

# Double Gammopathy of Undetermined Significance-A First Case Report from Pakistan

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## ABSTRACT

Monoclonal Gammopathies are a group of disorders that show high levels of a monoclonal immunoglobulin (M-protein). It is produced by a clone of abnormally proliferating B-lymphocytes and/or plasma cells. This M-protein can be evaluated by Serum or Urine Protein Electrophoresis (SPEP), which yields a single distinct band (M-band), usually in the gamma globulin region. Rarely two separate M-bands appear simultaneously at different positions during SPEP-A condition known as Biclinal Gammopathy, as a result of clonal expansion of two dissimilar neoplastic cell lines. Here, we report an atypical case of plasma cell dyscrasias where two distinct bands were found in gamma region during SPEP depicting bicalgammopathy in gamma region. This peculiar presentation of double M bands in gamma region was double gammopathy without any underlying plasma cell or Lymphoproliferative disorder. This unusual case of double Gammopathy is referred to as “Biclinal Gammopathy” with undetermined significance. To the best of our knowledge this is the first case of double Gammopathy to be reported from Pakistan.

**Key words:** B-lymphocytes; Electrophoresis; Neoplastic; Plasma cell

## INTRODUCTION

Monoclonal Gammopathy (MG) is the presence of a Monoclonal protein (M-protein) in serum and/or urine. This occurs as a result of increased production of monoclonal serum immunoglobulin (Ig) of a single isotype. This overproduction is caused by an abnormal clone of proliferating B-lymphocytes and/or plasma cells [1,2]. It is associated mostly with plasma cell dyscrasias such as Monoclonal Gammopathy of Undetermined Significance (MGUS), plasma cell myeloma, or Waldenström’s macroglobulinemia. However, monoclonal proteins may also occur in primary amyloidosis, cryoglobulinemia, lymphoproliferative disorders, solitary plasmacytoma, and certain infections such as Hepatitis C (HCV) etc. [3]. Serum or Urine Protein Electrophoresis (SPEP and UPEP, respectively) and immunofixation are the methods of choice for the detection of Monoclonal (M) proteins. M proteins on SPEP and UPEP appear as a single intense, discrete band on agarose gel and a sharp peak in the densitometer tracing. This band/peak can be noted in the gamma, beta-gamma, or beta-region depending on the type of monoclonal Igs being produced and secreted [3-5]. After an M protein is identified on electrophoresis, immunofixation is necessary for confirmation and determination of the heavy and light-chain class of the M protein. Immunofixation is more sensitive

than electrophoresis and allows detection of smaller amounts of M protein. [4] Further workup like bone marrow examination, flow cytometry, lymph node biopsy, skeletal surveys etc. are also carried out to rule out any underlying disorder. In very rare cases serum protein electrophoresis shows two distinct M-bands/ paraprotein. This condition is termed as “Double Gammopathy” (DMG). In many instances, the term biclinal gammopathy has also been used for similar condition. [5-7] It is seen in 3%-4% of all cases of gammopathy [6,7] Double Gammopathy are associated with MGUS (where it is appropriately called as BGUS), plasma cell myeloma and other hematological malignancies (leukemias and lymphomas) [6] (Figure 1). It is important to identify a Double Gammopathy. This can help in evaluating the disease behavior and response to treatment of both the clones during therapy. It may also assist in developing treatment strategies for the associated disease conditions.

## CASE REPORT

66-year-old male patient presented with history of progressive generalized weakness and lethargy for one year. He was vitally stable with marked pallor on examination. He had grade three hemorrhoids. No other significant finding/sign was noted on

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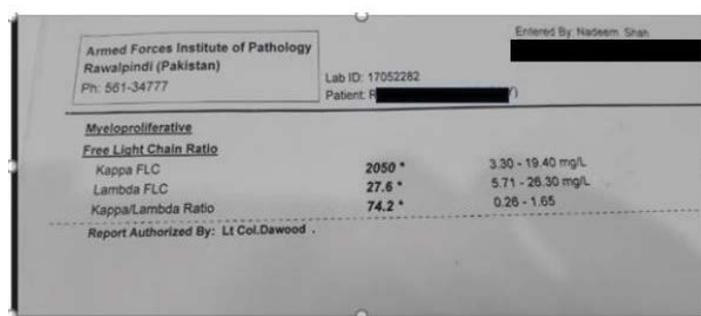
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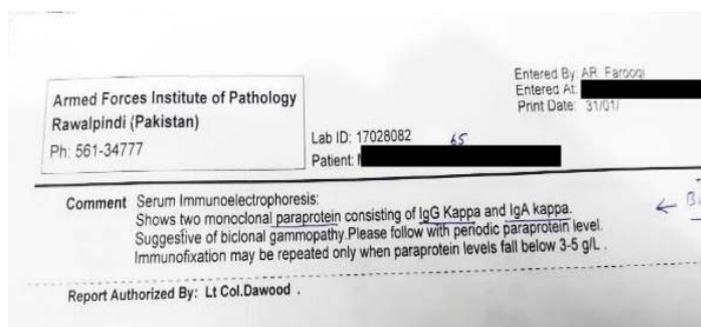
**Figure 1:** Serum protein electrophoresis showing two monoclonal bands in gamma region.

