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Biclonal gammopathy – A single-center experience

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Abstract:

BACKGROUND: Biclonal gammopathies are characterized by the production of two distinct monoclonal proteins. It is defined as the presence of two distinct M bands in serum protein electrophoresis. Biclonal myeloma accounted for approximately 1% of newly diagnosed cases of multiple myeloma.

OBJECTIVE: The aims was to study the clinical characteristics and treatment outcomes of 13 patients with biclonal gammopathy treated at a tertiary cancer center.

MATERIALS AND METHODS: The details of clinical presentation, diagnosis, treatment, and survival were noted from medical records.

RESULTS: The median age was 65 years, there were 10 males and 3 females. Eleven patients had multiple myeloma, one had plasmacytoma, and one had monoclonal gammopathy of undetermined significance (MGUS). Twelve patients had biclonal gammopathy at diagnosis and one developed biclonal gammopathy at relapse. Immunofixation showed IgG/IgA in seven cases, IgA/IgG in four, and IgG/IgG in two patients. The patient with MGUS is on follow at 44 months and one with plasmacytoma received radical radiotherapy and alive at 45 months. Ten patients with myeloma received systemic treatment, eight are alive with survival ranging from 44 to 110 months, and four patients are alive more than 5 years.

CONCLUSION: Biclonal gammopathies are rare characterized by the presence of two distinct monoclonal proteins. The most frequent combination was IgG/IgA. Treatment of biclonal gammopathy is similar to monoclonal gammopathy with comparable outcomes. During follow-up, both paraproteins have to be addressed.

Keywords:

Biclonal gammopathy, biclonal myeloma, immunofixation electrophoresis

Introduction

Multiple myeloma is a plasma cell disorder characterized by the proliferation of a single clone of immunoglobulin (Ig) secreting plasma cells. It accounts for 10% of all hematological malignancies. The monoclonal protein secreted by the plasma cells is detected by serum protein electrophoresis as a single discrete M band, often in the gamma globulin region. In a series of 1027 newly diagnosed patients with multiple myeloma, the Ig type was IgG in 52%, IgA in 20%, and free light chain only in 16% of cases.[1] Monoclonal IgD, IgE, and IgM is produced in about 2% of cases only.[1,2] In 3%–6% of myeloma patients, more than one monoclonal protein can be detected with different heavy chain or light chain or both.[3]

Biclonal gammopathies are characterized by the production of two distinct monoclonal proteins and are defined as the presence of two distinct M bands in serum protein electrophoresis. These additional monoclonal proteins may be identified at the time of initial diagnosis or may appear later. Biclonal myeloma accounted for

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approximately 1% of newly diagnosed cases of multiple myeloma in one series.[4] In a large review of 1027 myeloma patients, only 2% had biclonal gammopathy.[1] Treatment of biclonal myeloma is similar to monoclonal myeloma with comparable outcomes.

In this article, we present the clinical characteristics and treatment outcomes of 13 patients with biclonal gammopathy whom we have treated during a 6-year period at a tertiary cancer center.

Materials and Methods

This is a retrospective analysis of 13 patients who were diagnosed with biclonal gammopathy in the Department of Medical Oncology at a tertiary cancer center in India during the period 2014–2019. All patients were above 54 years of age. The details of clinical presentation, diagnosis, treatment, and survival were noted from medical records. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Treatment protocol

The standard treatment for multiple myeloma included systemic chemotherapy with the proteasome inhibitor bortezomib along with other drugs for 4–6 cycles or a combination of lenalidomide + dexamethasone as induction chemotherapy. This was followed by bortezomib or lenalidomide maintenance. Treatment response was assessed at regular intervals during induction and maintenance therapy. Radiotherapy was considered for patients with myeloma for spinal cord compression, pain relief, and for patients with solitary plasmacytoma. Patients with plasmacytoma and monoclonal gammopathy of undetermined significance (MGUS) were followed up at regular intervals to look for disease progression to active myeloma.

