

# Biclonal Gammopathy in Chronic Lymphocytic Leukemia: Case Report and Review of the Literature

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## ABSTRACT

Monoclonal gammopathies are frequently seen in B-cell malignancies. Monoclonal proteins are seen in a significant proportion of patients with chronic lymphocytic leukemia (CLL), which is a clonal disorder of mature B cells. The use of more sensitive laboratory methods has enabled the detection of monoclonal proteins or light chains in the serum and/or urine in the majority of these patients. The presence of some of these monoclonal proteins may explain the different autoimmune phenomena that are associated with this disease. Some reports indicate that the finding of monoclonal proteins has a negative impact on patients' survival. The presence of two different monoclonal proteins (i.e. biclonal gammopathy) is on the other hand rare. Most of the reported cases in the literature are of patients with plasma cell disorders. In this report, we describe a rare occurrence of biclonal gammopathy in a patient with CLL. Serum protein electrophoresis and immunofixation, which were negative at the time of initial diagnosis, showed biclonal immunoglobulin A (IgA) kappa and IgA lambda during the course of the disease. The patient's disease showed steady progression, despite multiple treatments. Although this could just be the result of using more sensitive laboratory techniques, biclonal gammopathy in this patient likely reflects the evolution of another clone, which would explain the encountered resistance to therapy. Because of paucity of reports, the impact of biclonal gammopathies in such patients is not known and an effort to collectively report the presentation and outcome of these patients is needed to further understand the pathophysiology and clinical significance of such a finding.

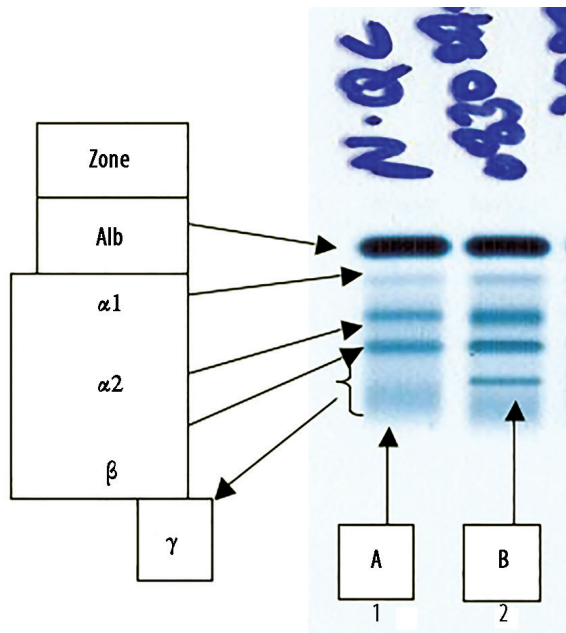
Being a mature B cell malignancy, the finding of monoclonal proteins is not unexpected in chronic lymphocytic leukemia (CLL). Recent reports indicate that over 60% of patients have circulating monoclonal proteins.<sup>1</sup> Biclonal gammopathy, defined as the simultaneous appearance of two different monoclonal protein components, is rare. It is thought to result from the production of two different components by a single clone or by two different malignant clones (developing simultaneously or one evolving from the other as a transformation event). Very few patients with CLL having biclonal gammopathies have been reported. We report the case of a patient with CLL who developed biclonal gammopathy with rapid progression and resistance to treatment.

## CASE REPORT

A 66-year-old man was seen in July 2003 for evaluation of generalized lymphadenopathy. He was asymptomatic and had no organomegaly. Blood tests

showed lymphocytosis of  $35 \times 10^9/L$ . Other blood counts were normal. Serum lactate dehydrogenase (LDH) and uric acid were also normal. Direct anti-globulin test (DAT) was negative. The majority of lymphocytes appeared mature on blood film examination. Prolymphocytes were less than 5%. Bone marrow aspirate (BMA) and biopsy showed infiltration with small-sized lymphoid cells that were kappa light chain restricted, CD5/CD19/CD20/CD23 positive and CD10/CD38/FMC7 negative. Cytogenetic studies were not performed. Chest X-ray and abdomen ultrasound were normal.

The patient was diagnosed with Rai stage I CLL and received no treatment. In 2005, he developed intermittent fever, hepatosplenomegaly, increasing lymphocytosis (lymphocyte count  $60 \times 10^9/L$ ), and neutropenia (absolute neutrophil count (ANC)  $0.7 \times 10^9/L$ ) with rising LDH,  $\beta_2$  microglobulin and uric acid. His prolymphocyte count remained less than 5% and there was no evidence of large cell transformation. Serum protein electrophoresis (SPEP) showed a mild decrease in immunoglobulin

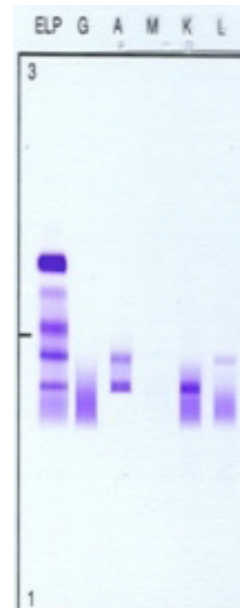


**Figure 1:** Serum protein electrophoresis (SPEP). (a) Normal control band and (b) patient's serum showing a sharp band in the mid gamma region.

