

Case Report

A Rare Case of Recurrent Euvolemic Hyponatremia and Monoclonal IgG Paraproteinemia in a Case of Multisystemic Sarcoidosis : A Case Report

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Abstract :

Introduction :

Sarcoidosis is a multisystemic inflammatory disorder of unknown etiology, characterized by the formation of non-caseating granulomas in various organs. While pulmonary involvement is most common, extrapulmonary manifestations can present significant diagnostic and therapeutic challenges. Neurosarcoidosis, particularly involving the hypothalamic-pituitary axis, is a rare but serious complication that can lead to endocrine dysfunction, including hyponatremia. The association between chronic inflammatory states like sarcoidosis and the development of monoclonal gammopathies is also recognized but remains an area of ongoing research.

Case Presentation :

We present the case of a 68-year-old female with a history of hypertension and type 2 diabetes mellitus who was admitted with severe prostration and uncontrolled hyperglycemia. Her history was notable for recurrent episodes of severe hyponatremia, uveitis, and skin lesions resembling erythema nodosum. Initial investigations revealed euvolemic hyponatremia and panhypopituitarism, including central hypothyroidism and adrenal insufficiency. Imaging studies, including Magnetic Resonance

Imaging (MRI) of the brain and a Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan, confirmed pituitary and myocardial involvement, leading to a diagnosis of multisystemic sarcoidosis. The patient responded dramatically to immunosuppressive therapy with steroids and levothyroxine replacement. However, six months later, she presented again with persistent weakness and anemia. Further evaluation revealed a monoclonal IgG lambda paraprotein on serum protein electrophoresis and immunofixation, with bone marrow examination showing dyspoiesis, consistent with Monoclonal Gammopathy of Undetermined Significance (MGUS).

Conclusion :

This case highlights the complex interplay of endocrine, inflammatory, and hematological manifestations in a single patient with sarcoidosis. It underscores the importance of considering neurosarcoidosis in the differential diagnosis of recurrent euvolemic hyponatremia and pituitary dysfunction. Furthermore, it illustrates the potential for chronic inflammation in sarcoidosis to predispose patients to plasma cell dyscrasias like MGUS. Clinicians should maintain a high index of suspicion for these associated conditions

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to ensure timely diagnosis and appropriate management, including long-term surveillance for the potential progression of MGUS to multiple myeloma.

Introduction :

Sarcoidosis is a complex, multisystemic disease characterized by the pathological hallmark of non-caseating granulomas in affected tissues.^[1] The etiology remains elusive, though it is widely believed to result from an exaggerated immune response to an unidentified antigen in genetically susceptible individuals. The clinical presentation of sarcoidosis is notoriously heterogeneous, ranging from asymptomatic incidental findings to severe, life-threatening organ dysfunction. While the lungs and lymphatic system are involved in over 90% of cases, virtually any organ can be affected.^[2]

Extrapulmonary sarcoidosis can pose a significant diagnostic challenge due to its diverse and often subtle manifestations. One of the rarer but more serious forms is neurosarcoidosis, which occurs in 5-10% of patients.^[3] Neurological involvement can affect any part of the central or peripheral nervous system, with cranial neuropathies, aseptic meningitis, and hydrocephalus being common presentations. Involvement of the hypothalamic-pituitary axis is a particularly infrequent manifestation, occurring in less than 1% of all sarcoidosis patients, but it can lead to profound endocrine disturbances.^[4] These disturbances may include diabetes insipidus, anterior pituitary hormone deficiencies (hypopituitarism), and disorders of water balance, such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), resulting in hyponatremia. Hyponatremia in sarcoidosis can also arise from other mechanisms, including primary polydipsia, adrenal insufficiency, or dysregulated calcium

metabolism.^[5]

Another intriguing and less understood association is the link between sarcoidosis and hematological abnormalities, particularly plasma cell dyscrasias. Chronic inflammation is a known risk factor for the development of monoclonal gammopathies, where a clone of plasma cells produces a monoclonal immunoglobulin (M-protein).^[6] Monoclonal Gammopathy of Undetermined Significance (MGUS) is the most common of these disorders and is considered a premalignant precursor to multiple myeloma.^[7] The persistent systemic inflammation and immune dysregulation inherent to sarcoidosis may create a microenvironment conducive to the clonal expansion of plasma cells, leading to an increased incidence of MGUS in this patient population.^[8]

This report details the intricate case of a 68-year-old woman who initially presented with features of pituitary insufficiency, leading to a diagnosis of multisystemic sarcoidosis with rare hypothalamic-pituitary and cardiac involvement. Her clinical course was further complicated by the subsequent development of a monoclonal IgG paraproteinemia, highlighting the confluence of endocrine and hematological sequelae of this multifaceted disease. Through this case, we aim to discuss the diagnostic pathway for neurosarcoidosis, the pathophysiology of associated hyponatremia, and the clinical implications of the co-occurrence of sarcoidosis and MGUS.