Statistical methods

The baseline patient characteristics, treatment details, and response assessment were analyzed using descriptive statistics (frequency, percentage, median, range, and mean). Overall survival is calculated from the date of initial diagnosis to the date of death from any cause or last follow-up visit.

Results

Thirteen patients were diagnosed with biclonal gammopathy during a period of 6 years. During this period, 1530 cases of myeloma were diagnosed, giving a biclonal incidence of 0.85%. The median age was 65 years (range 54–75 years), there were 10 males and 3 females. The most common presentations were low back ache in eight cases and tiredness in four. One patient each had paraparesis, cellulitis leg, and recurrent urinary tract infection as presenting features. The median duration of symptoms was 8 weeks. The baseline characteristics of all patients are summarized in Table 1.

Of the thirteen patients, eleven had multiple myeloma, one had plasmacytoma, and one had MGUS. Twelve patients had biclonal gammopathy at diagnosis and one developed biclonal gammopathy at relapse. Out of eleven patients with myeloma, eight had lytic bone lesions, seven had anemia (hemoglobin <10 g/dL), four had renal impairment (serum creatinine >2 mg/dL), and two had hypercalcemia >11.5 mg/dL. The mean hemoglobin was 10 g/dL. Serum lactate dehydrogenase was elevated in five patients. Six patients had compression fractures involving the thoracic and lumbar vertebra. The International Staging System was Stage 1 in three patients, II in three patients, and III in five patients. Immunofixation electrophoresis showed IgGκ/IgAλ in three, IgGκ/IgAκ in two, IgGλ/IgAλ in two, IgAκ/IgGκ in three, IgAλ/IgGλ in one, IgGκ/IgG λ in one, and IgGλ/IgGκ in one patient [Figures 1 and 2]. Cytogenetics risk stratification was not done since the facility was not available at our center during that time.

Details of treatment and outcome are summarized in Table 2. The patient with MGUS (Pt #5) is on follow at 44 months with no evidence of progression to myeloma. The patient with solitary plasmacytoma was treated with radical radiotherapy (RT) and is asymptomatic now on follow at 45 months. Out of 11 patients with multiple myeloma, 10 received systemic treatment. Six patients received BD (bortezomib + dexamethasone), three patients received LD (lenalidomide + dexamethasone), and one patient received VCD (bortezomib + cyclophosphamide + dexamethasone). All patients received induction chemotherapy for six cycles. The median duration to best response was 6 months. Response assessment was made according to the International Myeloma Working Group response assessment criteria.

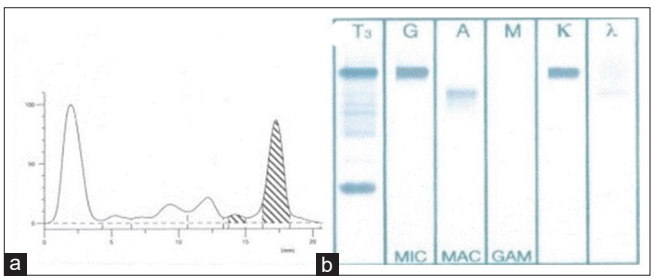

Figure 1: (a) SPE of patient number 1 showing two bands in gamma globulin region, (b) On IFE these two bands correspond to bands IgG κ and IgA λ. SPE = Serum protein electrophoresis, IFE = Immunofixation electrophoresis

