abnormal proteins *(5)*. For most applications, viscosity is measured in the serum or plasma component of blood. Serum viscosity is measured in our laboratory using a Cannon-Manning semi microviscometer at 37 °C. The flow of patient's sample is compared to the flow of Type I deionized water at the same physical conditions.

IgM is the immunoglobulin most commonly associated with HVS, partly owing to the large size of the IgM pentamer (925 kDa). It is worth noting however that only about 10%–30% of patients with increased IgM develop HVS *(5)*. Thus, other idiosyncratic features of immunoglobulins may be involved in development of HVS. IgG and IgA are less common causes of HVS and typically require concentrations in excess of 10 000 mg/dL and 7000 mg/dL, respectively, to manifest symptoms of HVS *(5, 10)*.

Severe HVS may cause reduction in cerebral blood flow, leading to symptoms such as confusion, dizziness, stroke, or coma *(5)*. HVS along with hypercalcemia likely explains the altered mental status, gait instability, and slurring of speech seen in this patient *(1, 5)*.

Therapeutic plasma exchange is the standard of care in the initial management of HVS. Definitive management for HVS is treatment of the underlying etiology *(5)*.

POINTS TO REMEMBER

- Manifestations of hypercalcemia include nausea, vomiting, abdominal pain, polydipsia, polyuria, and lethargy. More severe hypercalcemia may lead to confusion, altered mental status, gait instability, and coma.
- The 2 most common causes of hypercalcemia are primary hyperparathyroidism and malignancy.
- Multiple myeloma leads to increased protein concentration in the blood, which may cause HVS. HVS is managed initially by plasma exchange and definitively by treatment of the underlying etiology.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

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Commentary

Christopher R. McCudden*

Hyperviscosity syndrome (HVS) results in impaired blood flow through the microvasculature. This can cause end organ damage and often manifests with bleeding (e.g., spontaneous gingival bleeding or epistaxis) and neurologic abnormalities (e.g., paresthesias and visual disturbance). In this case, the authors identify that the neurological findings may have been exacerbated by the combination of hypercalcemia and HVS. The findings of rouleaux are also common to myeloma and HVS. From an analytical standpoint, it can be helpful to be aware of HVS and how it can affect instrumentation. Specifically, highly viscous samples are difficult to pipette. This would be noticeable to a technologist who pipettes such samples

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manually, or it could manifest as repeated error flags on automated instrumentation. Awareness and communication of viscosity findings to the clinical team may facilitate earlier diagnosis of HVS.

The diagnostic workup for this case involved measurement of parathyroid hormone-related protein (PTHrp) and parathyroid hormone (PTH). Interpretation of PTH results in combination with calcium is helpful (e.g., using a PTH nomogram). For example, high calcium with an increased PTH is consistent with primary hyperparathyroidism, whereas hypercalcemia in concert with suppressed PTH concentrations, as occurred in this case, points to PTH-independent hypercalcemia. PTHrp is often used inappropriately as a screening test for malignancy in the context of hypercalcemia. As the authors state, the dogma that PTHrp is increased in most malignancies has been disproven, yet orders for PTHrp abound. It has been recommended that sequential testing of PTHrp after confirmation of hypercalcemia and suppression of PTH is the most efficient approach *(1)*, as PTHrp alone has poor sensitivity (approximately 30%) for malignancy. In this case, PTHrp measurement is unlikely to have affected patient treatment given the diagnosis of myeloma with the presence of multiple lytic bone lesions.

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Commentary

David L. Murray*

The authors present an illustrative case of multiple myeloma (MM) that presented as symptomatic hypercalcemia. Although hypercalcemia is part of the "CRAB" diagnostic criteria (increased calcium level, renal dysfunction, anemia, and destructive bone lesions), symptomatic hypercalcemia is not a common presentation of MM. In a study of patients presenting with MM, anemia was present initially in 73% of patients, hypercalcemia (total calcium ≥11 mg/dL) in 13%, and a serum creatinine concentration ≥2 mg/dL in 19% *(1)*. In addition, most cases of hypercalcemia were not symptomatic but documented only on clinical suspicion of MM. Hence, it may be easy for clinicians to not associate symptomatic hypercalcemia with MM. The coexistent hyperviscosity syndrome, also a less common finding, most likely exacerbated the patient's symptoms. There are several clues presented in this case that should trigger suspicion of malignancy: the history of weight loss, symptomatic anemia, and the increased κ free light chains >100 mg/dL. As the authors point out, a decreased anion gap can also be a good clue for the presence of high concentration M protein. There are only a few causes for a decreased anion gap, with the 2 most common causes being hypoalbuminemia and high immunoglobulin concentrations. In a patient with increased total proteins, a decreased anion gap is a good indicator of an underlying plasma cell disorder. Lastly, this case highlights that MM typically presents without a prior diagnosis of monoclonal gammopathy of undermined significance when multiple studies have shown that multiple myeloma is consistently preceded by it *(2)*.

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