Plasmapheresis in a Patient with Sarcoidosis Who Developed Multiple Myeloma and Massive Free Kappa Light Chains Nephropathy

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KEY WORDS: multiple myeloma, lambda and kappa light chains, plasmapheresis, renal failure, myeloma cast nephropathy (MCN)

IMAJ 2018; 20: 324–326

Multiple myeloma, a plasma cell neoplasia, is one of the most common hematological malignancies. Precipitation of free light chains in the kidney resulting in renal failure is a frequent complication of this disorder. Chemotherapy and exchange transfusions have been partially successful for its treatment.

Renal failure is one of the main complications of multiple myeloma. Several factors contribute to the deterioration of renal failure in these patients. Precipitation of free light chains (FLC) resulting in myeloma cast nephropathy (MCN) is one of the most important mechanisms that causes renal damage in this disorder [1]. Whether an association with other diseases, such as sarcoidosis, exists has been questioned.

Following is the description of a patient with sarcoidosis who developed multiple myeloma with unusual Kappa FLC values that was treated with plasmapheresis. This patient had huge values of FLC and a rapidly declining renal function. A bone marrow biopsy showed a histological picture compatible with multiple myeloma concurrent with the presence of a granulomatous inflammation. Chemotherapy followed by plasmapheresis was given with initial success. The rare association of multiple myeloma and sarcoidosis in this patient with enormous elevation of FLC and its treatment with plasmapheresis is discussed. Although the patient responded initially to treatment, he suddenly deteriorated and died.

The particular association between multiple myeloma and sarcoidosis in this patient, the huge FLC values on presentation, and the role of plasmapheresis in the treatment of this disorder are discussed.

PATIENT DESCRIPTION

A 58 year old man with sarcoidosis for 8 years and thalassemia minor was admitted to our department of internal medicine because of deterioration in renal function (creatinine: 3.0 mg/dl, uric acid: 7.55 mg/dl) and hypercalcemia (calcium: 13.30 mg/dl corrected calcium level was 13.8 mg/dl). On admission, pancytopenia was present. A subsequent computed tomography showed mediastinal and abdominal lymphadenopathy and splenomegaly (the span of the spleen was 17 cm), which were attributed to the underlying sarcoidosis. He was treated with diuretics together with intravenous fluids and corticosteroids. Calcitonin was administered.

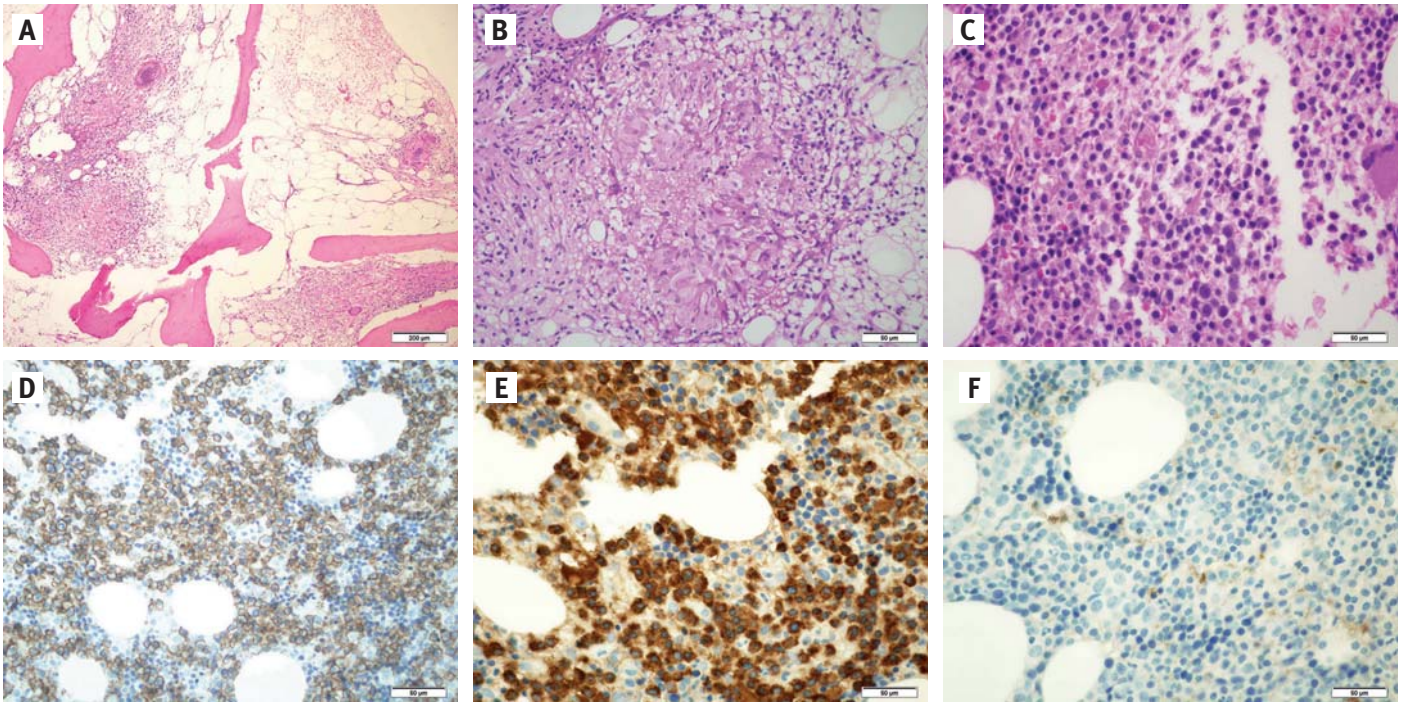
A blood test for immunoglobulins showed an exceedingly high light kappa chains fraction of over 340,000 mg/L (normal range 3.3–19.4 mg/L). The kappa-to-lambda ratio was 19,000. Beta 2 microglobulin level was 16,000 ng/ml (normal range 609–2366 ng/ml) and the urinary Bence–Jones level was 80%. Urinary kappa light chains were present. Bone marrow aspiration and biopsy as well as immunophenotyping were performed. Bone marrow aspiration showed massive infiltration of the marrow with about 90% of plasma cells. The biopsy showed infiltration of the bone marrow with plasma cells and granulomas, a picture compatible with multiple myeloma and sarcoidosis [Figure 1].