Table 1: Baseline characteristics of patients with biclonal gammopathy

Case number	Age and sex	Clinical features	Free κ	Free λ	IFE	M Band g/dL	BM % PC	ISS stage	CRAB	Diagnosis
1	55 male	Backache	363.3	24.09	IgGκ IgAλ	2.87 0.20	30	I	$CRA^{+}B^{+}$	MM
2	70 Female	Backache, DOE	293	31	IgGκ IgAλ	1.30 0.40	10	III	$C^{+}RA^{+}B^{+}$	MM
3	74 Male	Cellulitis leg	3790	15	IgGκ IgAκ	0.55 0.18	20	III	$CR^{+}A^{+}B$	MM
4	72 Male	Backache LOA LOW	13.2	142.6	IgGκ IgGλ	3.17 0.39	10	I	$CRAB^{+}$	MM
5	65 Female	Backache	25.6	20.2	IgGκ IgAκ	0.40 0.14	5	NA	NA	MGUS
6	57 Female	Back ache tiredness	25.6	104	IgGλ IgAλ	2.60 Not measurable	15	I	$CRAB^{+}$	MM
7	63 Male	Low backache	1208	10.6	IgAκ IgGκ	1.86 Not measurable	45	II	$CRA^{+}B^{+}$	MM
8	65 Male	Leg pain	11.4	609.8	IgAλ IgGλ	4.50 0.31	63	III	$CR^{+}A^{+}B^{+}$	MM
9	72 Male	Paraparesis	40	133.4	IgGλ IgGκ	0.5 Not measurable	2	NA	NA	Plasmacytoma
10	60 Male	Backache, tiredness	24.2	279.7	IgGλ IgAλ	0.44 Not measurable	30	II	$CRAB^{+}$	MM
11	64 Male	Low backache	215.5	16.9	IgAκ IgGκ	2.16 Not measurable	11	III	$C^{+}R^{+}AB^{+}$	MM
12	75 Male	Anemic symptom	149.4	6.3	IgAκ IgGκ	3.2 0.29	68	II	$CR^{+}A^{+}B$	MM
13	54 Male	Recurrent UTI	248	138	IgGκ IgAλ	Not measurable	18	III	$CR^{+}A^{+}B$	MM

IFE=Immunofixation electrophoresis, BM=Bone marrow, PC=Plasma cells, ISS=International staging system, CRAB=Hypercalcemia, Renal impairment, Anemia and bone lesions, MM=Multiple myeloma, MGUS=Monoclonal gammopathy of undetermined significance, DOE=Dyspnea on exertion, LOA=Loss of appetite, LOW=Loss of weight, NA=Not applicable, UTI=Urinary tract infection

Complete response (CR) was achieved in one patient, five patients had a very good partial response (VgPR), three had partial response (PR), and one had stable disease. Post induction, in one patient (Pt #13), both major and minor bands disappeared. In the seven patients with VgPR/PR, the minor band disappeared and major band persisted. In the patient with PR (Pt #3), both major and minor bands persisted. Patient #12 had obstructive urinary symptoms also, his serum prostatic specific antigen of 22 ng/ml and was diagnosed with nonmetastatic high-risk adenocarcinoma prostate. He received androgen deprivation therapy with leuprolide and was planned for RT. Five patients received maintenance chemotherapy, bortezomib in three, and lenalidomide in two patients. Three patients with myeloma received palliative RT.

Five patients relapsed, three with both major and minor bands (Pt #1, 2, and 12). Two patients relapsed with both bands at progression (Pt #3 and 8). Two patients received melphalan-based chemotherapy, one received lenalidomide + dexamethasone, and another patient received carfilzomib + lenalidomide + dexamethasone as second-line chemotherapy. Patient #8 failed four lines of chemotherapy and died at 2 years due to pneumonia and sepsis. None of the patients underwent autologous stem cell transplants due to logistical reasons. Eight patients are alive, with survival ranging from 44 months to 110 months, and four patients are alive more than 5 years.

