International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

When Autoimmunity Masquerades as Plasma-Cell Dyscrasia: Castleman's Disease with POEMS Features in RA-Sjögren's Syndrome

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Abstract: ***Chronic autoimmune disorders such as rheumatoid arthritis (RA) and Sjögren's syndrome (SS) are marked by persistent immune activation and polyclonal B-cell proliferation. In rare instances, they may evolve into lymphoproliferative syndromes such as Castleman's disease (CD) or paraneoplastic entities like POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes). Differentiating reactive plasmacytosis secondary to autoimmunity from plasma-cell dyscrasias is diagnostically challenging yet critical for management. We report a 54-year-old woman with seropositive RA and secondary SS who developed anemia, splenomegaly, and lymphadenopathy with a monoclonal IgG-κ spike. Lymph-node histology revealed plasma-cell variant Castleman's disease, while bone-marrow evaluation and flow cytometry demonstrated polyclonal plasmacytosis without clonal restriction. The constellation of findings favored autoimmune-associated Castleman's disease with POEMS overlap. Recognition of such cytokine-driven reactive lymphoproliferation in autoimmune backgrounds is vital to prevent misdiagnosis as multiple myeloma and to direct appropriate immunomodulatory rather than cytotoxic therapy.***

Keywords: Rheumatoid arthritis; Sjögren's syndrome; Castleman's disease; POEMS syndrome; Reactive plasmacytosis; Plasma-cell dyscrasia; IL-6; Autoimmune lymphoproliferation.

1. Introduction

Rheumatoid arthritis (RA) and Sjögren's syndrome (SS) are systemic autoimmune diseases characterized by chronic antigenic stimulation, polyclonal hypergammaglobulinemia, and B-cell hyperactivity.[1,2] This persistent immune activation can, in rare circumstances, culminate in non-clonal lymphoproliferative disorders such as Castleman's disease (CD) or paraneoplastic syndromes like POEMS.[3] Castleman's disease, first described by Benjamin Castleman in 1956, represents a benign lymphoid hyperplasia driven by interleukin-6 (IL-6) overproduction and can present as a unicentric or multicentric disease. The plasma-cell variant of multicentric Castleman's disease (MCD) is particularly associated with autoimmune disorders and can mimic plasma-cell myeloma due to hypergammaglobulinemia and organomegaly.[5,6]

POEMS syndrome, on the other hand, is a multisystem paraneoplastic disorder arising from an underlying plasma-cell dyscrasia and characterized by elevated vascular endothelial growth factor (VEGF) levels, leading to widespread capillary permeability and organomegaly. Both entities—Castleman's and POEMS—may coexist or overlap in autoimmune settings, creating diagnostic ambiguity.[7]

Here we describe a 54-year-old woman with long-standing RA and secondary SS who developed anemia, splenomegaly, and a monoclonal IgG-κ spike. Evaluation revealed plasma-cell variant Castleman's disease with POEMS features but without clonal myeloma, highlighting the importance of comprehensive hematologic assessment in autoimmune patients presenting with lymphadenopathy and monoclonal bands.

2. Case Presentation

A 54-year-old female, first evaluated in October 2022 with features suggestive of rheumatoid arthritis and secondary Sjögren's syndrome, was subsequently diagnosed and managed for these autoimmune conditions. She was lost to follow up and non compliant to treatment, presented in July 2025 with progressive shortness of breath, fatigue, and a chronic non-healing ulcer over the left foot. Additionally, she complained of paresthesia in bilateral lower limbs suggestive of sensory neuropathy. She had intermittent joint swelling and sicca symptoms but no weight loss or night sweats. Past history included controlled hypertension and prior varicose-vein surgery.

First Admission (October 2022)
She initially presented with fatigue, black stools, and abdominal pain. Physical examination revealed pallor, bilateral parotid swelling, and mild hepatosplenomegaly. Laboratory evaluation showed hemoglobin 6.2 g/dL, ESR 101 mm/hr, and total protein 8.5 g/dL (albumin 3.4 g/dL, globulin 5.0 g/dL). CT abdomen revealed mild hepatosplenomegaly with multiple mesenteric and iliac lymph nodes, and ultrasound neck showed bilateral parotid cystic degeneration. A left external iliac lymph-node biopsy demonstrated preserved follicles with hyalinized germinal centers and dense interfollicular plasmacytosis (Figure 1).