Case Presentation :

A 68-year-old female with a long-standing history of hypertension and type 2 diabetes mellitus presented to the emergency department of Ramakrishna Mission Seva Pratishthan

Vivekananda Institute of Medical Sciences with a one-month history of severe weakness and uncontrolled hyperglycemia. She also reported intermittent vomiting and anorexia for the preceding six months.

Past Medical History and Further Enquiry :

On further questioning, the patient revealed a more extensive history of symptoms spanning several years. For the last five years, she had experienced low back pain, intermittent holocephalic headaches, and multiple episodes of painful red eyes, which had been diagnosed as recurrent uveitis. Over the past three to four years, she had developed recurrent, painful subcutaneous nodules over her shins, suggestive of erythema nodosum. She had no other significant past medical history and had reached menopause at the age of 49. A detailed negative history revealed no prior surgery, no symptoms suggestive of diabetic micro- or macrovascular complications, no autonomic neuropathy, and no history of tuberculosis exposure or recent fractures.

Clinical Examination :

Upon examination, the patient was alert and oriented but appeared severely asthenic. Her vital signs were : blood pressure 110/70 mmHg, pulse 102 beats per minute, and respiratory rate 18 breaths per minute. Her weight was 66 kg, and her BMI was 28.1kg/m². There were no signs of dehydration or edema. Physical examination revealed pallor, but no lymphadenopathy or icterus. The remainder of the systemic examination was within normal limits.

Initial Investigations and Diagnosis of Neurosarcoidosis :

Initial laboratory investigations were significant

for hyponatremia (Na: 123 mEq/L), uncontrolled hyperglycemia (Fasting Blood Sugar: 125 mg/dL, Post-Prandial Blood Sugar: 243 mg/dL), a normocytic, hypochromic anemia (Hb: 10.1 g/dL), and a markedly elevated erythrocyte sedimentation rate (ESR: 100 mm in 1st hour).

Given the constellation of recurrent uveitis, erythema nodosum, and new-onset hyponatremia with weakness, an underlying systemic inflammatory disease was suspected. Endocrine evaluation was pursued to investigate the cause of the euvolemic hyponatremia. The results were consistent with panhypopituitarism:

- **Thyroid Axis :** Low free T4 (fT4: 0.86 ng/dL; ref 0.93-1.7) with an inappropriately normal TSH (0.55 mIU/mL; ref 0.27-4.2), indicating central hypothyroidism.

- **Adrenal Axis :** An 8 AM serum cortisol level was inappropriately normal, which, in the context of severe systemic stress and illness, pointed towards central adrenal insufficiency.

- **Gonadotropic Axis :** Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were inappropriately normal for a postmenopausal woman, further supporting pituitary dysfunction.

- **Prolactin :** Prolactin was mildly elevated at 28.4 ng/mL (ref 4.79-23.3), likely due to pituitary stalk compression ("stalk effect").

To localize the pathology, an MRI of the hypothalamo-pituitary region was performed. It revealed diffuse enlargement of the pituitary gland with diffuse contrast enhancement and significant thickening of the pituitary stalk. These findings, in a patient with multisystemic inflammatory features, were highly suggestive of neurosarcoidosis.

Further investigations were conducted to assess the extent of systemic involvement and rule out mimics.

- **Serum Angiotensin-Converting Enzyme (SACE) :** The SACE level was elevated at 73 U/L.

- **High-Resolution Computed Tomography (HRCT) of the Thorax :** Showed a few scattered, calcified granulomas in both lung fields but no evidence of active inflammation, hilar lymphadenopathy, or pulmonary fibrosis.

- **Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Scan :** A planned bronchoscopy was abandoned due to the patient's

frailty. An FDG-PET scan was performed instead, which revealed metabolically inactive calcified granulomas in the lungs. However, it demonstrated mildly increased FDG uptake in the pituitary region and, significantly, increased FDG uptake in the left ventricular myocardium with a minimal pericardial effusion, confirming active cardiac sarcoidosis.

- **Cardiac MRI :** Showed no evidence of myocardial scarring or late gadolinium enhancement.

