CLINICAL VIGNETTE

Smoldering Multiple Myeloma in a Young Newly Diagnosed Diabetic with Microalbuminuria

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Case Report

A 49-year-old male with a past medical history of Class I obesity, hypertension, and hyperlipidemia, and a long history of daily cigar smoking presented for a routine annual physical. His only medication was amlodipine 10 mg daily. Family and social history were non-contributory. A review of systems was notable for occasional palpitations when smoking cigars. On physical exam, his body mass index was 33.3 kg/m^2, blood pressure was 114/71 mmHg, and the remainder of his vital signs were within normal limits. Other exam findings included mild gynecomastia and a 1/4 early diastolic murmur at the right upper sternal border. Laboratory test results showed a normal glomerular filtration rate (>89 mL/min/1.73 m^2), and elevated levels of calcium (10.6 mg/dL), albumin (5.2 g/dL), LDL-cholesterol (169 mg/dL), triglycerides (247 mg/dL), glucose (115 mg/dL), and hemoglobin A1c (7.3%). Following confirmation of diabetic-range hyperglycemia with second elevated hemoglobin A1c (7.4%), screening for microalbuminuria revealed a urine albumin/creatinine ratio of 200.1 mcg/mg (normal <30.0 mcg/mg), and the patient was referred to nephrology for further evaluation.

Subsequent testing confirmed mild microalbuminuria; albumin/creatine ratio = 35.3 mcg/mg. Total protein/creatinine ratio, urinalysis, creatine kinase, parathyroid hormone, vitamin D, phosphorus, and urine immunofixation were all within normal limits, and hepatitis B antigen and surface antibody, hepatitis C antibody, and HIV Ag/Ab tests were negative. Serum immunofixation revealed a monoclonal IgG kappa protein. Quantitative serum free light chain analysis demonstrated an elevated kappa free light chain level (135.36 mg/L, normal range = 3.30-19.40 mg/L) and an elevated kappa/lambda light chain ratio (24.88, normal range 0.26 - 1.65).

The patient was referred to oncology for further evaluation and management. Additional laboratory evaluation included a hemoglobin of 12.9 g/dL and beta-2-microglobulin 1.3 mg/L. Calcium level normalized to 10.1 mg/dL. Serum protein electrophoresis quantitated the monoclonal protein to be 0.2 g/dL. Twenty-four-hour urine testing for monoclonal protein and free light chains was unremarkable. Bone marrow aspiration and biopsy revealed plasma cell dyscrasia with kappa light chain restriction involving 20% of the bone marrow specimen. Myeloma panel fluorescence in situ hybridization (FISH) showed +1q, +11q, and IgH gene rearrangement. Whole body PET-CT scan did not show evidence of active bone disease.

Patient was diagnosed to have smoldering multiple myeloma. The oncologist discussed management options of observation verses treatment with lenalidomide. Patient chose to proceed with lenalidomide therapy and was referred to the stem cell transplant team for stem cell collection in anticipation of future need.

Discussion

There is no clear guideline on the level of proteinuria and amount of testing to be done. History taking and looking for subtle clues can be extremely vital as demonstrated in this case. This patient had microalbuminuria. History clearly revealed he was not diabetic when he was tested a year ago. It was 'too soon' for him to develop microalbuminuria. The reported prevalence of microalbuminuria among patients with type 2 diabetes approximately 10 years after diagnosis ranges from 25-40%.[1] Diabetes could not explain the cause for his microalbuminuria. His urine being otherwise benign with no active urine sediment and history not suggestive of any autoimmune disease essentially ruled out autoimmune nephritis. Another important clue that led to looking for multiple myeloma was mild hypercalcemia and anemia.[2] Non albuminuric proteinuria was another important clue, though not marked in this patient. Though the patient's urine protein creatinine ratio was 0.2, albumin was only 35.3 mcg/mg. He had predominantly non albuminuric protein in the urine, which was low molecular weight protein from immunoglobulins. Simultaneous measurement of urine protein creatinine ratio and urine microalbumin creatinine ratio is crucial.