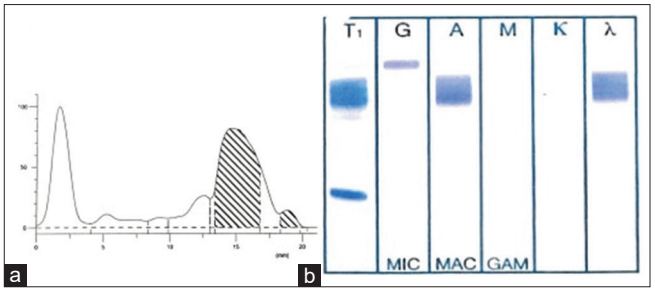

Figure 2: (a) SPE of patient number 8 showing one major and a minor band in gamma globulin region, (b) On IFE, these two bands correspond to bands IgG λ and IgA λ. SPE = Serum protein electrophoresis, IFE = Immunofixation electrophoresis

Discussion

Multiple myeloma clinically presents with features of end-organ damage such as hypercalcemia, renal insufficiency, anemia, bone pain (CRAB features), and recurrent infections. It is characteristically

Table 2: Treatment and outcome of patients with biclonal gammopathy

Case number	Chemo therapy	Response	Maintenance	At relapse	Second line	RT	PFS (months)	OS (months)	Outcome
1	VCD×6	VgPR IgGκ persisted IgAλ resolved	Bz×5 years	IgGκ Monoclonal	KRD×9 – On len maintenance for 4 months	-	66	85	Alive
2	BD×6	SD IgGκ persisted IgAλ resolved	-	IgGκ Monoclonal	MPT×6	10 Gy/5#	2	57	Alive
3	BD×6	PR IgGκ persisted IgAκ Persisted	BD×2 months	IgGκ and IgAκ Biclonal	MP×6	-	1	26	Expired
4	BD×6	PR IgGκ persisted IgGλ resolved	Bz×1 year	Nil	-	8 Gy/1#	38	50	Alive
5	-	-	-	-	-	-	-	44	Alive
6	LD×6	VgPR IgGλ persisted IgAλ resolved	Len×1 year	Nil	-	-	80	92	Alive
7	LD×6	VgPR IgAκ persisted IgGκ resolved	Len×2 years	Nil	-	-	67	79	Alive
8	BD×9	VgPR IgAλ persisted IgGλ resolved	-	IgAλ and IgGλ Biclonal	Thal Dexa POMDexa, MPL VCD Carfil Dexa	30 Gy/10# rib lesion	1	24	Expired Pneumonia, sepsis
9	-	-	-	-	-	45Gy/25#	39	45	Alive
10	Nil	-	-	-		-	-	-	Defaulted Rx
11	LD×6	PR IgAκ persisted IgGκ resolved	-	-	-	-	4	-	Lost follow up
12	BD×6	VgPR IgAκ persisted IgGκ resolved	Bz×10 months	IgAκ Monoclonal	LD	-	10	-	Lost follow up
13	BD×6	CR IgGκ resolved IgAλ resolved	-		-	-	98	110	Alive

RT=Radiotherapy, PFS=Progression-free survival, OS=Overall Survival, Rx=Treatment, VCD=Bortezomib, cyclophosphamide, dexamethasone, BD=Bortezomib, dexamethasone, LD=Lenalidomide, dexamethasone, Bz=Bortezomib, Len=Lenalidomide, MP=Melphalan, prednisolone, MPT=MP Thalidomide, Thal Dexa=Thalidomide, dexamethasone, POMDexa=Pomalidomide+dexamethasone, Carfil Dexa=Carfilzomib, dexamethasone, MPL=MP lenalidamide, CR=Complete response, VgPR=Very good partial response, PR=Partial response, SD=Stable disease, Gy=Gray, #=Fractions, KRd =Carfilzomib+ Lenalidamide+ Deaxamethasone

associated with an increase in monoclonal (M) protein concentrations (IgG/IgA/IgM/IgD/IgE) and/or light chain concentrations (kappa or lambda) in serum or urine identified by protein electrophoresis.