Autoimmune and Infectious Workup : Tests for SS-A, SS-B, ANCA, and IgG4 were all negative, ruling out other systemic autoimmune diseases.

Routine Investigations	
FBS	125 mg/dL
PPBS	243 mg/dL
Na	123 mg/dL
K	4.9 mg/dL
Corrected Ca	9.1 mg/dL
Creatinine	1.2 mg/dL
Uric Acid	6.2 mg/dL
Urine MACR	35.3
Hb	10.1 gm/dL
TC	8700/cmm - $N_{72}L_{21}M_{5}E_{2}B_{9}$
ESR	100 mm in 1 st hour

Further Investigations	
TSH	0.55 mIU/mL (0.27-4.2 mIU/mL)
FT4	0.86 ng/dL (0.93-1.7 ng/dL)
TT3	0.98 ng/mL (0.8-2.0 ng/mL)
LH	1.7 mIU/mL (1.1-7.0 mIU/mL)
FSH	9.73 mIU/mL (1.7- 12.0 mIU/mL)
Prolactin	28.4 mIU/mL (4.79-23.3 mIU/mL)
8am S. cortisol	26.0 mg/mL (4.82-19.5 ng/dL)
SACE	73 U/L
COVID-19 RTPCR	Negative
COVID Ab	26.0 mg/mL (4.82-19.5 ng/dL)
Echo	Concentric LVH, LVEF – 60%, E/E' – 11, grade 1 LVDD

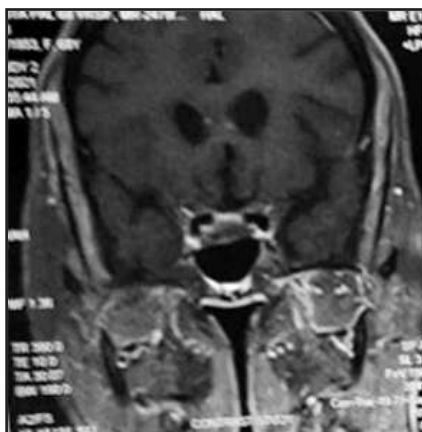


Image 1, Image 2 : Diffuse enlargement of the pituitary gland with diffuse contrast enhancement and significant thickening of the pituitary stalk.

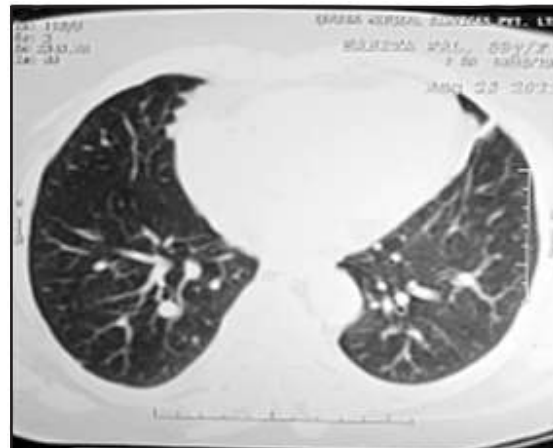


Image 3, Image 4: few scattered, calcified granulomas in both lung fields.

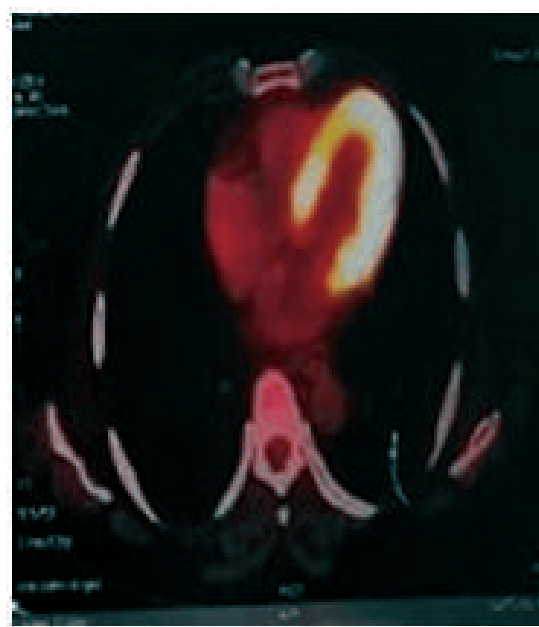
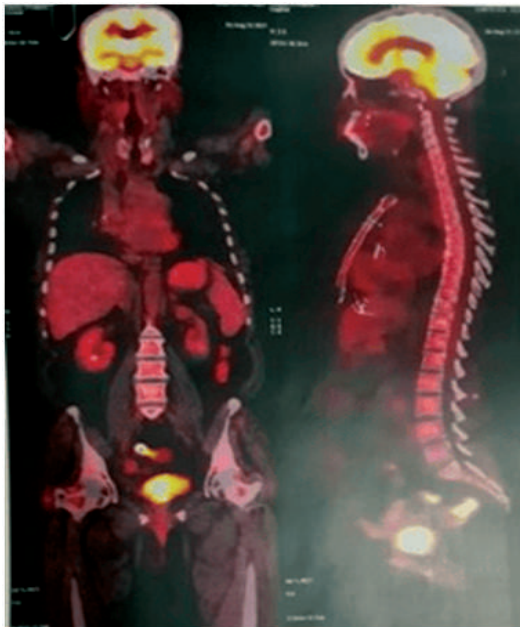


