How to Diagnose, Treat, and Monitor Treatment Response in Patients with Multiple Myeloma

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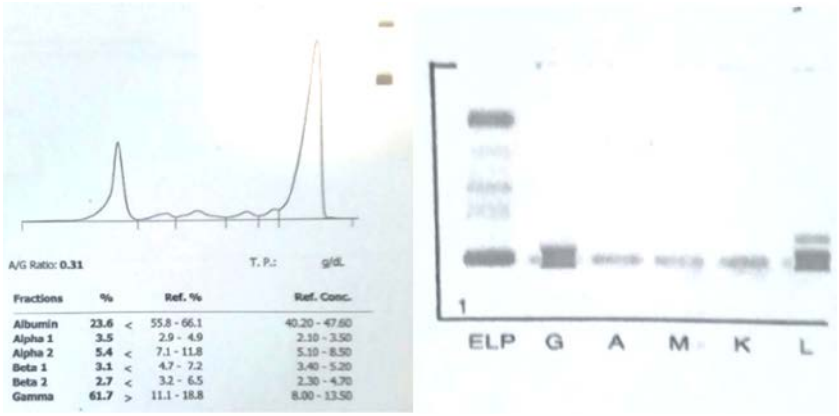

Figure 1. Serum protein electrophoresis and immunofixation showed the presence of gammopathy IgG and lambda light chain

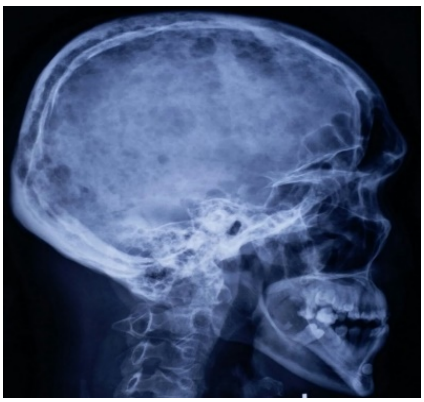

Figure 2. Skeletal radiography: multiple osteolytic lesions in calvaria.

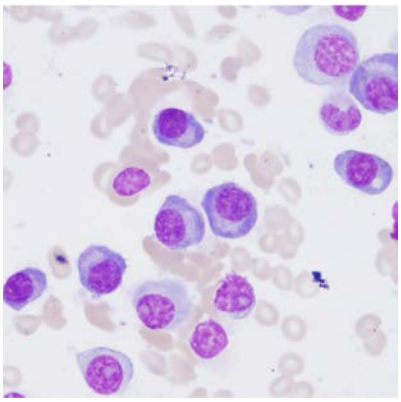

Figure 3. Percentage of plasma cells in the bone marrow in the patient: 46%.

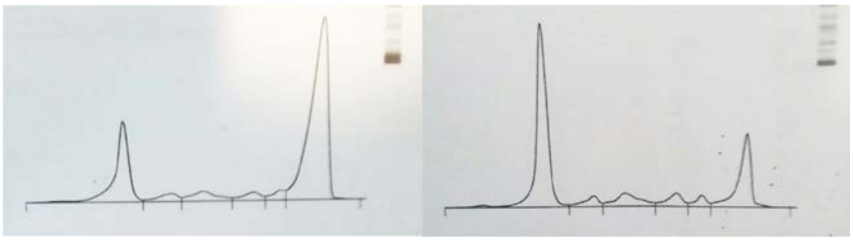

Figure 4. Response of treatment after four cycles of induction VCD

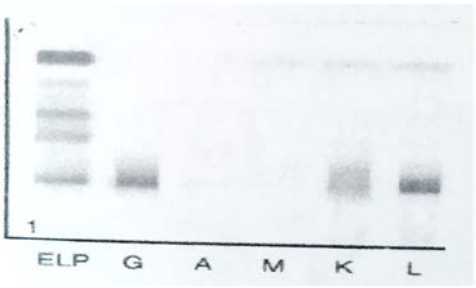

Figure 5. Immunofixation still detected IgG and lambda light chain after four cycles of induction VCD

Multiple myeloma (MM) is a B-cell malignancy characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein production in the serum, and organ dysfunction.[1] It is part of a disease spectrum called plasma cell disorders,[2] and to establish the diagnosis, a bone marrow biopsy should be conducted with clinical signs of end-organ damage and/or significantly elevated monoclonal protein (M-protein). MM can also be diagnosed without end-organ damage when certain conditions are met since the International Myeloma Working Group (IMWG) has come up with new diagnostic criteria for multiple myeloma.[2]

Treatment for all patients with MM aims to enhance the depth and duration of response while limiting drug toxicity to lengthen survival, improve quality of life, alleviate symptoms and prevent further organ damage.[3] Development of new drugs has improved the survival of patients[4] Available tests for monitoring of patients with MM most often include assessments of monoclonal paraprotein and serum-free light chain levels with bone marrow examination, which directly identifies the level of malignant plasma cells.[5]

