

Hyperviscosity Syndrome in Patients With Multiple Myeloma

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A.W., a 50-year-old woman with a six-month history of frequent nosebleeds, was diagnosed with multiple myeloma. Before A.W. could meet with an oncologist, she presented to the emergency room with an uncontrollable nosebleed and spontaneous bleeding in her gums. Her menstrual period, which usually occurs over five or six days, lasted 10 with unusually heavy flow. A.W. also reported prolonged bleeding from cuts but had not noticed petechiae or unusual bruising. She was not taking anticoagulants, such as aspirin or other nonsteroidal anti-inflammatory medications. She felt fatigued and noticed that her blurry vision was getting worse. A.W.'s husband characterized her short-term memory as sluggish, although he did not think she was confused. A.W. also complained of lower back pain that limited her ability to perform usual activities.

The emergency room team determined that A.W. was anemic, with a hemoglobin of 9.1 g/dl, a hematocrit of 30.5 g/dl, and a platelet count of 135,000 per ml. Her serum chemistry values showed hyponatremia (sodium = 123 meq/l, normal range 136–143 meq/l), blood urea nitrogen 26 mg/dl (normal range = 7–20 mg/dl), creatinine 1.3 mg/dl, hypercalcemia (calcium = 8.7 mg/dl, normal range = 8.5–10.5 mg/dl), and hyperproteinemia (total protein = 12.5 g/dl, normal range = 6.5–8.2 g/dl). Her liver and thyroid function tests were normal. A.W.'s prothrombin time was 13.4 sec-

onds, activated partial thromboplastin time 33 seconds, international normalized ratio 1.3 (normal range = 0.7–1.2), and fibrinogen 144 mg/dl (normal range = less than 250 mg/dl). Quantitative immunoglobulins showed an elevated immunoglobulin G (IgG) (11,200 mg/dl, normal range = 620–1,400 mg/dl), but immunoglobulin A (IgA), immunoglobulin D (IgD), and immunoglobulin M (IgM) levels were within the normal range. Serum viscosity level was 4.7 centipoise (cp) (normal range = 1.4–1.8 cp).

A physical examination revealed a thin woman in no acute distress. Vital signs were stable: temperature 37.1°C, blood pressure 108/70 mmHg, pulse 90 beats per minute, respiration 20 breaths per minute, and oxygen saturation 93% on room air, 88% with exertion. The fundoscopic examination revealed peripheral retinal vein hemorrhages. Oral mucosa showed blood oozing from her upper and lower gingivae. Dried and crusted blood was found bilaterally along her nasal mucosa, but A.W. was not actively bleeding. Her neurologic examination was nonfocal. On the Mini Mental State examination, A.W. was unable to recall the three objects she was asked to remember. She was oriented to time, place, and person, and her skin was warm and dry and without petechiae, purpura, or ecchymoses.

A.W. was given normal saline IV at 150 cc per hour and oxygen at 2 L by nasal cannula. She also was given furosemide 20 mg IV. An ear, nose, and throat examination did not

reveal any active bleeding, but a prominent blood vessel seen running along the floor of the left nostril was noted. Various areas with prominent submucosal blood vessels but no evidence of active bleeding were seen on the right nostril. No masses or lesions were noted in either nostril, nasal septum, or nasopharynx. An ophthalmologic examination found midperipheral hemorrhages and vascular tortuosity in the retinae. A fluorescein angiogram revealed moderate delay of transit time in the retinal veins, indicative of hyperviscosity. The healthcare team decided to correct A.W.'s underlying disorder immediately; therefore, she was sent for plasma exchange. After the third plasma exchange, A.W.'s IgG level was down 50% to 5,550 mg/dl and her serum viscosity level dropped to 2.9 cp. In addition, her serum calcium, sodium, and total protein levels normalized. A.W.'s nosebleeds resolved, and her memory and vision improved.

What are the key assessments in patients with multiple myeloma?

The initial assessment of patients presenting with multiple myeloma include determining the type of myeloma (IgA, IgG, or IgD). Quantitative immunoglobulins, serum protein electrophoresis, urine protein electrophoresis, and the percentage of bone marrow involvement should be included in the initial workup. Screening patients for the presence of an M-protein, if they present with signs or symptoms of hyperviscosity syndrome, is prudent (Cook & MacDonald, 2007). A complete blood count with differential is necessary because patients

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with multiple myeloma usually present with anemia. A chemistry panel will assess for hypercalcemia and hyperproteinemia, both commonly seen in multiple myeloma. Assessing for fatigue level, performance, and respiratory and mental status is helpful. Increased pain level and grade of neuropathy also are common symptoms of multiple myeloma.

What are the clinical manifestations of hyperviscosity syndrome?

