Biclonal Multiple Myeloma- A Case Series

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Abstract

Multiple myeloma is a prototype of plasma cell dyscrasias characterized by monoclonal abnormal proliferation of immunoglobulin secreting plasma cell in the bone marrow; resulting in production of monoclonal (M) protein (IgG, IgA, IgM, IgD) and or light chain concentrations (kappa or lambda) identified by protein electrophoresis and or immunofixation of serum or urine. The term biclonal multiple myeloma are defined by coexistence of two different M components, which could be either from a single clone or two separate clones producing two distinct bands in electrophoresis and or immunofixation of serum or urine. Biclonal gammopathy is a rare entity with upto 1% of newly diagnosed case of multiple myeloma have two M component in serum immunofixation electrophoresis. Here we share our experience of four cases of biclonal myeloma successfully diagnosed and treated with standard chemotherapy with satisfactory clinical outcome from a single tertiary care centre.

Introduction

Multiple myeloma is a plasma cell disorder characterized by proliferation of single clone of immunoglobulin (Ig) secreting plasma cells with secretion of monoclonal M protein detected by serum protein electrophoresis (SPEP) and or immunofixation (IF) of serum or urine. Biclonal myeloma is defined by coexistence of two distinct M bands in immunofixation electrophoresis due to either proliferation of two separate clones of plasma cell, each producing an unrelated monoclonal Ig or it may result from a single clone of plasma cell producing two monoclonal proteins. Biclonal myeloma is a rare entity and accounts for approximately 1% of newly diagnosed case of multiple myeloma have two M component in serum immunofixation electrophoresis. It presumed that the neoplastic clones which secrete one type of M protein might have undergone isotype switching resulting in secretion of another subtype of M protein by the same clones producing biclonal spikes. Although light chain isotypes reported in literature, but the most common biclonal combination is IgG and IgA (33%) followed by IgM and IgG (24%). It usually presents with common clinical signs and symptoms like monoclonal gammopathy although subsets of population having features of waldenstrom macroglobulinaemia. Treatment with biclonal myeloma is similar with monoclonal gammopathy with comparable survival outcome.

Case History

From May 2019 to January 2020 total four cases of biclonal myeloma was diagnosed in our centre based upon history, clinical examination, routine blood investigations, skeletal survey, serum protein electrophoresis with immunofixation, bone marrow aspiration with trephine biopsy along with cytogenetic study by FISH (Myeloma Panel). In our series there were one female and three male with median age of 52 years. In all the patients common presenting symptoms was weakness, fatigue with one patient presented with back pain. The baseline details of four cases are summarized in Table 1. As all of them were transplant ineligible, three patients were treated with induction chemotherapy with Bortezomib, Lenalidomide and Dexamethasone regimen (VRD) along with monthly Zoledronic acid. One patient was treated with five cycles of Bortezomib, Dexamethasone, Rituximab chemotherapy (BDR) regimen in the line of treatment like waldenstrom macroglobulinaemia and kept under observation as partial response was achieved. After 3 cycles, after 6 cycles and after 9 cycles of VRD regimen serum protein electrophoresis with immunofixation was done for response evaluation. Figure 1,2,3,4 showed the respective SPEP with IF pattern of our four cases.

Response evaluation was done as per International Myeloma Working Group (IMWG) uniform response assessment criteria. As because there was no undue toxicities and good compliance to therapy; chemotherapy with same regimen was planned to continue until diseases progression. Table 2 demonstrates chemotherapy regimen, response and their
outcome. Although we were not able to identify separately of different clonal subtype, overall our patients responded well with standard line of therapy.

Table 1
Patients Characteristics

| Case no | Age | Sex | ECOG-PS | M-band baseline gm/dL | Free kappa baseline mg/dL | Free lambda baseline mg/dL | SPEP with IF | CRAB | ISS Stage | FISH study | Risk |
|---------|-----|-----|---------|------------------------|---------------------------|-----------------------------|--------------|------|-----------|------------|------|
| 1       | 70  | F   | 1       | 0.5                    | 83.62                     | 23.97                       | IgG Kappa and IgG Lambda | C    | III       | Not done   | NA   |
| 2       | 54  | M   | 1       | 6.1                    | 74.51                     | 15.27                       | IgA Kappa and IgA Kappa  | C    | III       | Normal     | SR   |
| 3       | 47  | M   | 1       | 9.5                    | 1065                      | 13                          | IgG Kappa and IgA Kappa  | C    | III       | Trisomy 5, 7 and 9 | SR   |
| 4       | 51  | M   | 1       | 4                      | 1026                      | 16                          | IgM Kappa and IgM Lambda | C    | II        | Not done   | NA   |