Image 5, Image 6 : metabolically inactive calcified granulomas in the lungs. However, it demonstrated mildly increased FDG uptake in the pituitary region and, significantly, increased FDG uptake in the left ventricular myocardium with a minimal pericardial effusion, confirming active cardiac sarcoidosis.

Based on the combination of clinical evidence (uveitis, erythema nodosum), biochemical evidence (panhypopituitarism, high SACE), and characteristic imaging findings (pituitary stalk

thickening on MRI, cardiac and pituitary uptake on PET scan), a provisional diagnosis of multisystemic sarcoidosis with pituitary and cardiac involvement was made.

Management and Initial Outcome :

The patient was started on hormone replacement therapy with levothyroxine and a therapeutic dose of oral steroids for the management of sarcoidosis, which was later tapered to a maintenance dose. Her hyperglycemia was managed with insulin. The patient showed a dramatic clinical improvement. Her weakness resolved, and she had no further episodes of hyponatremia or uveitis.

Follow-up and Development of Monoclonal Gammopathy :

Six months after her initial diagnosis and treatment, the patient presented again with generalized body ache and persistent weakness. Repeat laboratory workup revealed a worsening anemia (Hb: 8.8 g/dL) and a persistently elevated ESR (73 mm/hr). Her iron profile was consistent with iron deficiency, but her symptoms and elevated ESR did not improve despite iron replacement therapy.

This prompted a further hematological investigation.

- **Serum Protein Electrophoresis (SPEP) :** Revealed an M-band in the gamma globulin region.
- **Serum Immunofixation :** Confirmed the presence of a monoclonal IgG lambda paraprotein.
- **Quantitative Immunoglobulins :** IgG level was 13.5 g/L (within the normal range).
- **Serum Free Light Chains :** Showed elevated free kappa (58.68 mg/L; ref 3.3-19.4) and lambda chains (95.59 mg/L; ref 5.71-26.3), with a normal kappa/lambda ratio of 0.61.
- **Beta-2 Microglobulin :** Was elevated at 3.28 mg/L (ref 0.6-2.45).

A bone marrow examination was performed to rule out multiple myeloma. The aspirate and biopsy showed evidence of dyspoiesis, erythroid hyperplasia, and dysmegakaryopoiesis. Plasma cells were within normal limits (1.8-2%), and there was no evidence of granulomas, infiltration, or infection.

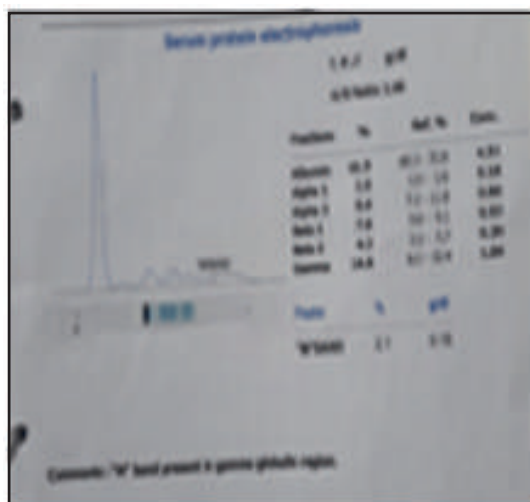


Image 7 : M-band in the gamma globulin region.

