CLINICAL VIGNETTE

IgG Lambda Myeloma in a Young Man Presenting with Acute Renal Failure

Rietta Goodglick, MD and Michael E. Lazarus, MD

A 41-year-old white male with a prior medical history of insulin dependent diabetes and hypertension was admitted from outpatient clinic with nausea, emesis, back pain and an elevated creatinine level above his baseline. He works as a correctional officer and noted back injury about six months prior while transferring a patient off a stretcher. Over the past month, his back pain flared intermittently with moderate exercise. He described the pain as sharp and radiating down his back into his bilateral buttocks. He denied any weakness in his lower extremities and had no bowel or bladder incontinence. His pain improves with ibuprofen, up to 600 milligrams every six hours and methocarbamol. He had obtained the most relief from 30 mg ketorolac injections administered at two separate visits to his local emergency department over the last two weeks. He controls his diabetes with daily injections of insulin glargine. He has no known complications of diabetes including neuropathy, nephropathy or retinopathy. He is compliant with his diabetic diet but has not exercised regularly for several months due to back pain. His weight increased over the past year with current body mass index of 31 kg/m^2. Family history is significant for diabetes mellitus in both parents. He has no personal or family history of malignancy and denies alcohol, tobacco or illicit drug use. In the emergency department, he was alert and oriented. On physical exam, his vital signs were normal but his mucus membranes were dry. His cardiac, lung and abdominal exam was unremarkable. His strength and sensation was intact and he was able to raise both lower extremities without exacerbation of his back pain. He had point tenderness over his lumbar spine. His nausea and vomiting improved with eight milligrams of intravenous ondansetron and he received two liters of intravenous saline. Labs were remarkable for a creatinine of 3.7 mg/dL from a baseline of 1.1 mg/dL one year prior. His blood urea nitrogen was 53 mg/dL; his potassium 3.7 mmol/L; sodium 130 mmol/L; albumin 3.0 g/dL, total protein of 11.9 g/dL (5.9-8.3). His hemoglobin was 9.9 g/L with a mean corpuscular volume of 87.8 fL, a ferritin of 2142ng/ml (<322) was observed. His calculated anion gap was zero. He had an elevated white cell count (11.50×109/L) and a neutrophilia (10.19×109/L) with a raised C reactive protein (235.3 mg/L) and erythrocyte sedimentation rate ESR of 74. Urine microscopy was notable for scattered renal tubular epithelial cells, cellular casts and urine eosinophils were 19%. His corrected calcium level was 13.9 mg/dL with ionized calcium of 1.8. His beta-two-macroglobulin was 4.56 mg/dL (<2.52). Serum quantitative immunoglobulin analysis revealed a very elevated IgG lambda of 7160 mg/dL (313-723mg/dL). His serum immune fixation revealed IgG Lambda monoclonal band. Urine protein electrophoresis was notable for trace protein, positive albumin, an IgG Lambda monoclonal band, and light chains within the normal range. HIV and Hepatitis B serology was negative. On ultrasound, the right kidney measured approximately 12.5 cm while the left kidney measured 13 cm. The renal parenchymal echogenicity appeared mildly increased, suggestive of medical renal disease. There was no hydronephrosis. He underwent kidney biopsy consistent with acute tubular injury with some deposition of calcium phosphate crystals and rare intraluminal casts which partly stained for lambda light chains. Computed tomographic scan of his thoracic spine was significant for a small abnormality in T12 described as a "chronic superior endplate deformity". After admission, he continued to have episodes of emesis and his creatinine continued to rise to a peak of 6.1. The patient received 45 mg of pamidronate and two doses of calcitonin. His positron emission tomogram (PET) was remarkable for diffuse osteopenia and small lytic lesions throughout the axial/appendicular skeleton associated with a diffuse pattern of increased ^{18}F-fluoro-deoxyglucose (FDG) uptake throughout the bone marrow, consistent with diffuse bone marrow plasma cell infiltration as well as compression deformities of T12 through L5 vertebral bodies. Bone marrow aspirate and biopsy from the right posterior superior iliac spine revealed lambda light chain restricted monotypic plasma cells (22% of the total), no excess blasts, no monotypic B-cell populations nor any discrete pan T-cell aberrancy. Congo red stain was negative for amyloid. He was diagnosed with IgG lambda myeloma and started on a treatment regimen called "CyBorD". Cyclophosphamide, Bortezomib, and Dexamethasone given over a twenty-eight-day cycle. He started on acyclovir for prophylaxis. His renal insufficiency was thought to be secondary to hypercalcemia of malignancy, excess non-steroidal anti-inflammatory use, and acute tubular necrosis ATN from calcium phosphate deposits. His creatinine and serum calcium levels significantly improved at discharge and he was scheduled for follow up with nephrology and oncology.

