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Amyloidosis Unveiled During Evaluation of LRTI in a Case of Minimal Change Disease: An Underlying Monoclonal Gammopathy

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A 70-year-old female with a known diagnosis of nephrotic syndrome was initially managed based on renal biopsy findings consistent with minimal change disease (MCD). She was started on immunosuppressive therapy comprising oral prednisolone (initial dose 1 mg/kg/day tapered over several weeks) and tacrolimus (initiated at 0.05 mg/kg/day in two divided doses), to which she showed partial clinical response. Therapeutic drug monitoring (TDM) was undertaken periodically to maintain tacrolimus trough levels between 5–10 ng/mL, balancing efficacy with the risk of adverse effects, particularly infections.

Several months into therapy, she presented with symptoms suggestive of a lower respiratory tract infection (LRTI) including fever, productive cough, and breathlessness. Given the immunocompromised status, she underwent a detailed evaluation, which included chest X-ray and high-resolution CT (HRCT) scan of the thorax, sputum culture, blood cultures, and bronchoalveolar lavage (BAL) in view of persistent symptoms. Empiric antibiotic therapy with broad-spectrum coverage was initiated, which included piperacillin-tazobactam and azithromycin, later modified based on culture sensitivity reports. Fungal and mycobacterial workup including serum galactomannan and GeneXpert were also negative. Imaging studies performed as part of the evaluation revealed mediastinal lymphadenopathy. A right paratracheal lymph node biopsy was undertaken to rule out infective or malignant causes. Histopathological examination revealed amyloid deposits highlighted on Congo red staining.

This unexpected finding prompted further evaluation for systemic amyloidosis. Serum protein electrophoresis (SPEP) did not reveal 'M' spike. Serum free light chain (FLC) assay showed an abnormal kappa/lambda ratio of 0.07, with markedly elevated lambda light chains (375 mg/L) and suppressed kappa light chains (26 mg/L), suggestive of a lambda light chain clone. Urinary Bence-Jones proteins were not detected; however, 24-hour urinary protein quantification demonstrated nephrotic-range proteinuria (5.2 g/day). Serum albumin was reduced (2.5 g/dL), and serum cholesterol was elevated (352 mg/dL), consistent with ongoing nephrotic syndrome. Serum creatinine and electrolytes remained within normal limits.

In view of the confirmed amyloid and abnormal monoclonal protein studies, a skeletal survey was performed but did not reveal any lytic bone lesions. Hemogram showed mild normocytic, normochromic anemia (Hb 10.1 g/dL) with normal leukocyte and platelet counts. No abnormal cells were seen on the peripheral smear.

A bone marrow aspiration and biopsy were then performed and sent to our reference laboratory to assess for a possible plasma cell dyscrasia. The aspirate was cellular, with trilineage hematopoiesis and a myeloid-to-erythroid ratio of 1.56:1. Plasma cells were not increased (3% of nucleated cells) and no atypical or immature forms were noted. The biopsy revealed ~30% cellularity with normoblastic erythropoiesis and progressive myeloid maturation. Scattered mature plasma cells and lymphocytes were seen without clustering. Within the interstitium, amorphous, homogenous, eosinophilic material was noted on Hematoxylin and Eosin (H&E) staining. These deposits raised suspicion for amyloid (Figure 1). Subsequent Congo red staining confirmed the nature of the material, which displayed apple-green birefringence under polarized light microscopy, consistent with amyloid deposition (Figure 2).

To further rule out multiple myeloma, fluorescence in situ hybridization (FISH) analysis was performed on CD138-enriched plasma cells. The panel was negative for 1q21 gain, deletions of 13q14, 13q34, 17p13, and translocations t (11;14), t (4;14), and t (14;16), indicating absence of high-risk cytogenetic abnormalities.