A skeletal survey revealed generalized lytic bone lesions. Treatment with high dose dexamethasone 40 mg daily for 4 days and pamidronate disodium was started.

The patient was discharged but readmitted 1 month later because of worsening of renal function (creatinine 5.73 mg/dl) and pancytopenia (hemoglobin: 8.2 g/dl, leukocytes 3000/mm^3, and platelets 4000/mm^3). At readmission, his calcium level was 8.93 mg/dl and albumin 3.99 g/dl. He was treated with intravenous hydration and, after further decrease of the hemoglobin value to 6.3 g/dl, red blood cell transfusion was administered. Further treatment with erythropoietin alpha at a dose of 10,000 units thrice weekly was given.

Treatment with bortezomib, cyclophosphamide, and high dose dexamethasone (VCD protocol) was given. As the patient had high values of kappa light chains in his blood and massive proteinuria with only minimal albuminuria, MCN was suspected and plasmapheresis treatment was started. Due to the very high clinical probability of cast nephropathy and the very low hemoglobin level (~7 g/dl), renal biopsy was considered as non-obligatory

Figure 1. Bone marrow biopsy of sarcoid-like granulomas and plasma cell myeloma **[A]** Epiteloid granuloma, H&E stain (original magnification ×100, scale bar 200 μm), **[B]** Epiteloid granuloma (original magnification ×400, scale bar 50 μm), **[C]** Plasma cell myeloma (original magnification ×600, scale bar 33.3 μm), **[D]** CD138 positive plasma cells (original magnification ×4100, scale bar 50 μm), **[E]** Kappa positive plasma cells (original magnification ×600, scale bar 33.3 μm), **[F]** Lambda negative plasma cells (original magnification ×100, scale bar 200 μm)



and potentially dangerous at this stage, and therefore was not performed.

At discharge, the patient continued treatment with VCD (6 cycles) and 11 sessions of plasmapheresis, and was scheduled for an autologous stem cell transplant. Kappa light chains level dropped by over 90% to 14,326 mg/L and the creatinine value decreased to 2.07 mg/dl. Since the hematological response was still considered inadequate, chemotherapy was intensified to bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide protocol.

After completing his first cycle of treatment, the patient developed severe pancytopenia and died suddenly at home. An autopsy was not performed.

COMMENT

FLC are proteins produced by plasma cells during the process of antibody synthesis. Their production reflects plasma cell activation and can give insight into the activity of the adaptive immune system [1].

This patient with prior sarcoidosis presented with extraordinarily high levels of kappa FLC. To the best of our knowledge, similar high values of FLC are exceptionally uncommon and have not been described before. The bone marrow biopsy was in accordance with multiple myeloma and suggested the presence of sarcoidosis in the marrow.

Renal failure is a main complication of MCN, the most frequent lesion resulting in kidney injury in multiple myeloma.

