

## Monoclonal Gammopathy in Chronic Lymphocytic Leukemia: A Case Report and Review of its Literature

### Abstract

The presence of monoclonal gammopathies in B-cell malignancies occurs frequently. Monoclonal proteins are present in a significant number of patients with chronic lymphocytic leukemia (CLL), which is a disorder of antigen-stimulated mature B-cells. The recognition of monoclonal proteins or light chains in the serum and/or urine is increased in the majority of CLL patients with the use of highly sensitive laboratory methods such as serum immunofixation studies. A different autoimmune phenomenon may explain the presence of some of these monoclonal proteins. Some reports indicate that the finding of monoclonal proteins has a negative impact on patients' survival. However, there is no clear evidence to suggest the prognostic significance of monoclonal proteins in patients with CLL. Although the presence of monoclonal proteins in CLL occurs usually at an incidence of 60%–80%, there are very few cases reported in literature. We report a case of CLL diagnosed in 2009 who developed disease progression along with the presence of immunoglobulin kappa monoclonal gammopathy. Although the presence of monoclonal gammopathy might be due to the use of highly sensitive methods, this can be due to autoimmune phenomenon or development from the same or different clone of B-cells.

**Keywords:** *Chronic lymphocytic Leukemia, Monoclonal gammopathy, Serum immunofixation studies*

### Introduction

Chronic lymphocytic leukemia (CLL) is considered as a disorder arising from antigen-stimulated mature B-cells by avoiding apoptosis. The presence of monoclonal proteins in association with CLL is less with conventional techniques and increases with the use of highly sensitive techniques. We report the case of a patient with CLL who developed monoclonal gammopathy associated with progressive disease in the form of anemia, thrombocytopenia, lymphadenopathy, and splenomegaly. Reports of gammopathy in CLL are very few. A total of three cases were reported in literature. The most recent case of biclonal gammopathy in CLL was reported in 2015 by Khalil.

### Case Report

A 49-year-old male presented with left supraclavicular swelling on April 4, 2009. Clinical examination revealed palpable nontender left supraclavicular lymph node. Rest of the systemic examination was normal. His investigation revealed hemoglobin – 12.6 g/dl, leukocyte

count – 18,300/cumm with lymphocytosis, and platelets – 126,000/ $\mu$ l. Lactate dehydrogenase and serum uric acid were normal. Total bilirubin was 0.7 mg/dl, serum glutamic oxaloacetic transaminase was 23 U/L, and serum glutamic pyruvic transaminase was 23 U/L. Direct and indirect Coombs test was negative. Flow cytometry revealed CD5, CD23, CD19, and CD20 positive. Bone marrow biopsy was suggestive of CLL with nodular, paratrabecular, and interstitial pattern. Karyotyping revealed 46XY in majority. Fluorescence *in situ* hybridization was normal in 87% of cells, heterogeneous deletion of 11q23 was observed in 8% of cells, Trisomy 12 was observed in 2% of cells, and deletion in 13q was observed in 7% of cells. Chest X-ray was normal. Ultrasound abdomen was suggestive of well-defined heterogeneous space-occupying lesion in segment IV of liver. Computed tomography of abdomen and pelvis showed segment 4a, 4b hypodense hepatic lesions with enhancement pattern, highly suggestive of hemangioma and mild splenomegaly. The patient was diagnosed as Chronic B-cell Lymphocytic leukemia Rai Stage - 0/1.

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He was on regular follow-up with complete blood counts and physical examination. He later presented on January 2017 with complaints of easy fatigability. Examination revealed presence of pallor, bilateral cervical, axillary lymphadenopathy, and massive splenomegaly (spleen palpable up to umbilicus). Investigations revealed hemoglobin  $-6.2\text{gm/dl}$ , leukocyte count  $-34,000/\text{mm}^3$  with lymphocytosis and smudge cells in peripheral smear, and platelet count  $-80,000/\mu\text{l}$ . Serum quantitative immunofixation showed total immunoglobulin (IgG) to be  $6190\text{ mg/dl}$  (normal:  $700-1600$ ), total IgA to be

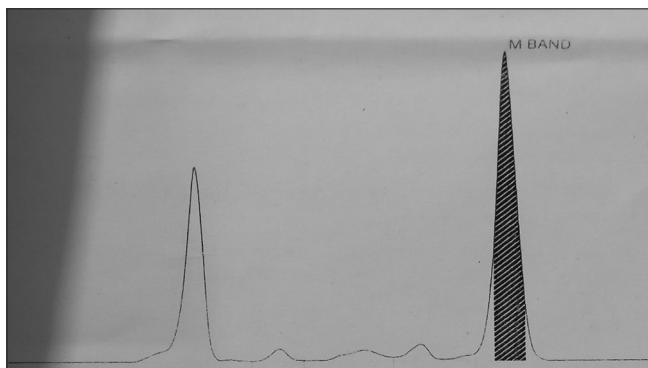


Figure 1: Serum protein electrophoresis showing "M" band in gamma globulin region