Neurologic abnormalities, vision changes, and mucosal bleeding are the three primary clinical manifestations of hyperviscosity syndrome (Ghobrial, Gertz, & Fonseca, 2003). Mucosal bleeding from gingivae, nares or nasal septum, gastrointestinal, and occasional ureteral or vaginal bleeding may be present. Vision abnormalities include diplopia, retinal vein thrombosis and tortuosity, papilledema, and retinal hemorrhage. Headache, syncope, seizure, cerebral hemorrhage, ataxia, and coma are common neurologic abnormalities (Ghobrial et al.). The clinical presentation of hyperviscosity syndrome is not limited to these classic signs. Patients also may present with dyspnea, chest pain, pulmonary edema, or congestive heart failure as a result of increased plasma volume (Kundu, Dey, & Sengupta, 2003). Acute renal failure and stroke also have been reported (Wong, Mak, Lo, Tong, & Wong, 2000). Sensorineural hearing loss has been reported and is caused by increased resistance of blood flow or thrombus formation in the middle ear (Syms, Arcila, & Holtel, 2001).

How is hyperviscosity syndrome diagnosed?

Hyperviscosity syndrome should be suspected in a patient who presents with neurologic abnormalities, vision changes, and mucosal bleeding in combination with known plasma cell dyscrasia. Several tests or laboratory values support a hyperviscosity syndrome diagnosis. Complete blood count is helpful because anemia is common in patients with hyperviscosity syndrome. Hyperproteinemia, pseudohyponatremia (caused by an elevated protein level), and hypercalcemia also are commonly seen in patients with hyperviscosity syndrome. A peripheral blood smear with rouleaux formation (appearance of red blood cells resembling a pile of coins) also may suggest hyperviscosity (Rampling, 2003). Hyperviscosity syndrome is considered present when viscosity levels reach 4–5 cp (normal level = 1.4–1.8 cp) (Mehta & Singhal, 2003). The correlation between serum viscosity levels and symptoms may not be consistent from patient to patient as some can be asymptomatic even with high serum viscosity. Patients with a serum viscosity less than

4 cp may not have symptoms of hyperviscosity syndrome.

Symptoms of hyperviscosity syndrome also occur when levels reach 4,000 mg/dl for IgM, 5,000 mg/dl for IgG, and 70 gm/dl for IgA (Park et al., 2005). A.W.'s symptoms developed when her serum viscosity level reached 4.7 cp and 11,200 mg/dl IgG.

What is the immediate and long-term treatment for hyperviscosity syndrome?

Symptomatic hyperviscosity syndrome requires emergency treatment. Aggressive IV hydration with diuresis and plasmapheresis relieves symptoms, reduces the blood protein concentration, and restores homeostasis (Drew, 2002). Because of increased plasma volume in patients with hyperviscosity, diuretics, such as furosemide, prevent fluid overload.

Automated plasma exchange (plasmapheresis) reduces the viscosity of the blood by decreasing immunoglobulin concentration (Zarkovic & Kwaan, 2003). Plasmapheresis can be used as short-term treatment in conjunction with other systemic treatments. Usually one or two plasma exchanges will result in dramatic improvement, as seen in A.W.'s case. Long-term use is reserved for adults older than 65 years, those with severely compromised performance status (a performance level greater than 2 on the Eastern Cooperative Oncology Group scale), and chemotherapy-naïve patients (Mehta & Singhal, 2003). Patients with anemia requiring blood transfusions should have plasmapheresis first to avoid fluid overload (Ghobrial et al., 2003).

The long-term management of hyperviscosity syndrome is directed at controlling the underlying disease. In multiple myeloma, treatment usually includes systemic chemotherapy alone or in combination with steroids and an eventual stem cell transplantation (National Comprehensive Cancer Network, 2007).

What are the nursing implications in caring for patients with hyperviscosity syndrome?

Hyperviscosity syndrome is an oncologic emergency that, if not managed promptly and appropriately, could lead to multiple-organ failure. Nurses often are the first healthcare providers to assess patients and they should be aware of the signs and symptoms of hyperviscosity syndrome so they can immediately triage patients for further care.

When the patient is stable, the nurse's role should be support and education. Nurses can act as patient advocates to ensure that patients are well informed about the illness and treatment. Nurses should facilitate patient discussions with the hematologist regarding treatments and available options.

Because care for hyperviscosity syndrome involves treating the underlying disease, patients must understand that they need further treatments after hyperviscosity has resolved. Patients must be educated on how to manage their symptoms during treatment. Patients with multiple myeloma, whether receiving treatment or not, need close monitoring of paraprotein, immunoglobulin, chemistry, and complete blood count levels (National Comprehensive Cancer Network, 2007). Nurses should encourage patients to be clinically evaluated for any signs of disease relapse, progression, or complications.