Discussion

Multiple myeloma (MM) results from the neoplastic transformation of plasma cells. These cells produce monoclonal immunoglobulins. Ongoing proliferation within the bone marrow, usually results in extensive skeletal osteolytic lesions, osteopenia, and in advanced cases pathologic fractures. MM accounts for 1 to 2 percent of all cancers and roughly seventeen percent of hematologic malignancies.[1] It is more common in men and those of African American descent. Approximately

13,000 deaths/year are attributed to MM in the United States.[2] This correlates with an annual incidence of approximately seven per 100,000 men and women per year.[3] Mean age at presentation is seventy, but 36 percent are under sixty-five years. The risk of MM increases with body mass index.[4] There is an association between Agent Orange exposure and MM.[4] The diagnosis of MM is suspected when one (or more) of the following clinical findings occur at presentation: Increased serum creatinine level, renal insufficiency, anemia and bone lesions. (CRAB)[5]. All four were present on admission in our patient. Given the non-specific nature of this quartet, these factors must be related to an underlying plasma cell proliferative disorder to make the diagnosis. More specific clinical presentations include increased total serum protein concentration and/or the presence of a monoclonal protein in the urine or serum; hypercalcemia, can be either symptomatic or discovered incidentally. Systemic signs or symptoms suggestive of malignancy (unexplained anemia), and bone pain with lytic lesions discovered on routine skeletal films or other imaging modalities. Interestingly as in our case, MM-related bone pain as a presenting complaint occurs in approximately sixty percent of patients. Pain typically involves the central skeleton and is induced by movement.[6] Positron emission tomography (PET/CT), and magnetic resonance (MRI) have a higher sensitivity than skeletal surveys for detection of bone lesions and enables earlier detection which improves prognosis.[7] MRI is the most sensitive modality for bone involvement, while PET/CT may be more sensitive for non-osseous tissue involvement.[8] Despite the lower sensitivity, CT is used most frequently for its convenience and lower cost.

Acute renal failure is a rare presentation and can manifest with a bland urinalysis or rarely nephrotic syndrome due to concurrent immunoglobulin light chain (AL) amyloidosis. The two major causes of renal insufficiency in patients with MM are light chain cast nephropathy (also called myeloma kidney) and hypercalcemia. Patients who do not secrete light chains are not at risk for myeloma kidney. In the absence of other causes of renal failure, a presumptive diagnosis of light chain cast nephropathy is made in the setting of high free light chain (FLC) levels. Renal biopsy should be performed to characterize the histologic changes in patients who may have other potential risk factors for renal impairment, in whom the mechanism of kidney injury is not clear such as seen in our case. Renal insufficiency, can be acute or insidious in onset, occurs in approximately fifty percent of patients with MM. A variety of etiologic mechanisms may be involved. These include excess production of monoclonal light chains causing cast nephropathy, deposition of intact light chains causing nephrotic syndrome (light chain deposition disease), amyloidosis, hypercalcemia[9]; radiocontrast media-induced acute renal failure (usually due to dehydration in the presence of Bence Jones proteinuria) and, infrequently, very high levels of uric acid. Ionized calcium should be measured if the patient has a high serum calcium level but no symptoms of hypercalcemia, as elevation of serum calcium concentration may not occur due to binding of the M protein with calcium.[7] Severe hypercalcemia can act as an unmeasured cation and result in a low anion gap as seen in our case. Decreased anion gap may also be due to the high IgG molecule manifesting as additional cations. All patients with MM should take precautions to minimize risk of renal damage. These include avoidance of nephrotoxins such as aminoglycosides and NSAID's and maintenance of hydration by drinking enough fluids to produce 3 liters of urine per day. Certain medications frequently used for the treatment of MM or its complications such as zoledronic acid may require dose adjustment for renal insufficiency or may contribute to renal failure. The treatment of renal insufficiency is directed at the underlying cause and may require the use of plasmapheresis and/or hemodialysis in the setting of acute renal failure. The presence of acute renal failure due to light-chain cast nephropathy may also have an impact on the choice of initial chemotherapy. Our patient was treated with bortezomib, cyclophosphamide, plus dexamethasone, which do not need dose reductions for renal failure. Weekly doses of the drugs used in these regimens can be adjusted based on counts and other adverse effects.[10,11] Usually, renal function improves with therapy, as in our patient.

