

Case Report

Diagnosis of Concomitant Plasma Cell Myeloma and Chronic Lymphocytic Leukemia in a Single Patient: A Case Report

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Plasma cell myeloma (PCM) and chronic lymphocytic leukemia (CLL) are hematologic malignancies that occur at different stages of the B-cell maturation pathway. Although both diseases are relatively common malignancies in elderly individuals, their concomitant occurrence in one patient is rare. Here we report a patient with a 9-year history of CLL who was subsequently diagnosed with coexisting PCM after she was found to have bilateral pathologic clavicular fractures. We provide immunohistological and immunophenotypic evidence for these separate and simultaneous diseases within the same patient.

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INTRODUCTION

Plasma cell myeloma (PCM) and B-cell chronic lymphocytic leukemia (CLL) are both lymphoproliferative diseases that occur at different stages in the B-cell maturation pathway. In PCM, the malignant cells are thought to originate from a post-germinal center plasma cell, in which the immunoglobulin genes have undergone class switch and somatic hypermutation. In CLL, the neoplastic cells are antigen-experienced B cells that have occurred with or without somatic hypermutation.¹ As separate entities, both are common hematologic neoplasms, each constituting about 10-11% of all hematologic malignancies.^{2,3} However, the coexistence of PCM and CLL in the same patient is quite rare and to date, there have been only isolated case reports with the largest series of 15 such patients reported by Alley et al in 2013.⁴ Whether there is a clonal relationship between these diseases in such patients has yet to be elucidated. Here we present a case in which a patient had stable, non-treated CLL for 9 years before consecutive pathologic clavicular fractures incited a workup that revealed progression to Rai stage VI CLL with development of concomitant stage II PCM.

CASE REPORT

In June 2006, a 66-year-old female with a history of osteopenia was referred to the Hematology department for lymphocytosis, diagnosed coincidentally. Physical examination was negative for lymphadenopathy and organomegaly. Her initial laboratory studies displayed a hemoglobin (Hb) level of 12.1g/dL, white blood cell (WBC)

count of 18.2 k/cumm with 83.2% lymphocytes, and platelet (plt) count of 166 k/cumm. Her lactate dehydrogenase (LDH) and beta-2-microglobulin levels were normal. Immunophenotyping of the B-cells showed a kappa light chain-restricted monoclonal population co-expressing CD19, CD20, CD5, and CD23. The cells did not express ZAP-70 and CD38, indicating a favorable prognosis. Fluorescence *in situ* hybridization (FISH) analysis revealed no chromosomal abnormalities. She was diagnosed as Rai stage 0 B cell CLL. She did not require treatment and remained asymptomatic with no evidence of disease progression for the next 9 years.

In December 2012, the patient fell and suffered a fracture to her sternum, which was noted to be slow to heal. There were no reports of lytic lesions on x-ray at the time. Her creatinine was 0.85mg/dL and serum calcium was 9.5 mg/dL (normal range 8.5 - 10.5 mg/dL). She remained pan-hypogammaglobulinemic. In 2015, the patient experienced a series of clavicular injuries within the span of several months. In April, she suffered a left acromioclavicular joint separation from a lifting injury. In June, she fractured her right clavicle without any clear inciting event. In September, she was hospitalized for chest pain and was found to have fractured her left clavicle, again, without clear etiology.

This last clavicular injury raised concern that the underlying etiology of her recent injuries may have been either related to her CLL, although this would have been a very atypical manifestation of the disease, or a plasma cell disorder. Lab workup over the prior 9 years showed a steadily climbing WBC count to 36.0 k/cumm at the time of her left clavicular fracture; Hb was 11.1 g/dL and the platelet count was 151 k/cumm. Basic metabolic panel (BMP) showed a creatinine of 0.83mg/dL and total serum calcium of 9.6 mg/dL.

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She was found to have an elevated free serum lambda light chain level at 1532 mg/L with free kappa/lambda ratio of 0.01. Immunofixation did show a monoclonal lambda light chain despite a negative serum protein electrophoresis. Skeletal survey displayed multiple punched out lucent lesions in the skull and bilateral humeri. CT of the abdomen and chest revealed lytic lesions in the bilateral medial clavicles and manubrium, and hepatomegaly with retroperitoneal and aortocaval lymphadenopathy. Bone marrow examination showed a hypercellular marrow (90%) with multiple lymphoid aggregates and subtle plasmacytic infiltrates between lymphoid nodules, as shown in **Figure 1a**. Further detail is shown in **Figure 1b**, which shows PAX5 highlighted lymphoid nodules, while **Figure 1c** shows CD138 staining of plasma cells. Bone marrow cytogenetic analysis revealed a