Immunohistochemistry showed CD138-positive plasma cells without light-chain restriction. (Figure 2) A diagnosis of reactive plasmacytosis consistent with early plasma-cell variant Castleman's disease was made She improved with antibiotics and steroids and was discharged on hydroxychloroquine.

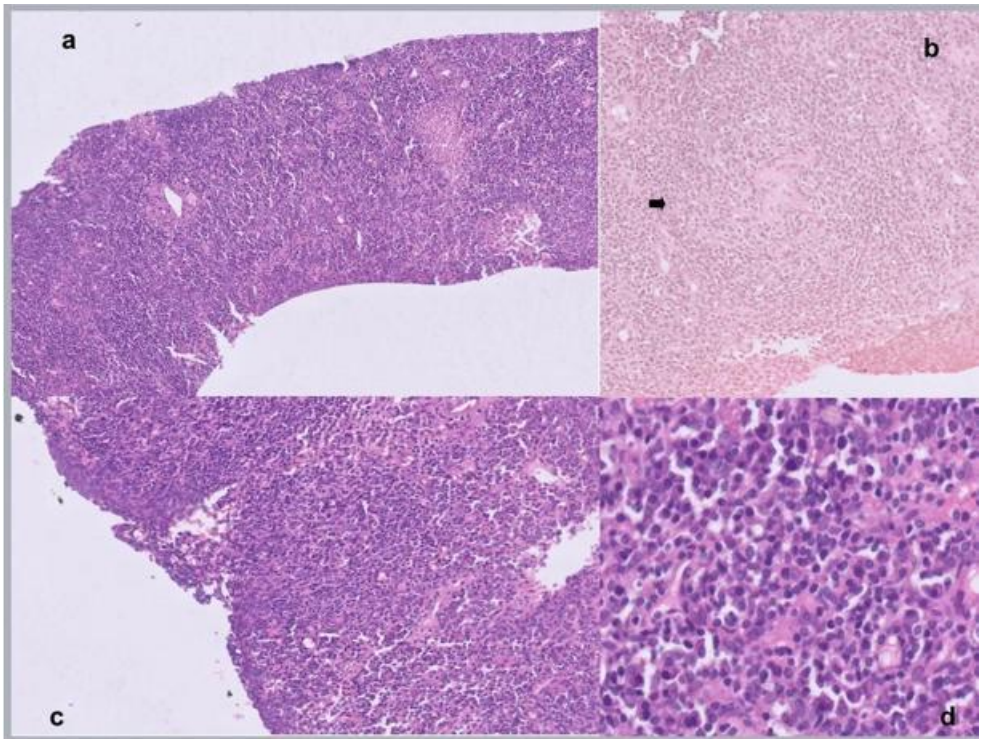


Figure 1: (a) Core Biopsy of the node shows paracortical expansion- H & E, 10x (b) Germinal Centre showing a hyalised vessel in the centre- H & E, 10x (c) The interfollicular zone show many plasma cells- H & E, 40x (d) Plasma cells- H & E, 40x