This case highlights a complex diagnostic evolution from presumed minimal change disease (MCD) to systemic amyloidosis

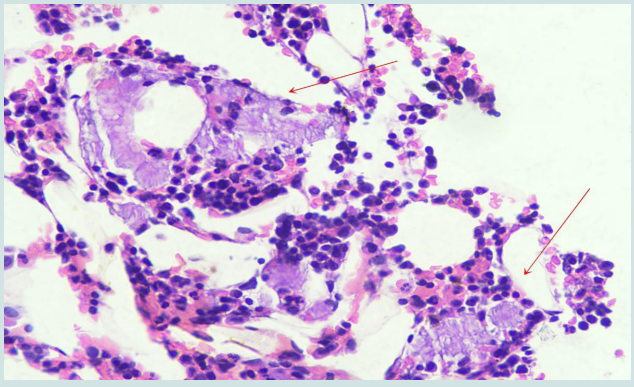

Figure 1: Bone marrow biopsy, Hematoxylin and Eosin Stain (x400) is cellular for age and shows amorphous, homogenous, eosinophilic material.

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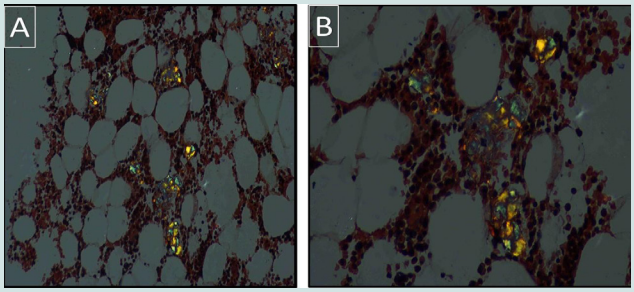

Figure 2: Bone marrow biopsy, congo red stain shows apple-green birefringence under polarized light microscopy. A) x200. B) x400.

secondary to a monoclonal plasma cell disorder in an elderly female patient. While MCD is typically steroid-responsive and more common in pediatric populations, its occurrence in older adults warrants careful evaluation, especially in cases with partial or atypical therapeutic response.

The subsequent discovery of mediastinal lymphadenopathy and biopsy-proven amyloidosis prompted reevaluation of the initial diagnosis. Systemic light chain (AL) amyloidosis often arises from an underlying plasma cell dyscrasia, such as multiple myeloma or monoclonal gammopathy of renal significance (MGRS), and is characterized by deposition of misfolded light chains in various organs. In this patient, renal involvement was evident from the persistent nephrotic syndrome and was later confirmed by Congo red-positive deposits in bone marrow biopsy.

A key aspect of this case was the diagnostic utility of serum free light chain (FLC) assay, which revealed a markedly elevated lambda chain concentration and an abnormal kappa/lambda ratio, despite a negative serum protein electrophoresis (SPEP). This underscores the limitations of SPEP in detecting light chain-only disease and the importance of incorporating FLC testing and immunofixation for comprehensive evaluation of suspected monoclonal gammopathies. Although Bence-Jones proteinuria was not detected, the elevated lambda chains and renal dysfunction suggest light chain–mediated renal injury.

The absence of classical features of multiple myeloma such as lytic bone lesions, hypercalcemia, or a high marrow plasma cell burden along with a negative FISH panel, supports the diagnosis of MGRS. MGRS represents a spectrum of clonal proliferative disorders that do not meet the criteria for multiple myeloma but still cause significant organ damage through deposition of monoclonal immunoglobulin components [1,2].

The identification of amyloid deposits in both lymph node and bone marrow, without overt systemic symptoms such as cardiomyopathy or hepatosplenomegaly, suggests an indolent yet progressive disease process. In elderly patients, atypical presentations of amyloidosis are not uncommon and can delay diagnosis. The association with MCD-like features on initial biopsy may reflect either an overlapping pathology or sampling limitations in a focal disease process.

Therapeutically, MGRS and AL amyloidosis are managed with regimens targeting the underlying plasma cell clone. Options include proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies such as daratumumab. Early treatment is crucial, as irreversible organ damage can ensue if amyloid deposition progresses unchecked [3,4].

In summary, this case highlights an unusual diagnostic sequence where mediastinal lymph node amyloidosis in a patient with MCD led to the diagnosis of an underlying monoclonal gammopathy. The findings are consistent with AL amyloidosis, possibly representing monoclonal gammopathy of renal significance (MGRS) in the absence of overt multiple myeloma.

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