(Ig) M (0.32g/L; reference range 0.46–3.04) with no monoclonal band. He was treated with fludarabine and cyclophosphamide (FC). His counts normalized and he had complete regression of the lymphadenopathy and hepatosplenomegaly. However, after the fourth cycle he developed prolonged cytopenia and treatment was withheld.

He remained well until 2008, when he started to have increasing lymphadenopathy and lymphocytosis. At this time, SPEP and immunofixation showed two monoclonal bands: an IgA lambda (in the beta region) and an IgA kappa (in the gamma region) with a total IgA of 5.12g/L, IgM of 0.18g/dL and IgG of 9.6g/L [Figures 1 and 2]. The IgA kappa band in the mid gamma region was quantified as 5.2g/L. The IgA lambda band could not be quantified as it was buried in the beta region with other non-monoclonal proteins.

He was treated with chlorambucil and remained stable until February 2010 when he developed a chest infection and was found to have a lymphocyte count of  $236 \times 10^9/L$ , ANC of  $0.9 \times 10^9/L$ , hemoglobin 6g/dL (DAT negative), and platelets of  $71 \times 10^9/L$ . He had generalized lymphadenopathy and splenomegaly. BMA with repeat flowcytometry showed CD5/CD19/CD20/CD22/CD23/FMC7 positive, kappa light chain restricted lymphoid cells. Zapp 70 and CD38 were both negative. Cyclin D1 was



**Figure 2:** Patient's serum protein immunofixation electrophoresis. Serum protein immunofixation shows two discrete IgA bands: an IgA lambda band in the beta region and an IgA kappa band in the mid-gamma region i.e. biclonal gammopathy. Key: G: IgG, A: IgA, M: IgM, K: kappa light chain, L: lambda light chain.

negative and cytogenetic studies were unremarkable. Translocation of t(11;14) was not demonstrated.

He received fludarabine, cyclophosphamide and rituximab (FCR), which was complicated by febrile neutropenia and hepatitis B reactivation (which was successfully treated with entecavir). He then developed progressive lymphocytosis with evidence of bone marrow failure and enlarging lymph nodes. He received alemtuzumab but developed repeated infections and finally succumbed to multi-drug resistant acinetobacter sepsis with multiple organ failure in the setting of active disease. He did not have any other clinical, radiological, or laboratory findings to suggest concomitant multiple myeloma or other lymphoproliferative disorders.

## DISCUSSION

Besides hypogammaglobulinemia<sup>2</sup> and the poly-reactive autoantibodies,<sup>3</sup> patients with CLL have been shown to have monoclonal proteins. These can even precede the diagnosis of CLL.<sup>4</sup> It is estimated that between 60% to 80% have a demonstrable monoclonal proteins in their serum.<sup>1,5</sup> In addition, over 60% of patients have monoclonal proteins in

their urine (Bence-Jones proteinuria).<sup>6</sup> IgG kappa is the most common followed in order of frequency by IgG lambda, IgM kappa, IgM lambda, and IgA lambda.<sup>7</sup> However, with the use of serum free light chain (FLC) assays, monoclonal FLC appear to be the most commonly detected paraproteins in CLL.<sup>8</sup>

Compared to monoclonal gammopathies, reports of biclonal proteins are very few and the finding of biclonal gammopathy in CLL is very rare. Biclonal gammopathies have been reported in multiple myeloma and in patients with gammopathies of undetermined significance.<sup>9</sup> However, there are very few case reports of true biclonal gammopathies in CLL.<sup>10,11</sup> In three reported cases, the combinations of monoclonal proteins included: IgG kappa and IgM kappa in one patient, and IgM kappa and IgM lambda in two patients. One patient with lambda FLC and IgG lambda simulating a biclonal gammopathy was reported.<sup>12</sup> In addition, one case report of CLL with intracytoplasmic IgM lambda and IgG lambda inclusion.<sup>13</sup> One rare case of CLL producing four monoclonal proteins has also been reported with the combination of IgG lambda, IgG kappa, IgA kappa, and IgM kappa.<sup>14</sup>

The impact of finding monoclonal or biclonal proteins on patients' outcome is not very clear in CLL. In the case of monoclonal proteins, some reports suggest that there is a negative impact on patients' survival independent of the clinical stage.<sup>7,15</sup> Using FLC assays, it has also been shown that monoclonal FLC were associated with poor overall survival.<sup>8</sup> For biclonal gammopathy, the clinical significance and prognostic impact in patients with CLL is uncertain. It is possible that the appearance of a second protein could be a marker of disease progression with possible transformation into a more aggressive disease, as was reported in some patients with biclonal gammopathy. Since very few cases of CLL with biclonal gammopathy have been reported, it is difficult to draw any conclusions.

## CONCLUSION

Biclonal gammopathy is rare. Its clinical significance is, as yet, unclear given the paucity of reports. Given the rarity of such a finding, more collaborative efforts are required to accumulate enough data for more meaningful analysis and conclusions. Such results could help us to better understand the pathophysiology behind diseases like CLL and

may result in better clinical prognostic systems and establish more effective and individualized therapies.

### Disclosure

The authors reported no conflict of interest.

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