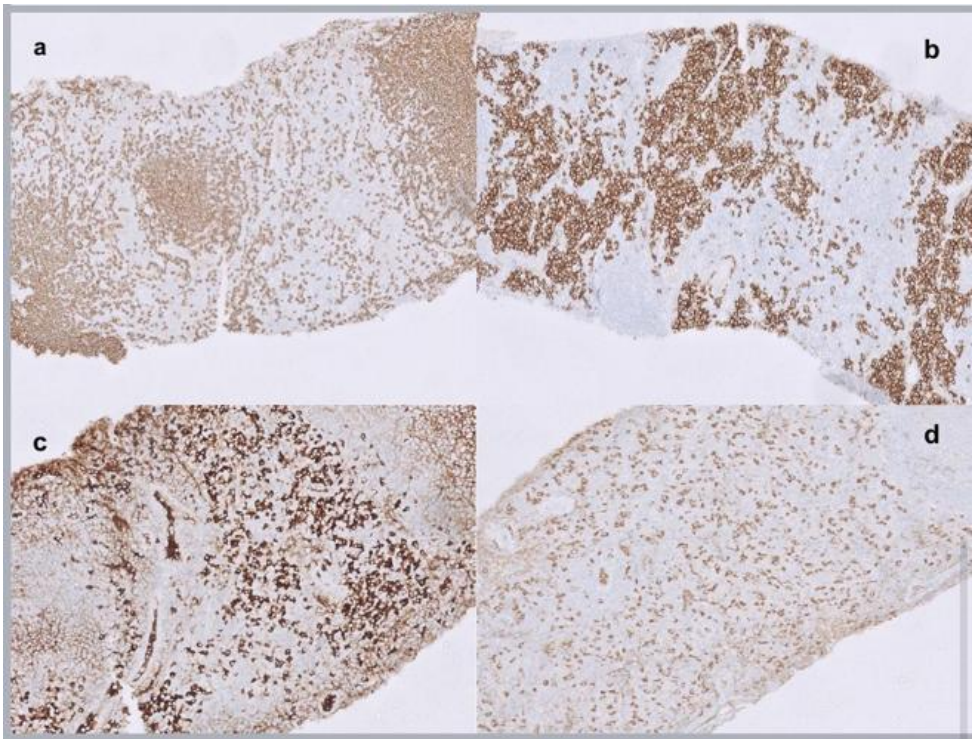


Figure 2: IHC (a) CD20 highlights the germinal centre (b) Many CD 38 positive plasma cells in the interfollicular zone (c) Kappa light chain and (d) Lambda light chain do not show light chain restriction

Second Admission (July 2025)

She presented with dyspnea, anemia, and worsening fatigue. Examination revealed pallor, mild hepatosplenomegaly, and a chronic ulcer on the left foot. There was no palpable lymphadenopathy. She was afebrile and hemodynamically stable.

3. Investigations

Table 1: Summary of Laboratory and Imaging Findings

Parameter	Oct 2022 (First Admission)	Jul 2025 (Second Admission)	Interpretation
Hemoglobin	6.2 g/dL	7.1 g/dL	Chronic inflammatory anemia
Total Leukocyte Count	$4.9 \times 10^3/\mu L$	$4.2 \times 10^3/\mu L$	Mild leukopenia
Platelet Count	$2.27 \times 10^5/\mu L$	$2.23 \times 10^5/\mu L$	Normal
ESR	101 mm/hr	103 mm/hr	Markedly elevated inflammation
Total Protein / Albumin	8.5 / 3.4 g/dL	8.36 / 3.56 g/dL	Hypergammaglobulinemia
Creatinine	1.44 mg/dL	1.66 → 1.54 mg/dL	Mild AKI; non-CRAB
β_2-Microglobulin	–	9.69 mg/L ↑	IL-6-mediated inflammation
LDH	–	228 U/L ↑	Mild rise; not neoplastic
RF / ANA	RF +, ANA 3+ speckled	RF +, ANA 3+	Autoimmune activity
Anti-CCP	Negative	Negative	
SPEP / Immunofixation	Polyclonal	IgG-κ M-band	Monoclonal band within reactive background
κ / λ Ratio	–	0.61	Polyclonal pattern
Urine	1+ protein	1+ protein, 25–30 RBC/hpf	Mild proteinuria and hematuria
Imaging	CT: hepatosplenomegaly, lymphadenopathy	Persistent hepatosplenomegaly	Suggestive of multicentric involvement
Lymph-node biopsy	Reactive plasmacytosis / Castleman's pattern	–	Plasma-cell variant Castleman's disease
Bone-marrow biopsy	–	Normocellular; 8–10 % plasma cells ($CD138^+$)	Reactive plasmacytosis
Flow cytometry	–	Polyclonal κ/λ; no abnormal clone	Excludes myeloma
Cytogenetics	–	46, XX (normal)	No clonal abnormality
Echocardiogram	Normal	Normal	No cardiac involvement
NCV	–	Demyelinating polyneuropathy	For POEMS evaluation
VEGF	-	980 pg/ml	Markedly elevated; cytokine-driven endothelial activation