The initial evaluation of our patient found him eligible for high-dose therapy (HDT) based on his age, performance status, and limited comorbidities. With the introduction of novel agents, thalidomide, bortezomib and lenalidomide, as part of induction treatment have markedly improved the rate of complete response (CR). These have not increased toxicity and improved time to progression (TTP). Progression-free survival (PFS) and overall survival (OS) have significantly improved.[11] Long term follow-up and disease progression will determine further treatment.

REFERENCES

1. **Siegel RL, Miller KD, Jemal A**. Cancer statistics, 2020. **CA Cancer J Clin**. 2020 Jan;70(1):7-30. doi: 10.3322/caac.21590. Epub 2020 Jan 8. PMID: 31912902.
2. **Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ 3rd**. Incidence of multiple myeloma in Olmsted County, Minnesota: Trend over 6 decades. *Cancer*. 2004 Dec 1;101(11):2667-74. doi: 10.1002/cncr.20652. PMID: 15481060.
3. **Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Martin-Hirsch P, Tsilidis KK**. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ*. 2017 Feb 28;356: j477. doi: 10.1136/bmj.j477. PMID: 28246088; PMCID: PMC5421437.
4. **Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR**. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003 Jan;78(1):21-33. doi: 10.4065/78.1.21. PMID: 12528874.
5. **Turesson I, Velez R, Kristinsson SY, Landgren O**. Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. *Mayo*

Clin Proc. 2010 Mar;85(3):225-30. doi: 10.4065/mcp. 2009.0426. PMID: 20194150; PMCID: PMC2843108.

6. **Kim PJ, Hicks RJ, Wirth A, Ryan G, Seymour JF, Prince HM, Mac Manus MP.** Impact of 18F-fluorodeoxyglucose positron emission tomography before and after definitive radiation therapy in patients with apparently solitary plasmacytoma. *Int J Radiat Oncol Biol Phys*. 2009 Jul 1;74(3):740-6. doi: 10.1016/j.ijrobp.2008. 08.037. Epub 2008 Nov 27. PMID: 19038505.
7. **Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, Raje N, Sezer O, Zweegman S, Shah J, Badros A, Shimizu K, Moreau P, Chim CS, Lahuerta JJ, Hou J, Jurczyszyn A, Goldschmidt H, Sonneveld P, Palumbo A, Ludwig H, Cavo M, Barlogie B, Anderson K, Roodman GD, Rajkumar SV, Durie BG, Terpos E**. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. *J Clin Oncol*. 2015 Feb 20;33(6):657-64. doi: 10.1200/JCO.2014.57.9961. Epub 2015 Jan 20. PMID: 25605835.
8. **Annesley TM, Burritt MF, Kyle RA**. Artifactual hypercalcemia in multiple myeloma. *Mayo Clin Proc*. 1982 Sep;57(9):572-5. PMID: 6810030.
9. **Bladé J, Kyle RA**. Multiple myeloma in young patients: clinical presentation and treatment approach. *Leuk Lymphoma*. 1998 Aug;30(5-6):493-501. doi: 10.3109/ 10428199809057562. PMID: 9711912.
10. **Angelova EA, Li S, Wang W, Bueso-Ramos C, Tang G, Medeiros LJ, Lin P**. IgM plasma cell myeloma in the era of novel therapy: a clinicopathological study of 17 cases. *Hum Pathol*. 2019 Feb;84:321-334. doi: 10.1016/ j.humpath.2018.09.008. Epub 2018 Sep 25. PMID: 30266252.
11. **Moreau P, Avet-Loiseau H, Harousseau JL, Attal M**. Current trends in autologous stem-cell transplantation for myeloma in the era of novel therapies. *J Clin Oncol*. 2011 May 10;29(14):1898-906. doi: 10.1200/JCO.2010. 32.5878. Epub 2011 Apr 11. PMID: 21482979.