detailed physical examination. Upon basic tests his CBC showed severe hypochromic microcytic anemia with a hemoglobin of 4 gm/dL. Total leucocyte count and platelets were normal ( $6.28 \times 10^9/L$  and  $140,000/cm^3$ ). Peripheral smear morphology showed hypochromia and microcytosis with pencil cells. No abnormal cells were seen. His ESR was 140 mm at the end of first hour. Biochemical investigations of the serum revealed normal Liver function tests, renal functions tests (Serum urea 5.7 mmol/L, serum creatinine 70 mmol/L), serum electrolytes and serum total calcium levels (2.22 mmol/L). Serum ferritin was below the normal range. Total protein was 7.63 with an albumin-globulin ratio of 1. His serum protein electrophoresis showed hypoalbuminemia (3.9 g/dL) with two discrete peaks of paraprotein/M band in the gamma region. Overall paraprotein (including both peaks) was 34% (absolute value: 2.7 g/dL). The first peak was 20.2% and 2nd peak was 14.6% respectively. Serum immunofixation facility is not available at our center so it was outsourced to a referral Lab. Meanwhile his bone marrow aspirate and trephine biopsy were performed. Bone marrow aspirate showed 5% plasma cells with prominent binucleate forms. Bone marrow trephine showed scattered plasma cells (Immunohistochemistry showed focal CD 38+, CD 138+). Immunophenotyping was not performed due to lack of facility. His further work up revealed a raised Serum  $\beta_2$ -microglobulin of 6.31 mg/mL (Normal range: 0.8-2.2 mg/mL). His ultrasound abdomen was normal. His skeletal survey revealed no lytic lesions. Bone scan was also performed that showed no conclusive evidence of any active focal bone pathology. Urine for Bence jones protein was also negative. His immunofixation report revealed two monoclonal paraprotein consisting of IgG Kappa and IgA Kappa. Serum free light chain ratio was Kappa/lambda ratio 74.2 (0.26-1.65), kappa Free Light Chain (FLC) was 2050 mg/L and Lambda FLC was 27.6 mg/L (Figure 2). Based on above lab reports and clinical picture of the patient a diagnosis of double Gammopathy with undetermined significance was made.

During his hospital stay the patient was transfused two units of red cell concentrates. Parenteral iron was also given. He was discharged on oral iron therapy. He was suggested to consult surgical department for treatment of hemorrhoids and a quarterly visit to medical OPD regarding BGUS (Figure 3).



**Figure 2:** Serum free light chain ratio of the patient.



**Figure 3:** Serum immunofixation report.

## DISCUSSION

Double Gammopathy or Biconal Gammopathy can be of three types:

- 1) Dissimilar heavy chains with similar light chains.
- 2) Dissimilar heavy chain with dissimilar light chains.
- 3) Similar heavy chains with dissimilar light chains.

Various heavy chain isotype combinations have been reported in literature. IgG-IgA has been reported to be the most common Heavy Chain (HC) isotype combination by Kyle et al. [1], whereas stated IgG-IgM as the most common HC isotype combination. Few other studies showed IgG-IgG as the most common combination. Our patient has two different heavy chains i.e. IgA and IgG. The disparity may be attributed to racial and geographical differences. About 3-4% of patients with a gammopathy have two monoclonal bands. It is seen mostly in cases of MGUS, followed by multiple myeloma, Waldenstrom's macroglobulinemia or other malignant lymphoproliferative disorders [6,7].

Our patient showed Double Gammopathy in a case of MGUS which is referred to as Biconal Gammopathy with undetermined significance. Microcytic hypochromic anemia (Iron deficiency anemia) in our patient is explained as bleeding from grade three hemorrhoids and is unrelated to the disease pathology of plasma cell myeloma [8]. To the best of our knowledge this is the first case of Double Gammopathy to be reported from Pakistan. A case of two monoclonal bands on serum protein electrophoresis has been locally published in 2011 which was in fact a case of two monoclonal bands of polymorphic IgA rather than true Double Gammopathy as in our case.

A study by Garcia et al. [7] showed that Biconal Gammopathy occurred in 2.8% of total cases of Gammopathies. It is mostly associated with Biconal Gammopathies of undetermined

significance. The most common paraprotein combination was IgG-IgG. According to that study no Biclonal Gammopathies of undetermined significance evolved to a malignant disease [8]. A study by Mullikin et al. [9] revealed that biclonal gammopathies appear to have a similar rate of progression compared to what has been historically described for MGUS and Smoldering myeloma. It raised the possibility of different processes leading to two clones and that they are not necessarily influenced by each other's presence, thus, behaving independently. Better outcomes were observed in biclonal plasma cell myeloma. Since this is the first case reported in Pakistan, an insight into the behavior, progression and treatment response of BGUS is not studied.

## CONCLUSION

Double Gammopathies represents a rare condition. The long-term tracking of these unusual cases may give us insight into the pathogenesis and clinical behavior of Double Gammopathies. Investigations related to genetics of these clones can indicate markers that lead to more aggressive conditions.

## DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to keep the anonymity.

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