Following the second admission, therapy was optimized toward **control of plasma cell hyperactivation and Castleman-like immune dysregulation** rather than only symptom management. The combination of **immunomodulators (hydroxychloroquine, folic acid, and low-dose corticosteroids)** likely mitigated the chronic autoimmune stimulus driving **IL-6–mediated plasmacytosis**. This, together with **antibiotic therapy (piperacillin-tazobactam followed by oral agents)**, reduced inflammatory cytokine load and secondary infection that perpetuated ulcer non-healing. **Daflon** further enhanced local venous and lymphatic drainage, improving tissue perfusion. On follow up, the attenuation of systemic immune activation and local ischemic stress, both **ulcer healing** and **constitutional symptoms** improved, reflecting a partial reversal of the **Castleman-like plasma cell activation state** rather than classic myeloma-type progression.

4. Discussion

The concurrence of rheumatoid arthritis (RA), secondary Sjögren's syndrome (SS), and plasma-cell variant Castleman's disease (PC-CD) represents an uncommon yet instructive intersection between chronic autoimmunity and benign lymphoproliferation.[1,2,3]

Castleman's disease, a non-clonal lymphoid hyperplasia driven by interleukin-6 (IL-6), is increasingly recognized as a potential downstream consequence of sustained autoimmune stimulation.[6] In RA and SS, persistent activation of autoreactive B-cells, high IL-6 and BAFF levels, and defective immune regulation perpetuate polyclonal plasmacytosis and hypergammaglobulinemia. Over time, this chronic immune activation can evolve into Castleman-like lymphoid proliferation, as reflected in our patient's iliac-node biopsy showing hyalinized germinal centers with dense interfollicular plasma-cell infiltrate and polyclonal light-chain expression.[8]

Such findings highlight that Castleman's disease in autoimmune hosts represents an IL-6–driven amplification of the same inflammatory pathways central to RA and SS.

The absence of light-chain restriction, polyclonal flow-cytometric pattern, normal cytogenetics, and lack of CRAB features (no lytic lesions, hypercalcemia, or renal cast nephropathy) confirm a reactive rather than neoplastic process such as multiple myeloma.[9]

This underscores the importance of multimodal correlation-clinical, histopathologic, and immunophenotypic- to avoid misclassification. Over-diagnosing myeloma in such patients leads to unnecessary cytotoxic therapy, whereas recognition of cytokine-driven pathology directs the clinician toward IL-6 blockade (siltuximab, tocilizumab) or B-cell depletion (rituximab), which are both effective and safer.[10]

The patient exhibited several hallmarks of POEMS syndrome—organomegaly, monoclonal gammopathy, elevated β_2-microglobulin, polyneuropathy and cutaneous changes[11,] It occurs due to representing partial expression of IL-6/VEGF-driven cytokine cascade that characterizes both Castleman's and classical POEMS.[12]

Bou Zerdan et al. (2023) reported a variant POEMS syndrome with typical VEGF elevation, organomegaly, endocrinopathy, and neuropathy but undetectable M-protein, highlighting that absence of monoclonal gammopathy should not preclude

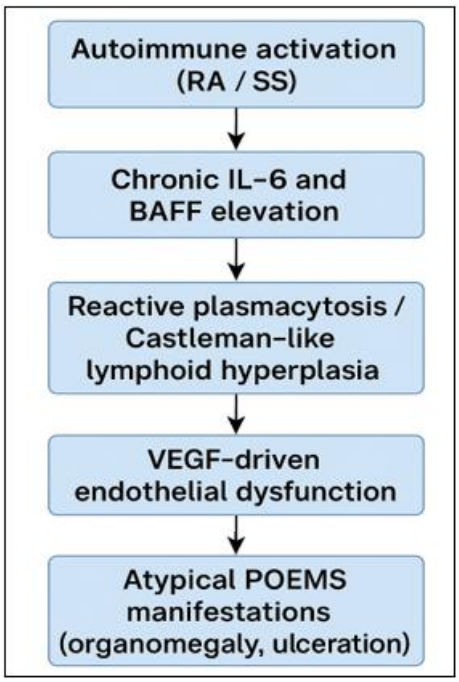
diagnosis when the clinical constellation and cytokine profile are characteristic.[13] Similarly, Khan AA et al. described a patient with Castleman's disease coexisting with multiple myeloma, successfully treated with bortezomib-based therapy, underscoring the pathogenic bridge between IL-6 overproduction and plasma-cell proliferation.[14] These reports validate that our patient, although lacking plasma cell dyscrasia but showing autoimmune polyclonal proliferation of plasma cells and M protein spike, lies within the same immunocytokine spectrum linking autoimmune inflammation, Castleman-like plasmacytosis, and POEMS.