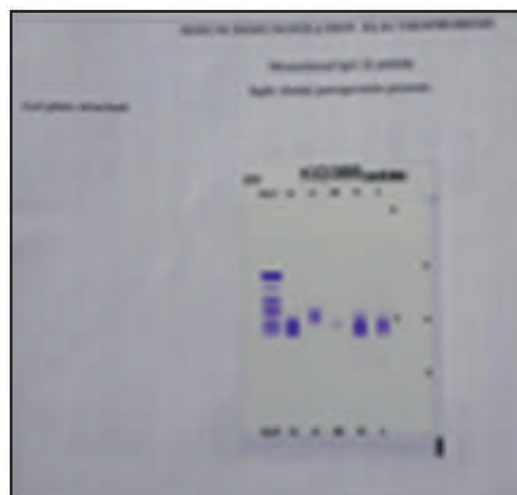


Image 8 : Confirmed the presence of a monoclonal IgG lambda paraprotein.

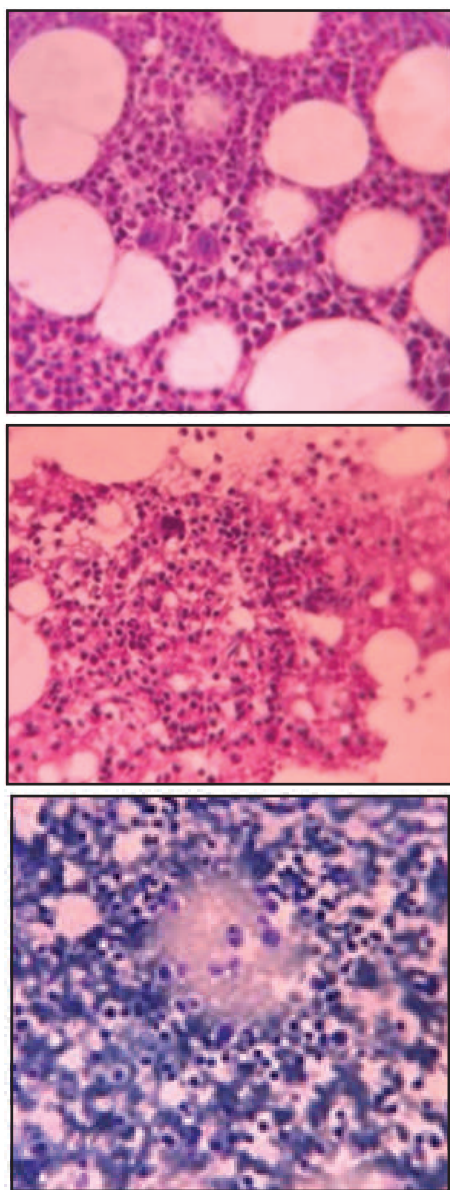


Image 9, Image 10, Image 11 : evidence of dyspoiesis, erythroid hyperplasia, and dysmegakaryopoiesis.

The final diagnosis was updated to multisystemic sarcoidosis with a concurrent Monoclonal Gammopathy of Undetermined Significance (MGUS). The diagnostic dilemma was whether

these were two separate disease entities or if the chronic inflammation from sarcoidosis had precipitated the plasma cell dyscrasia. The patient is currently under regular follow-up for both conditions, with surveillance for the potential progression of MGUS to multiple myeloma.

Discussion :

This case presents a remarkable convergence of rare manifestations and complications of sarcoidosis, offering valuable insights into the disease's diagnostic and management complexities. The discussion will focus on three key aspects of this case: the diagnostic challenge of neurosarcoidosis presenting as hyponatremia, the role of advanced imaging like FDG-PET in diagnosing multisystemic sarcoidosis, and the clinical significance of the subsequent development of MGUS.

Neurosarcoidosis, Hypopituitarism, and Hyponatremia :

Neurosarcoidosis is a chameleon of neurology, capable of mimicking a vast array of neurological disorders. Our patient's presentation with severe asthenia and recurrent hyponatremia ultimately pointed towards an endocrine etiology rooted in the central nervous system. The diagnosis of neurosarcoidosis involving the hypothalamic-pituitary region was established through a combination of clinical suspicion, biochemical evidence of panhypopituitarism, and characteristic MRI findings of pituitary stalk thickening and enhancement. This presentation is consistent with existing literature, which describes granulomatous infiltration of the pituitary stalk and hypothalamus as the primary mechanism of endocrine dysfunction in neurosarcoidosis.^[3, 4]

The hyponatremia in this patient was euvolemic and multifactorial. The primary driver was central

adrenal insufficiency, leading to impaired free water excretion due to the non-osmotic release of ADH. Central hypothyroidism likely contributed by reducing cardiac output and the glomerular filtration rate. While SIADH is a well-described cause of hyponatremia in neurosarcoidosis, often due to direct hypothalamic infiltration, the patient's inappropriately normal cortisol levels in the face of illness made adrenal insufficiency a more prominent factor. The dramatic resolution of hyponatremia following steroid and levothyroxine replacement therapy confirms the central role of these pituitary hormone deficiencies. This case underscores the critical importance of a thorough endocrine evaluation in any patient with sarcoidosis presenting with unexplained hyponatremia, as prompt hormone replacement is both diagnostic and life saving.