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Clinical Highlights: Hyperviscosity Syndrome in Patients With Multiple Myeloma

Definition

Hyperviscosity syndrome is the term used to describe the clinical signs and symptoms related to increased blood viscosity. Hyperviscosity is defined on the basis of the relative viscosity of blood compared to water (Park et al., 2005), with normal serum viscosity level 1.8 centipoise (cp).

Incidence

Approximately 50,000 Americans have multiple myeloma, with 19,900 new diagnoses in 2007 (Jemal et al., 2007). The disease is more common in men than women, and more common in African Americans than other ethnic groups. Hyperviscosity syndrome is a rare complication of multiple myeloma that occurs in about 2%–6% of patients, most frequently in immunoglobulin G (IgG) myeloma, with a reported incidence of 4.2% (Park et al., 2005).

Pathophysiology

Increased viscosity in patients with multiple myeloma is the result of increased circulating serum immunoglobulins produced by abnormal plasma cells. Immunoglobulins are large, asymmetric molecules with high carbohydrate content (Rampling, 2003), and most are found circulating in the bloodstream. When the concentration is increased, aggregate formation and binding to water occur, resulting in increased osmotic pressure, increased resistance to blood flow, and impaired transit through the microcirculation. Immunoglobulins also interact with red blood cells, increasing their internal viscosity and reducing their deformability (i.e., the ability of the red blood cells to change shape as they pass through a narrow channel). The outcome is vascular stasis and hypoperfusion of tissues, which, in turn, lead to tissue damage. Myeloma immunoglobulins also interfere with platelet function (Rampling).

Risk Factors

A diagnosis of multiple myeloma and elevated immunoglobulin levels are risk factors for hyperviscosity syndrome. Signs and symptoms of hyperviscosity usually occur when the viscosity level reaches 5–6 cp, levels usually reached at concentrations of approximately 40 g/L for immunoglobulin M (IgM), 50 g/L for IgG, and 70 g/L for immunoglobulin A (IgA) (Park et al., 2005). Patients who are refractory to treatment of the underlying disease also are at risk for developing hyperviscosity syndrome.

Clinical Presentations

Hyperviscosity syndrome presents with the clinical triad of mucosal bleeding and visual and neurologic abnormalities. Mucosal bleeding results from prolonged bleeding time caused by myeloma proteins interfering with platelet function. Bleeding usually occurs in the nose, gastrointestinal tract, gingivae, vagina, and uterus. Visual abnormalities are a result of the vascular stasis and include diplopia, retinal vein thrombosis, papilledema, and retinal hemorrhage. Classic findings on fundoscopic examinations in patients with hyperviscosity are dilation (or engorgement) and tortuosity of veins, referred to as fundus paraproteinaemicus (Chiang, Begley, & Henderson, 2000). If hyperviscosity is not promptly managed or treated, retinal vein occlusion, flame-shaped hemorrhages, microaneurysms, or proteinaceous exudates may occur. Changes in the retinal vein can lead to blurring, decreased visual acuity, and blindness if hyperviscosity syndrome is not properly managed. Neurologic manifestations include headache, dizziness, vertigo, ataxia, encephalopathy, or altered mental status, particularly delirium. The clinical signs and symptoms in patients with multiple myeloma may be caused by electrolyte abnormalities, such as hypercalcemia and hyponatremia, or intracerebral vascular occlusion as a result of increased immunoglobulins (Park et al., 2005). Neurologic changes in patients with multiple myeloma must be investigated thoroughly to determine the underlying cause. Coma, which is an extreme presentation of hyperviscosity syndrome, can occur if treatment is not initiated immediately (Chiang et al.).

Clinical manifestations of hyperviscosity syndrome are not limited to this triad. Cardiopulmonary symptoms, such as dyspnea and chest pain, have been reported (Kundu, Dey, & Sengupta, 2003). Renal insufficiency or failure also has been observed (Wong, Mak, Lo, Tong, & Wong, 2000).

Differential Diagnoses

The differential diagnoses include hemorrhagic and ischemic stroke, congestive heart failure, pulmonary edema, and diabetic ketoacidosis (Hemingway & Savitsky, 2007).

Treatment

Hyperviscosity syndrome is managed with plasma exchange followed by prompt chemotherapy institution (Cook & MacDonald, 2007). Multiple myeloma is considered a highly treatable but rarely curable disease, with systemic chemotherapy as the treatment of choice. An example of possible combina-

tion chemotherapy is cyclophosphamide, vincristine, doxorubicin, and dexamethasone. Oral agents such as thalidomide and lenalidomide also are effective agents for multiple myeloma (Cook & MacDonald). Local radiotherapy is indicated for treatment of skeletal disease or plasmacytomas. New agents, such as bortezomib, have shown promise (Colson, Doss, Swift, Tariman, & Thomas, 2004). Autologous stem cell transplantation is now standard therapy for patients younger than 75 (National Comprehensive Cancer Network, 2007).

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