Episode 47

Problem Representation
A 64-year-old woman recently treated for acute on chronic back pain presented with subacute altered mental status, found to have pancytopenia, kidney dysfunction, severe hypercalcemia, and a significant protein gap.

Schemas
This week's episode covered two schemas we addressed last season on the show - altered mental status (AMS) and hypercalcemia.

- The CPSers schema(s) for AMS (covered originally in Episode 1) introduced us to the “MIST” framework and also reminds us to consider mimics of altered mental status, such as aphasia and dysarthria.
- Many intriguing cases have featured hypercalcemia. This CPSers' approach from Episode 7 reminds us to use an endocrinologic approach, distinguishing initially between PTH-mediated and PTH-independent processes.

Diagnosis
Given the hypercalcemia, protein gap, and pancytopenia, the suspicion for multiple myeloma (MM) was high. Subsequent SPEP with immunofixation and bone marrow biopsy confirmed the diagnosis of IgG kappa MM.

Teaching points

- Multiple myeloma is a malignant disorder in which there is a clonal proliferation of plasma cells that produce a monoclonal immunoglobulin. Common manifestations include the “CRAB” findings (hypercalcemia, renal dysfunction, anemia, and bone disease). Myeloma bone disease[1] is typically characterized by lytic lesions and pathologic fractures. Interestingly, it is associated with alkaline phosphatase levels that are *not* elevated, due to a preferential activation of osteoclasts over osteoblasts.
- The workup for plasma cell disorders includes serum protein electrophoresis[2] (SPEP), immunofixation, and serum free light chains to help us identify if and which immunoglobulin component is being made in abundance. Addition of immunofixation and serum free light chains to SPEP alone increase the sensitivity to 97%.
- Clonal plasma cell disorders exist on a spectrum:
    - **Monoclonal gammopathy of undetermined significance** (MGUS) is defined by an M-spike of < 3g/dL, < 10% monoclonal plasma cells on bone marrow biopsy, and the absence of CRAB findings.
    - **Smoldering multiple myeloma** is diagnosed when there is an M-spike of > 3g/dL or 10-60% monoclonal plasma cells on bone marrow biopsy, but end-organ damage (CRAB criteria) is absent.
    - **Multiple Myeloma**[3] is diagnosed when there is > 60% of the bone marrow are monoclonal plasma cells, or 10-60% but with CRAB findings, or when the free light chain (FLC) ratio (of kappa to lambda, or lambda to kappa) is equal to or greater than 100, provided the involved FLC is 100 mg/L or more.

Clinical Reasoning Pearl

A constant struggle in interpreting data is separating ‘signal’ from ‘noise’, recognizing that not all of our data will be diagnostically fruitful. It can be helpful to pause to ask ourselves, "Does the finding make sense in the context of our case?"

<u>For example:</u>
Our patient was recently prescribed muscle relaxants and steroids, and it was tempting to prematurely close on this as the cause of her confusion. However, the finding of hypercalcemia better explained the patient's presentation.

References

1. Papadopoulou EC, Batzios SP, Dimitriadou M, Perifanis V, Garipidou V. Multiple myeloma and bone disease: pathogenesis and current therapeutic approaches. Hippokratia. 2010 Apr;14(2):76-81.
2. O'Connell TX, Horita TJ, Kasravi B. Understanding and interpreting serum protein electrophoresis. Am Fam Physician. 2005 Jan 1;71(1):105-12.
3. Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. Am Soc Clin Oncol Educ Book. 2016;35:e418-23.