PS- performance status, SPEP- serum protein electrophoresis, IF- immunofixation, NA- Not Applicable, CRAB- C-Calium, R- Renal insuciency, A- Anemia, B- Bony lesion (lytic), ISS- International Staging System for Multiple Myeloma, SR- standard risk

Table 2
Treatment and Outcome

| Case no | Chemotherapy (N = no of cycle) | Response after 3 cycles | Response after 6 cycles | Response after 9 cycles | Relapse free survival (months) | Outcome |
|---------|--------------------------------|-------------------------|-------------------------|-------------------------|--------------------------------|---------|
| 1       | VRD (n = 6)                     | PR                      | PR                      | NA                      | 8                              | ALIVE   |
| 2       | VRD (n = 12)                    | PR                      | PR                      | PR                      | 14                             | ALIVE   |
| 3       | VRD (n = 8)                     | PR                      | VGPR                    | NA                      | 6                              | ALIVE   |
| 4       | BDR (n = 5)                     | PR                      | PR                      | NA                      | 7                              | ALIVE   |

VRD- Bortezomib, Lenalidomide and Dexamethasone, BDR- Bortezomib, Dexamethasone, Rituximab, PR- Partial Response, VGPR- Very Good Partial Response, NA- Not Applicable
Discussion And Conclusion:

Among plasma cell disorders monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma and multiple myeloma all these are spectrum of same underlying disease biology with monoclonal proliferation of plasma cells in the bone marrow. The term biclonal gammopathy of undetermined significance (BGUS) represents coexistence of an active multiple myeloma plasma cell clone that produce largest monoclonal antibody and an MGUS cell clone produce relatively smaller monoclonal antibody. A study by Mullikin et al. with 23 out of 393 patients with BGUS showed that the dominant clone was the main player responsible for progression to symptomatic myeloma and other spectrum of plasma cell disorders. Usually biclonal cases showed two different Ig light chains (kappa and lambda) rather than two different types of Ig heavy chains and cases expressing both kappa and lambda light chain with two different types of heavy chain are extremely rare. There are few case reports where combinations of IgG/IgM, IgA/IgG with kappa/lambda light chains were seen. Kyle et al. described 57 cases of biclonal myeloma, out of which only six had two distinct IgG components with no difference in prognosis between biclonal and monoclonal gammopathy. Here we report two extremely rare biclonal pair of IgA Kappa plus IgA kappa and IgM Kappa plus IgM Lambda combinations. In such type of cases mostly arise from two independent plasma cell clones that exhibit either different light chain isotypes or the same light chain isotype unrelated with clonality. Lymphoplasmacytic lymphoma also known as waldenstrom macroglobulinaemia and other B-cell lymphoma with plasmacytic differentiation can produce similar paraproteins and has been reported to present with biclonal gammopathy. In our fourth case presents with features like waldenstrom macroglobulinaemia with SPEP showed two peaks consisting IgM Kappa plus IgM Lambda spikes and hence the patient was responded well with BDR regimen.

Clonality studies was most important to unfold whether this exceptional combination belongs to a truly biclonal population or rather a single neoplastic clone suffered two hits was the major limitation of our case series. It was seen that anti-myeloma therapy was more effective against multiple myeloma clones rather than MGUS clones in patients with biclonal gammopathy. In our patients both matched (Kappa/Kappa) and different light chain isotype (Kappa/Lambda) responded well with bortezomib and lenalidomide based therapy, indirectly indicating that there was myeloma clones rather than MGUS clone. To conclude more prospective research work needs to be done for better realization of the underlying diseases biology, pathogenesis and behavior of this rare disorder.

Declarations

Acknowledgement: Nil

Conflict of interest: None declared

Ethics: Written informed consent was obtained from the patients. Patients have given their consent for their images and other clinical information's to be reported in the journal.

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Figures

Figure 1

SPE of Case 1

Figure 2

IFE of Case 1
Figure 3
SPE of Case 2

Figure 4
IFE of Case 2

Figure 5
SPE of Case 3
Figure 6
IFE of Case 3

Figure 7
SPE of Case 4

Figure 8
IFE of Case 4

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