VEGF overproduction, triggered by IL-6 and plasma-cell activation, increases vascular permeability, leading to edema, skin changes, and organomegaly. In this patient, the chronic lower-limb ulcer and venous stasis may reflect subclinical VEGF-mediated endothelial dysfunction, [15] Notably, Castleman Disease-associated POEMS variants are reported to have indolent courses and respond best to cytokine-modulating therapy rather than myeloma-directed regimens. VEGF-driven angiogenic imbalance,a hallmark of both Castleman's and POEMS- creates fragile, leaky microvasculature that resists normal healing leading to non healing ulcers.[13,15]

Varicose veins, also represent a cytokine-mediated degenerative process. Elevated IL-6 and VEGF levels have been implicated in venous wall remodeling, valve incompetence, and stasis ulceration.[16] Thus, in this patient, recurrent varicosities and the non-healing ulcer likely mirror systemic endothelial activation rather than isolated local disease. Their persistence despite prior surgical correction underscores the role of systemic inflammation as a perpetuating factor.

Inter-Relationship of Disorders: A Continuum, Not Coincidence

The relationship among these entities can thus be conceptualized as a progressive immune-vascular continuum:



5. Conclusion

This case highlights the intricate relationship between chronic autoimmunity, cytokine dysregulation, and vascular pathology. In a patient with long-standing rheumatoid arthritis and secondary Sjögren's syndrome, the emergence of plasma cell–variant Castleman's disease with atypical POEMS features demonstrates how persistent IL-6 and VEGF–driven inflammation can extend beyond conventional autoimmune boundaries, leading to systemic lymphoproliferation and endothelial dysfunction. The accompanying non-healing ulcer and recurrent varicose veins represent direct vascular consequences of this cytokine excess rather than incidental comorbidities.

A multidisciplinary approach involving rheumatology, hematology, dermatology, and vascular surgery was critical to integrate seemingly disparate findings- autoimmunity, venous ulceration, and monoclonal activity—into a unified cytokine-mediated pathophysiologic framework. Recognizing Castleman's disease as the central hub prevented misdiagnosis as plasma-cell myeloma and guided appropriate therapy. Continued autoimmune control with hydroxychloroquine and cautious corticosteroid use remains appropriate, while IL-6 receptor blockade should be considered for persistent inflammation or organomegaly. Local measures- rigorous wound care, compression therapy, and possibly anti-VEGF adjuncts—target the endothelial component contributing to poor ulcer healing.

Prognostically, autoimmune-associated Castleman's disease carries a favorable outcome when identified early and treated with cytokine-directed therapy. Nonetheless, 10–15 % of cases may evolve into lymphoma or myeloma, necessitating long-term surveillance with serum electrophoresis, β_2-microglobulin, imaging, and neurophysiologic studies. Venous stasis and recurrent ulceration should be interpreted as manifestations of sustained cytokine activity and monitored accordingly.

In summary, this case exemplifies that Castleman's disease, atypical POEMS, chronic ulceration, and venous changes may represent a single cytokine-driven spectrum linking IL-6–mediated immune activation and VEGF-induced vascular injury. Recognizing this continuum enables precise biologic therapy and integrated management, transforming fragmented symptom-based care into a unified, pathophysiology-oriented strategy that improves diagnostic clarity and patient outcomes in complex immune-vascular syndromes.

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