The Role of FDG-PET/CT in Diagnosing Multisystemic Sarcoidosis :

A definitive diagnosis of sarcoidosis typically requires histological confirmation of non-caseating granulomas.^[2] However, obtaining tissue from sites like the pituitary or heart is often high-risk and impractical. In such cases, a probable diagnosis is made based on a compatible clinical and radiological picture after excluding other granulomatous diseases. Our patient's clinical frailty precluded bronchoscopy, a common diagnostic procedure. This is where FDG-PET/CT played a pivotal role. FDG-PET/CT is an invaluable tool in sarcoidosis, particularly for identifying occult sites of active inflammation, assessing the extent of disease, and guiding biopsies.^[10] In this case, the PET scan provided crucial, non-invasive evidence of active inflammation in both the pituitary gland and the myocardium. The finding of cardiac

sarcoidosis was particularly significant, as it is a major cause of morbidity and mortality in sarcoidosis, often leading to heart failure, arrhythmias, and sudden death.^[11] The PET scan not only solidified the diagnosis of multisystemic sarcoidosis but also fundamentally altered the patient's management by identifying life-threatening cardiac involvement that required aggressive immunosuppressive therapy. This highlights the recommendation from expert consensus statements to use advanced imaging like cardiac PET or MRI for screening in patients with evidence of extracardiac sarcoidosis.^[11]

Sarcoidosis and Monoclonal Gammopathy: A Causal Link?

The development of MGUS six months after the initial diagnosis raises questions about the relationship between sarcoidosis and plasma cell dyscrasias. A growing body of evidence suggests that this association is more than coincidental.^[8] Sarcoidosis is characterized by profound immune dysregulation, including polyclonal B-cell activation and hypergammaglobulinemia, driven by a T-helper 1 (Th1) and Th17 cytokine milieu. It is hypothesized that this state of chronic antigenic stimulation and inflammation can, over time, promote the emergence of a malignant or premalignant plasma cell clone.^[6]

Studies have reported a higher prevalence of MGUS in patients with sarcoidosis compared to the general population.^[8] A study by Blanchard et al. found that patients with chronic inflammatory diseases, including sarcoidosis, had a significantly increased risk of developing MGUS.^[6] The persistently elevated ESR and development of anemia of chronic disease (with a component of iron deficiency) in our patient, even after initial treatment, were red flags that rightly prompted a workup for an underlying

plasma cell disorder. The bone marrow finding of dyspoiesis further complicates the picture, suggesting a more global impact on hematopoiesis, which can be seen in both chronic inflammatory states and clonal hematologic disorders.

The diagnosis of MGUS carries significant clinical implications. While benign, MGUS has a consistent risk of progression to multiple myeloma or other lymphoproliferative disorders at a rate of approximately 1% per year.^[7] Therefore, our patient requires long-term hematological surveillance, including regular monitoring of her M-protein levels and clinical status, in addition to the ongoing management of her sarcoidosis. This dual diagnosis complicates management, as the immuno-suppressive therapies used for sarcoidosis could potentially impact the immune surveillance of the monoclonal clone.

Conclusion : This case report details the complex clinical journey of a patient with multisystemic sarcoidosis, whose presentation was marked by

rare endocrine and hematological complications. It highlights several key learning points for clinicians. First, neurosarcoidosis should be a key differential in patients presenting with panhypopituitarism and recurrent euvoletic hyponatremia, particularly in the presence of other systemic inflammatory signs. Second, advanced imaging modalities like FDG-PET/CT are indispensable for the non-invasive diagnosis and assessment of disease activity in sarcoidosis, especially when biopsy is not feasible and for detecting high-risk organ involvement like cardiac sarcoidosis. Finally, clinicians should be aware of the recognized association between sarcoidosis and plasma cell dyscrasias. Persistent inflammatory markers or unexplained anemia in a patient with sarcoidosis should prompt an evaluation for an underlying monoclonal gammopathy. This case serves as a powerful reminder of the protean nature of sarcoidosis and the importance of a multidisciplinary, vigilant approach to managing its diverse and challenging manifestations.

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