CASE REPORT

Aggressive plasmablastic multiple myeloma in a 42-year-old: is inflammatory bowel disease or infliximab treatment to be blamed?

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SUMMARY

A man in his early 40s with a history of ulcerative colitis, treated with infliximab, was diagnosed with plasmablastic multiple myeloma. He was treated with chemotherapy and stem cell transplant but developed recurrence and ultimately died from metastatic disease. Could inflammatory bowel disease or infliximab therapy have any role in development of myeloma in this young patient? The role of inflammatory bowel disease and infliximab therapy in the development of multiple myeloma is controversial but interesting and worth considering.

BACKGROUND

Multiple myeloma is the malignant proliferation of monoclonal plasma cells. It typically occurs in the seventh and eighth decade of life. The median age of diagnosis is 70 years and less than 4% of cases are diagnosed before the age of 45 years.¹ Multiple myeloma in a young patient brings out the possibility of the presence of other underlying factors that could have made the development of multiple myeloma more likely. Two such potential triggers identified in the forthcoming case are the use of immunosuppressive agent infliximab and the presence of inflammatory bowel disease.

CASE PRESENTATION

A man in his early 40s presented to his gastroenterologist's office for a routine follow-up for his diagnosis of ulcerative colitis. He did not have any active symptom during that visit. He was diagnosed with ulcerative colitis at the age of 18. He did not have any other significant comorbidities. He had been treated with 5-aminosalicylic acid products for his ulcerative colitis in the past and infliximab was added to his treatment regimen 4 years ago because of episodes of recurrent bloody stools. Since the addition of infliximab, his ulcerative colitis was under remission.

INVESTIGATIONS

A complete blood count drawn as part of the routine check-up showed the presence of blast population of 0.09 billion/L. Haemoglobin, white cell and platelet counts were normal. Repeat of the complete blood count and inspection of peripheral smear of the blood confirmed the presence of the blasts. Renal function panel and liver function tests did not show any significant abnormality.

Bone marrow biopsy and aspiration sample were drawn which showed extensive marrow involvement by plasma cell myeloma with plasmablastic features (figure 1). Immunohistochemical staining was strongly positive for CD138 and κ light chains. Flow cytometry evaluation was positive for a κ monoclonal population. Cytogenetics study revealed 45,XY,+add(1)(p10),-8,-13,-14,+add(14)(q32),+15[3]/46,XY[1] karyotype.

Full workup in the line of multiple myeloma was performed. He was found to have a stage III disease with a β_2 microglobulin level of 9.3 mg/L. Serum immunological examination revealed monoclonal gammopathy with free κ and free lambda levels of 1348 and 0.48 mg/dL, respectively.

Three weeks after his initial visit, he presented to the hospital with overt renal failure with creatinine of 5.6 mg/dL and blood urea nitrogen of 55 mg/dL along with hypercalcaemia (calcium of 14.6 mg/dL) and hyperuricaemia (uric acid of 16.5 mg/dL). These parameters were normal during his initial presentation 3 weeks before.

TREATMENT

The patient was initially treated with bortezomib, lenalidomide and dexamethasone and achieved remission. Eventually, he underwent stem cell transplantation. However, 6 months after the transplant, he was found to have a recurrence of the myeloma by bone marrow biopsy. At the same time, he was also found to have multiple lytic lesions in his bones. There were multiple lesions within his liver as well which was concerning for metastatic disease. He was treated with carfilzomib but did not respond to the treatment. He passed away from metastatic plasma cell myeloma around a year from the date of his initial asymptomatic presentation to his gastroenterologist's office.

DISCUSSION

Young patients with myeloma usually have a milder disease with favourable features.² However, in our patient, presence of plasmablasts³ and a high β_2 microglobulin⁴ level suggest an aggressive disease with poor prognosis. This raises the possibility of the presence of underlying triggers for precipitating an aggressive plasma cell myeloma. Two potential such triggers identified in our patient were the presence of ulcerative colitis and the use of infliximab treatment.

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Figure 1 Bone marrow biopsy showing extensive marrow involvement by plasma cell myeloma with plasmablastic features.

There have been 13 reported cases of association of multiple myeloma with inflammatory bowel disease.^{5–7} In addition, studies have shown higher incidence of multiple myeloma in patients with inflammatory bowel disease. A follow-up of 27 606 patients with ulcerative colitis hospitalised for the first time during the years 1964–2004, showed a standardised incidence ratio of 1.65 for multiple myeloma during the follow-up period.⁸ In another study from Italy, the authors found a significant excess of mortality from haemolymphopoietic neoplasms, in particular from multiple myeloma and non-Hodgkin lymphoma, in patients with ulcerative colitis.⁹

Whether these were coincidental findings or there is a true association between inflammatory bowel disease and multiple myeloma is difficult to prove. Theoretical possibilities for this association exist. Both conditions have an immune dysregulation component in their pathogenesis. Inflammatory cytokines such as interleukins (IL)-13, tumour necrosis factor (TNF) and IL-6 are increased in ulcerative colitis, which have a strong tendency to disrupt the intestinal cell barrier.¹⁰ This leads to an impaired clearance of foreign material from the bowel wall and a compensatory acquired immune response.¹¹ Hence, patients with inflammatory bowel diseases are more likely to have abnormal systemic responses to antigens crossing the intestinal mucosal barrier.^{5–11} This could lead to an increased ability to activate B cells and plasma cells and could explain why lymphoma or multiple myeloma is potentially more likely in the setting of inflammatory bowel disease.

The role of infliximab therapy in the development of myeloma is unclear. Infliximab is a monoclonal antibody that binds to TNF- α , neutralising its activity and inhibiting its binding to its receptors. It has been demonstrated that TNF- α is a potent inducer of apoptosis in multiple myeloma cell lines.¹² Based on this finding, it is hypothesised that blocking TNF activity with drugs such as infliximab could interfere with apoptosis and lead to increased proliferation in plasma cells. In a study of patients with refractory multiple myeloma treated with another TNF- α inhibitor, etanercept, there was no objective response and acceleration of disease occurred in 4 of 10 patients.¹³

There are two prior case reports of patients developing multiple myeloma after infliximab therapy for Crohn's disease.^{5–6} Other immunosuppressive agents such as azathioprine, cyclophosphamide and daclizumab have been implicated in case reports as well.^{5–6} Based on this, the role of infliximab in

precipitating multiple myeloma, if any, could be related to its immunosuppressive property. The finding of plasma cell myeloma in patients with HIV¹⁴ or in those on immunosuppressive therapy¹⁵ goes in the favour of immunosuppression as a prelude to myeloma.

Whether inflammatory bowel diseases and immunosuppressive therapy, alone or in combination, has any significant role in precipitating myeloma is very difficult to say and has not been studied well in prospective trials. Given this, it may be prudent to have a high degree of suspicion of multiple myeloma, even with minimal features, in patients on immunosuppressive therapy for inflammatory bowel disease. At the same time, prospective studies are needed in this area to establish the safety of immunosuppressive therapy in patients with inflammatory bowel disease. Meanwhile, the benefit of treatment with immunosuppressive therapy in patients with inflammatory bowel diseases may outweigh the risk of myeloma, if any.

Learning points

- ▶ Multiple myeloma is uncommon before the age of 50.
- ▶ The incidence of multiple myeloma is higher in patients with inflammatory bowel disease compared to the general population.
- ▶ Immunosuppression is theorised to be a prelude to myeloma.
- ▶ Although debatable, immunosuppressive agents such as infliximab has been associated with the development of multiple myeloma.

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Competing interests None.

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