Serum FLC levels are useful for diagnosing and monitoring responses in light chain myeloma, especially in the presence of renal failure. High values of FLC, as well as abnormal kappa-to-lambda ratio are related to a worse prognosis. In a study [2] performed on patients with multiple myeloma treated with chemotherapy, baseline FLC levels were available for 301 patients. Two years after the initiation of treatment, baseline levels of FLC were significantly associated with overall survival. High levels of light chains at the time of treatment administration were associated with more aggressive disease features, reflecting higher tumor burden. In a recent prospective study on 848 patients, Hutchison and colleagues [3] found that high levels of serum polyclonal immunoglobulin FLC levels predicted increased mortality in people with chronic kidney disease. However the significance of these findings for myeloma kidney with high FLC is not clear.

Prompt start of chemotherapy is the mainstay of the treatment of patients with myeloma kidney but usually several days or weeks are necessary before a response can be achieved. Data suggest that a rapid and sustained reduction in serum concentrations of FLCs is associated with improved renal recovery in patients with MCN. The inflammation causing cast nephropathy results from an excess of filtered monoclonal FLC transported to the interstitium

of the kidney via specific receptors in the proximal tubule. The receptors become overloaded by the light chains, forming obstructive casts in the renal tubules. Removal of FLC by plasmapheresis is a method that has been used as an adjunct to treatment to minimize nephrotoxicity until the effect of chemotherapy is attained.

Similarly, plasma exchange has been shown to remove light chains transiently and may have an adjunctive effect when combined with effective chemotherapy in the treatment of cast nephropathy. It has been shown that an important proportion of patients with cast nephropathy resolve their renal disease when a significant reduction in FLC occurred. Research papers reviewing this issue showed conflicting results and concluded that the role of plasmapheresis in improving renal prognosis and patient survival has not been proven conclusively and remains to be demonstrated.

Whether the improvement and the significant reduction of FLC in the patient reported in the present case was secondary to plasmapheresis is not clear. As he presented with extremely high FLC values, reflecting severe disease, a prompt reduction in light chains that could improve his disease seemed indicated.

This patient had associated sarcoidosis. The association between multiple myeloma and sarcoidosis was described several years ago but seems to be particularly uncommon. We are not aware of similar reports during the last years. Sen and colleagues [4] reported the presence of both diseases in a patient in 2002. In their review, the authors found only 10 previous cases reporting the association of these two disorders. In the cases reviewed, the diagnosis of sarcoidosis preceded the diagnosis of multiple myeloma in 83.3% of the patients. A large study conducted by Brincker and Wilbek [5] demonstrated that the risk of lymphoproliferative disorders in patients with sarcoidosis was 11.5 times higher than expected. Patients with sarcoidosis have immune system dysregulation, including activation of CD4-positive T-helper/inducer cells, increased secretion of various cytokines, and decreased C D8-positive T-suppressor/cytotoxic cells. It has been speculated that a common primary immunological derangement or a common etiological factor might underlie the development of both, sarcoidosis and multiple myeloma. Whether the very high levels of FLC in this case were related to the presence of sarcoidosis in the bone marrow is not clear, but the unusual presentation and the extraordinary elevated FLC could be related to the simultaneous presence of multiple myeloma and sarcoidosis in this patient.

CONCLUSIONS

Although the role of plasmapheresis in the treatment of renal failure attributed to cast nephropathy is controversial, the outcome of this patient, presenting with extremely high values of kappa FLC, suggests a possible contribution of plasmapheresis to his response.

Larger scale randomized controlled trials will probably clarify the role of plasmapheresis in the treatment of these patients.

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Capsule

Developing and refining new candidate criteria for systemic lupus erythematosus classification: an international collaboration

Tedeschi and co-authors defined candidate criteria within multiphase development of systemic lupus erythematosus (SLE) classification criteria, which was jointly supported by the American College of Rheumatology and the European League Against Rheumatism. Earlier steps included item generation and reduction by Delphi exercise, further narrowed to 21 items in a nominal group technique exercise. These objectives were to apply an evidence-based approach to the 21 candidate criteria, and to develop hierarchical organization of criteria within domains. A literature review identified the sensitivity and specificity of the 21 candidate criteria. Data on the performance of antinuclear antibody (ANA) as an entry criterion and operating characteristics of the candidate criteria in early SLE patients were evaluated. Candidate criteria were hierarchically organized into clinical and immunologic domains, and definitions were refined in an iterative process. Based on the data, consensus was reached to use a positive ANA of ≥ 1:80 titer (HEp-2 cells immunofluorescence) as an entry criterion and to have 7 clinical and 3 immunologic domains, with hierarchical organization of criteria within domains. Definitions of the candidate criteria were specified. Using a data-driven process, consensus was reached on new, refined criteria definitions and organization based on operating characteristics. This work will be followed by a multi-criteria decision analysis exercise to weight criteria and to identify a threshold score for classification on a continuous probability scale.

Arthritis Care Res (Hoboken) 2018; 70: 571

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