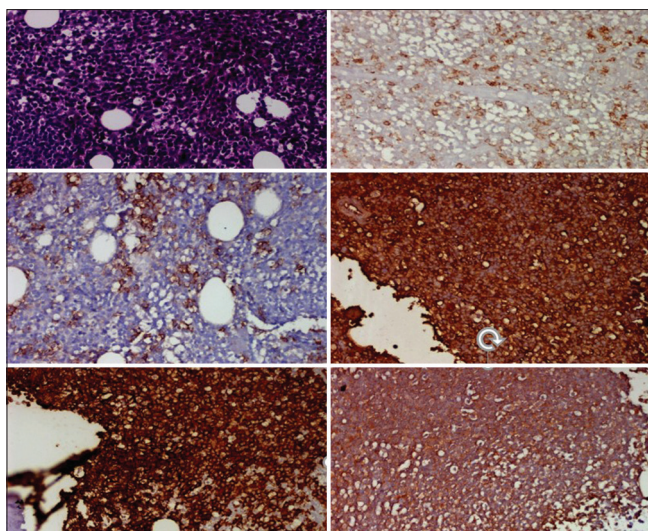


Figure 2: Bone marrow biopsy showing mature lymphocytes with immunohistochemistry positive for CD5, CD138, CD20, kappa, and lambda, respectively

$18.80\text{ mg/dl}$  (normal:  $70-400$ ), and total IgM to be  $11.40\text{ mg/dl}$  (normal:  $40-230$ ). Serum-free kappa (light chain) was  $823\text{ mg/L}$  (normal:  $3.3-19.4$ ), Serum-free lambda was  $6.86\text{ mg/L}$  (normal:  $5.71-26.3$ ), and free kappa lambda ratio was  $119.62$  (normal:  $0.26-1.65$ ). Beta-2 microglobulin was  $3353\text{ ng/ml}$ . Serum protein electrophoresis revealed "M" band of  $4.85\text{ gm}\%$  in gamma region [Figure 1]. Urine for Bence-Jones protein was negative. Bone marrow biopsy revealed mature lymphocytes with immunohistochemistry positive for CD5, CD138, CD20, kappa, and lambda, suggesting CLL without any evidence of multiple myeloma [Figure 2]. Whole-body positron emission tomography scan revealed evidence of low-grade metabolically active disease in bilateral cervical, axillary, deep pectoral, abdominal, retroperitoneal, and bilateral pelvic lymph nodes and spleen and diffuse marrow uptake findings compatible with CLL [Figure 3]. Cytogenetics revealed deletion of p53 in 3% cells, Trisomy 12 in 17% cells, and deletion of 13q14 in 23% cells [Figure 4a-c]. The patient was diagnosed with CLL modified Rai Stage IV with monoclonal IgG kappa gammopathy and he received 3 units of packed red blood cells and was started on tablet ibrutinib  $140\text{ mg}$  thrice a day. After 2 weeks of ibrutinib treatment, the patient's lymph nodes and spleen clinically decreased in size and he was discharged in stable condition and advised for regular follow-up.

## Discussion

CLL is associated with progressive hypogammaglobulinemia that can involve one or more IgG subclasses.<sup>[1]</sup> The incidence of monoclonal proteins in patients with CLL ranges between 60% and 80%.<sup>[2,3]</sup> IgG kappa is the most common abnormality detected in CLL followed by IgG lambda, IgM kappa, IgM lambda, and IgA lambda in the order of frequency.<sup>[4]</sup> Free light chains are also commonly detected abnormalities in CLL. They can occur in 30%–40% of patients in CLL.<sup>[5]</sup> The exact pathophysiology of this monoclonal proteins is not known, it might be due to autoimmune phenomenon, derivation from same or different clone of B-cells. Some studies have shown that serum-free light chain abnormalities are associated with poor prognosis in CLL.<sup>[6,7]</sup> The exact role of monoclonal or biconal proteins in CLL is not clear, even though some studies have shown that the presence of monoclonal or biconal proteins is a poor prognostic factor.<sup>[8]</sup> It is difficult to draw conclusions from previously reported cases

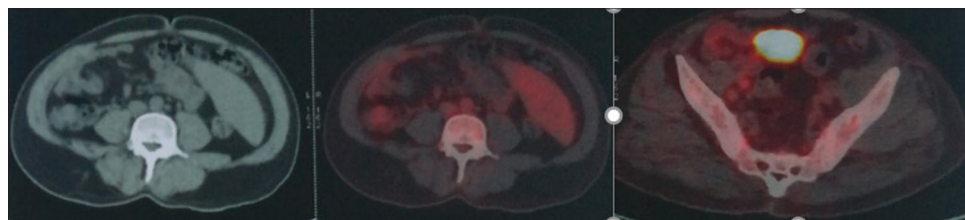


Figure 3: Positron emission tomography scan showing low-grade metabolically active abdominal, retroperitoneal, and bilateral pelvic lymph nodes and spleen and diffuse marrow uptake consistent with chronic lymphocytic leukemia



**Figure 4:** Fluorescence *in situ* hybridization in bone marrow aspirate showing (a) Two green and one orange signals indicating heterogeneous deletion of p53 in 3% of cells. (b) Three green, two orange, and two aqua signals indicating Trisomy 12 in 17% of cells. (c) Two green, one orange, and two aqua signals indicating heterogeneous deletion of 13q14.3 in 23% of cells

regarding their role in CLL as there are few cases reported and as there are no randomized controlled studies done regarding this issue.

### Conclusion

The clinical and prognostic significance of monoclonal proteins in CLL is not clear. More data, studies, and evidence are required for better understanding of its pathophysiology and use of this information in clinical practice for better outcomes. This may help us in therapeutic decision-making in the future.

### 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 conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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