytes, CD4+ T-cell activation, aberrant cytokine release, cutaneous anergy to specific antigens like tuberculin purified protein derivative, and hypergammaglobulinemia, such immune disruption has been postulated to contribute to the interrelation of sarcoidosis with lymphomas. The polyclonal hypergammaglobulinemia frequently encountered in sarcoidosis is because of the activated CD4+ T-lymphocytes persistently activating B-cells which accounts for the extended half-lives of B-cells and plasma cells, hence driving certain gene mutations that pave way for the development of plasma cell neoplasms like MM.[3]

In current case, contrary to expected, the serum ACE (SACE) levels were only marginally raised with normal serum calcium. SACE has a low specificity as 25% of untreated sarcoidosis patients may not have high ACE levels.[9] Based on the population investigated, presence of hypercalcemia in sarcoidosis patients can vary between 2-63%; the reason for such wide disparities in frequency of hypercalcemia has been ascribed to the diversity in blood calcium testing in addition to the fluctuating disease course of sarcoidosis.[5,10]

Conclusion

A patient presenting simultaneously with sarcoidosis and smouldering MM at the time of diagnosis is extremely unusual, and transforming into MM is even rarer. Hence, dismissal as a mere coincidence should be disdained as prospective epidemiological research will largely depend on it, and a strong index of suspicion is warranted with thorough workup and very close follow-up as it bears a dismal prognosis.

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