Simultaneous Primary Biliary Cholangitis and Smoldering Multiple Myeloma: Etiologic explanations and therapeutic implications, case report and literature review

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INTRODUCTION

- Smoldering multiple myeloma (SMM) refers to the presence of > 10% of bone marrow plasmacytosis and > 30 g/L of M-protein level but no evidence of end-organ damage or amyloidosis.
- Primary biliary cholangitis (PBC) is an autoimmune disease associated with inflammation of the interlobular and septal bile ducts as well as the presence of anti-mitochondrial antibodies, eventually leading to liver cirrhosis.
- The simultaneous development of these 2 conditions has been reported in the literature. Several hypotheses and therapeutic implications have been put forward.

CASE PRESENTATION

- A 71-year-old-female was evaluated for asymptomatic abnormal LFTs. She had very slowly increased ALP (1191 U/L) , with mild elevation of AST (69 U/L and ALT (72 U/L) and normal bilirubin. She had no jaundice or pruritus.
- Testing to differentiate hepatic vs skeletal cause for the elevated ALP revealed mixed results. ALP skeletal isoenzyme and GGT were both elevated. NM bone scan and skeletal survey were was negative for bone disease. She had positive anti-mitochondrial antibody testing. Elevated total proteins was noted, and Plasma protein electrophoresis showed possible monoclonal protein.

FURTHER TESTING

- Serum immunoglobulin results included low IgA (41 mg/dL), IgG (698 mg/dL)) and IgM (<10 mg/dL)) with Elevated free kappa (849.6 mg/L) and free lambda (7.5 mg/L) with elevated free kappa to lambda ratio (113.28). Immunofixation showed possible monoclonal immuno-globulin.
- Hepatitis panel was negative. No associated anemia or renal dysfunction were noted.
- MRCP showed No evidence of intrahepatic or extra hepatic biliary ductal disease or any suspicious focal liver lesions.

MAKING THE DIAGNOSIS

- Bone marrow biopsy showed 40-50% kappa predominant plasma cells and variably cellular 30-60% erythroid predominant trilineage hemato-poiesis.
- Congo red stain was negative for amyloid with normal cytogenetics.

- Liver biopsy revealed marked cytokeratin 7 positive ductular metaplasia of periportal hepatocytes with mild periportal and sinusoidal fibrosis. Atypical portal and lobular infiltrates of lymphoplasmacytic cells with mild portal and central venulitis.

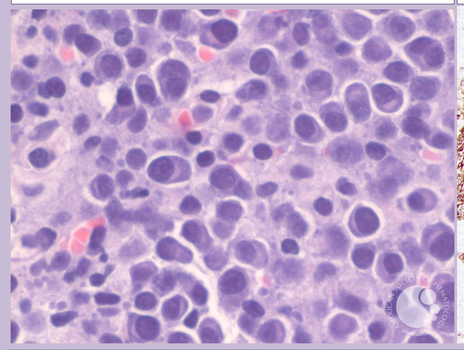

Image 1: Bone marrow biopsy of patient with MM.
Source: hematology.org

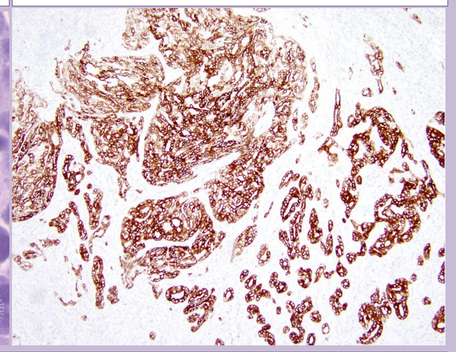

Image 2: Liver biopsy showing cytokeratin 7 positive staining of hepatocytes
Source: pathologyoutlines.com

Antibody	Result	Interpretation	Disease Association
Anti-M2 Mitochondrial IgG	45	Positive	PBC
Anti-Myeloperoxidase	<1.0	Negative	Glomerulonephritis
Anti-Proteinase-3	<1.0	Negative	Granulomatosis with polyangiitis
B2 Microglobulin	1.74	Negative	Multiple myeloma
ANCA	Neg	Negative	Autoimmune vasculitis
IgG-4 Subclass	14.5	Negative	Cystic fibrosis, vasculitis, cancer

Table 1. Patient's antibody testing with interpretation.

DISCUSSION & LIETRATURE REVIEW

- Several plausible explanations have been put forward to explain the simultaneous development of these 2 conditions:
  - Genetic *mutations*, especially t(4;14) resulting in FGFR3 overexpression. chromosome 1q21 *microdeletion* leading to overexpression of oncogenes CKS1B and SKP2, or single-nucleotide *polymorphism* affecting the HLA-DQB
  - Could PBC trigger the development of MM? Autoimmune diseases have been implicated in the pathogenesis of malignant lymphoproliferative disorders due to excess B and T cell activation. PBC is uniquely associated with impaired hepatic clearance of antigens.
  - Could MM trigger the development of PBC? Neoplastic proliferation of plasma cells in MM leads to the production of monoclonal immunoglobulin that deposit in the liver and biliary tree and can trigger an autoimmune response due to antigenic mimicry.
- Therapeutic implications:
  - While the current guidelines for managing SMM recommend observation as the first line treatment, understanding that the disease could be contributing to the pathogenesis of PBC can trigger early initiation of chemotherapy.
  - Due to the lack of definitive answers about the etiogenesis of this association, referral to specialized academic center and genetic testing is preferred.
- Case resolutions: Urodeoxycholic acid and chemotherapy VRD (bortezumab (Velcade), Lenalidomide (Revlimid), and Dexamethasone were initiated.

REFERENCES

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