Presentation and diagnosis of smoldering multiple myeloma are learning points in this case. Though multiple myeloma is generally a clonal plasma cell malignancy of the elderly, it is important not to use age criteria for exclusion. Early diagnosis and risk stratification of smoldering multiple myeloma, may have an impact on prognosis. Smoldering multiple myeloma is defined by serum monoclonal protein (IgG or IgA) level of ≥3 g/dL or urinary monoclonal protein ≥500 mg/24 hours and/or clonal bone marrow plasma cells ≥10% with the absence of myeloma defining events or amyloidosis.[3] It can be distinguished from active myeloma (multiple myeloma) by the absence of hyper**c**alcemia (calcium >1 mg/dL higher than upper limit of normal or >11 mg/dL), **r**enal failure (creatinine clearance <40 mL/min or creatinine >2mg/dL), **a**nemia

(hemoglobin >2 g/dL below lower limit of normal or <10 g/dL), or lytic **b**one lesions (acronym CRAB) attributable to clonal plasma cells. Other features that define multiple myeloma include bone marrow plasma cells ≥60%, involved/uninvolved serum free light chain ratio ≥100, or >1 bone lesion on MRI. The risk of progression of smoldering multiple myeloma to multiple myeloma is about 10% per year in the first 5 years after diagnosis. Historically, treating smoldering multiple myeloma with alkylator chemotherapy did not improve survival and patients were observed without treatment until progression, unlike multiple myeloma which requires immediate treatment.

Risk stratification of smoldering multiple myeloma led to discovery of a subgroup that is at higher risk of progression and end organ damage and may be better served with closer monitoring or upfront treatment. Lakshman et al[4] found that the following three risk factors independently predicted a shorter time to progression of smoldering multiple myeloma from diagnosis to requiring therapy: 1) Bone marrow plasma cells > 20%. 2) Monoclonal protein >2 g/dL. 3) Free light chain ratio >20. Using this Mayo 2018 20/2/20 criteria, a high-risk group (defined as having ≥2 of the 3 risk factors) was found to have a shorter time to progression of 29 months, compared to low-risk (0 of 3 risk factors) or intermediate-risk (1 of 3 risk factors) groups, which had times to progression of 110 and 68 months, respectively. This high-risk group had an estimated risk of progression of 24% per year during the first 2 years, 11% per year for the next 3 years, and 3% per year for the following five years. This patient had 2 of the 3 risk factors (bone marrow plasma cells >20% and free light chain ratio >20) and was classified as high-risk. In addition to these risk factors, chromosomal abnormalities del(17p), t(4;14), gain 1q, and hyperdiploidy were found to independently predict higher risk of progression in smoldering myeloma.[5] Gain 1q was found by bone marrow FISH in this patient.

The question of whether treating smoldering multiple myeloma will improve survival was readdressed in the era of modern therapy. A phase III trial by Mateos et al[6] randomized 119 patients with high-risk smoldering multiple myeloma to treatment with lenalidomide plus dexamethasone versus observation. Lenalidomide is an analogue of thalidomide with less neurotoxicity used to treat multiple myeloma. After a median follow-up of 40 months, treatment with lenalidomide and dexamethasone led to a significantly higher 3-year survival rate compared to observation (94% vs 80%), with a hazard ratio for death of 0.31. Another randomized trial by Lonial et al[7] of lenalidomide versus observation in smoldering multiple myeloma found that high-risk patients defined by the Mayo 2018 20/2/20 criteria had significant progression-free survival benefit with treatment compared to observation. Patients meeting this high-risk criteria were recommended by the authors to receive treatment with lenalidomide rather than being observed. After thorough discussion of prognosis and management options with our patient, he was recommended to initiate treatment with lenalidomide, with which he agreed.

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