A 40 years old male suffered from back pain and fatigue for 6 months. Physical examination only showed pale conjunctiva, indicating anemia, which was confirmed by test results with a hemoglobin level of 8.5 g/dL. In addition, there were slightly elevated blood ureum 58 mg/dL (normal value: 20-50 mg/dL), serum creatinine 1.73 mg/dL (normal value: 0.7-1.2 mg/dL), and low serum calcium level 7.8 mg/dL (normal value: 8.5-10.5 mg/dL). The value of elevated total protein, low albumin, and highly elevated serum globin was 14.1 g/dL (normal value: 6.6-8.7 g/dL), 2.8 g/dL (normal value: 3.4-4.8 g/dL), and 11.3 g/dL (normal value: 1.5-3.0 g/dL), respectively. Serum protein electrophoresis and immunofixation confirmed the presence of IgG and lambda light chain gammopathy. Meanwhile, the level of serum IgG, free light chain (FLC) kappa, FLC lambda was 10,741 (normal value: 800-1,813 mg/dL), 17.36 ng/L (normal value:3.3-19.4 ng/L), and 1,650 ng/L (normal value: 5.71-26.3 ng/L), respectively, with serum free light chain ratio = 95. Multiple osteolytic lesions in the calvaria and compression fractures in the 6^{th}, 9^{th}, 11^{th}, 12^{th}, and 13^{th} thoracic vertebrae were seen on skeletal radiography. Bone marrow aspiration showed the presence of plasma cells comprising 46% of all cells.

The Revised IMWG 2014 updated criteria for the diagnosis of multiple myeloma has developed the diagnostic criteria of: clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more myeloma defining events:[2,6]

a. Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, also known as the "CRAB" mnemonic: hypercalcemia (serum calcium >11 mg/dL), renal insufficiency (serum creatinine >2 mg/dL or creatinine clearance <40 mL per min), anemia (Hemoglobin <10 mg/dL), or bone lesions [on skeletal radiography, computed tomography (CT), or positron emission tomography (PET) -CT].
b. One or more of the following malignancy biomarkers: clonal plasma cells in bone marrow ≥60%, ratio of serum FLC ≥100 (involved FLC≥100 mg/dL), or >1 focal lesion found by magnetic resonance imaging (MRI).[2]

The Revised IMWG 2014 criteria established the diagnosis of multiple myeloma in this patient based on the ≥10% percentage of bone marrow plasma cells with organ damage anemia and lytic bone lesions. European Hematology Association and European Society for Medical Oncology (EHA-ESMO) Clinical Practice Guidelines for diagnosis, treatment, and follow-up recommend three-drug combination VRd (Bortezomib, lenalidomide, and dexamethasone), VTD (Bortezomib, thalidomide, and dexamethasone), or VCD (Bortezomib, cyclophosphamide, and dexamethasone) as induction chemotherapy regimen. These were followed by stem cells mobilization, harvesting, and High Dose Melphalan (HDM) 200 mg/m^2 with autologous stem cell transplantation (ASCT).[5] Furthermore, the patient's induction chemotherapy regimen was administered with a three-drug combination of Bortezomib, cyclophosphamide, and dexamethasone (VCD) for four cycles.

The diagnostics now available to evaluate the patient's response to therapy for MM include periodic evaluations of M-protein and serum FLC levels, immunofixation, and bone marrow examination to detect residual malignant plasma cells. However, serological/morphological complete response (CR) may still underestimate residual disease. This is because the IMWG has incorporated Minimal Residual Disease (MRD) assessed by multicolor immunofluorescence flow cytometry and gene sequencing into MM response criteria with the absence of bone disease on PET-CT scanning.[1,5,7] The treatment response after four cycles of VCD was partial response (PR) since the immunofixation was still detected. Plasma cells in the bone marrow were 7.5%, and the patient achieved normal measurable serum IgG and lambda light chain: IgG 1,500 mg/dL (normal value: 800-1,813 mg/dL) and lambda 15.5 ng/L (normal value: 5.71-26.3 ng/L).

This VCD regimen, also known as CyBorD, has been utilized as the standard induction in transplant-eligible newly diagnosed MM. The combination therapy has shown good outcomes when continued with ASCT.[8] The patients were promoted to continue with HDM and ASCT after the discussion. The patient evaluated in this research is a good candidate for transplantation since he is young and free of comorbidities. The preparation for transplantation requires multi-disciplinary team coordination and support from the healthcare facility. The possibility of mortality and morbidity due to post-transplant complications should also be communicated effectively with the patient and families. Additionally, this medical illustration shares the experience of diagnosing, treating, and monitoring the therapeutic response of patients with newly diagnosed multiple myeloma.

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