Biclonal gammopathies are rare characterized by the presence of two distinct monoclonal proteins. In the study reported by Kyle *et al*., approximately 1.5% of multiple myeloma patients presented with biclonal paraproteinemia.[5] In a multicentric UK trial on 6399 newly diagnosed patients with myeloma, only 58 had biclonal gammopathy giving a frequency of 0.91%.[4]

The mean age of biclonal gammopathy was 69 years.[4] In our series, the median age was 65 years, with male predominance. Eleven patients had multiple myeloma, one each had plasmacytoma and MGUS.

Both clones may be seen at the time of diagnosis or the second clone may appear during the course of treatment of during follow-up. In the present series, 12 patients had biclonal gammopathy at diagnosis and one patient developed this at relapse.

Biclonal myeloma usually shows two different Ig light chains rather than two different heavy chains. Cases expressing both kappa and lambda light chains are extremely rare.[6] Kyle *et al*. described 57 cases of biclonal gammopathy, 30 (57%) had IgG and IgA components, 15 (26%) had IgG and IgM, six had two IgG components,

three had IgA and IgM, one had two IgA components, one had IgA and IgE, and one had triclonal gammopathy. Of the 115 light chains, 70% were κ, the chains were both κ or both λ in 63% of the biclonal pairs.[5] A combination of two IgG components constitutes <10% of all biclonal gammopathy.[7] In the multicentric UK clinical trial, the predominant Ig subtype was IgG in 39, IgA in 14, IgD in one, and free light chains in four patients. IgG/IgG was the most common combination, followed by IgA/IgG and IgG/IgA.[4]

In one study, IgG/IgM was observed as the common isotype.[8] A combination of IgG/IgG was the most common in some studies.[4,9] Banerjee *et al*. reported biclonal myeloma IgA λ + IgG κ as an extremely rare type of biclonal gammopathy.[6] Coexpression of kappa and lambda light chain by the same plasma cell is rare but reported.[10] In the present study, seven patients had IgG/IgA, four had IgA/IgG, and two had IgG/IgG as the Ig isotypes. Both bands disappeared with treatment in one patient who achieved CR. In the other seven patients who achieved VgPR/PR, the minor band disappeared with treatment; however, the major band persisted. At relapse, three patients had a relapse of major bands only and two patients relapsed with both major and minor bands.

Biclonal gammopathy results from the proliferation of two clones of plasma cells, each producing an unrelated monoclonal Ig or it may result from the production of two monoclonal proteins by a single clone of the plasma cell.[5] It is also presumed that the neoplastic clone which secretes one type of M protein might undergo isotype switching resulting in the production of the second type of M protein resulting in biclonal gammopathy.[11] Gallart *et al*. have reported a case of primary IgG with minor IgD shifting to predominant IgD after chemotherapy.[12] Another case with the shift from IgG κ to IgG κ and IgD κ has also been reported.[13]

The phenomenon of biclonal gammopathy is not restricted to plasma cell neoplasms. Certain B cell lymphomas with plasmacytic differentiation, such as lymphoplasmacytic lymphoma, can also produce paraproteins which can rarely result in biclonal gammopathy.

The treatment of biclonal myeloma is similar to that of monoclonal disease. The therapeutic response in biclonal myeloma has been reported to be similar to that of monoclonal disease.[3] Few studies have shown that the second clone has a protective role and is associated with better therapeutic response, remission rates, and slower progression.[14] The determinant of the behavior of the disease is thought to be the dominant clone which increases over time. Mullikin *et al*. reported that 23 out of 393 patients with biclonal gammopathy of unknown significance progressed, with the dominant clone being the determinant throughout the course.[3] Among our patient group, eight patients are alive with survival ranging from 44 months to 110 months, four patients are alive more than 5 years.

Conclusion

Biclonal gammopathies are rare characterized by the presence of two distinct monoclonal proteins. The most frequent combination was IgG/IgA. Treatment of biclonal myeloma is similar to monoclonal myeloma with comparable outcomes. During follow-up, both paraproteins have to be addressed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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