normal 46,XX genotype. FISH analysis was negative for the CLL panel, including for the t(11;14) translocation, however was positive within the PCM panel for deletion of 5'IGH. The lymphocytes were shown to be positive for CD5, as shown in **Figure 1d** and negative for cyclin D1, as shown in **Figure 1e**, while the plasma cells showed the opposite staining pattern. Flow cytometry demonstrated a CD5 positive monoclonal B cell population with dim kappa light chain expression, shown in **Figure 2**. In situ hybridization showed lambda light chain restricted plasma cells, shown in **Figure 3**. Based on these clinicopathological findings, the patient was diagnosed with concomitant stage IV CLL and stage II plasma cell myeloma. She is currently undergoing treatment with lenalidomide, dexamethasone, bortezomib, and denosumab.

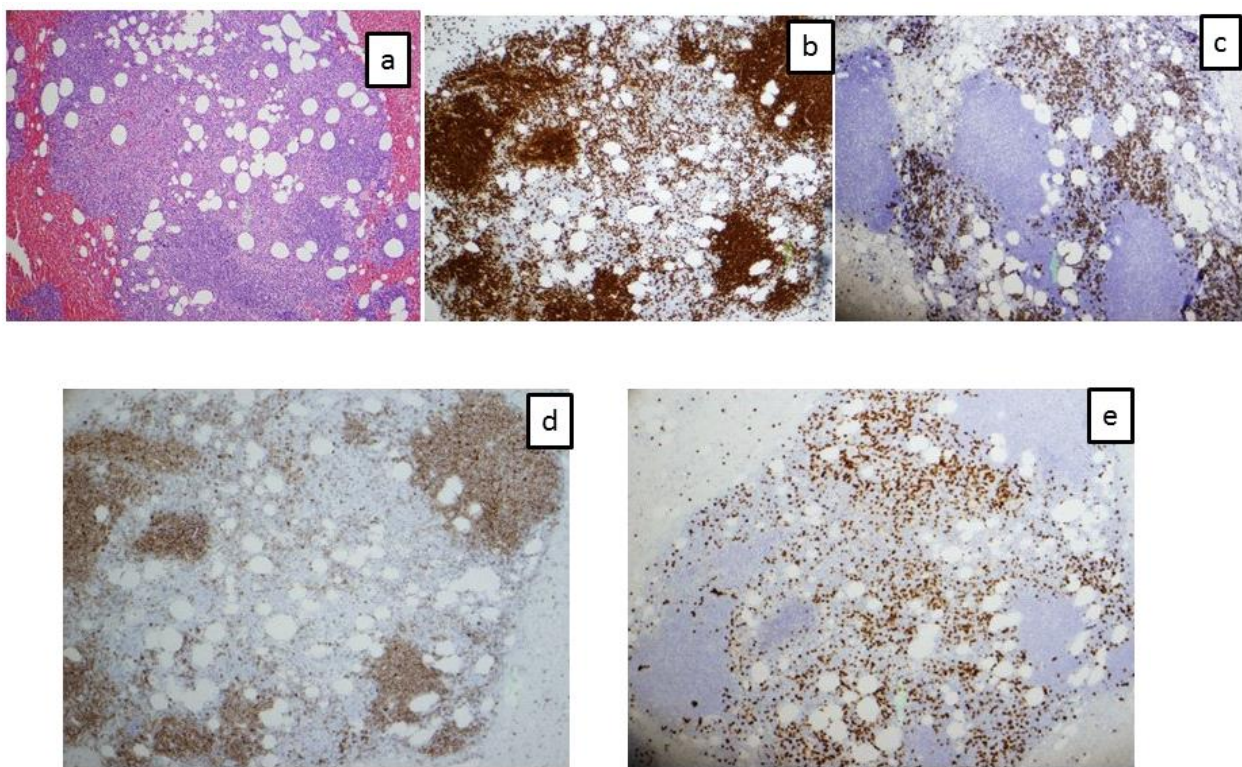


Figure 1. a. Bone marrow biopsy, HE 100X. b. Immunostain of PAX5, 100X. c. Immunostain of CD138, 100X. d. Immunostain of CD5, 100X. e. Immunostain of cyclin D1, 100X.

DISCUSSION

Plasma cell myeloma and CLL comprise the two most common B-cell malignancies within the older adult population.² Despite the relatively high incidence of both malignant processes, the concomitant occurrence of PCM and CLL in one patient is rare.¹ Our patient's bone marrow examination shows obvious nodular lymphocytic aggregates with a subtle but present plasmacytic infiltrate. Our patient's flow cytometric analysis reported a CD5 positive, CD23+, kappa light chain restricted monoclonal B-cell population, consistent with CLL. Morphologic evaluation of her bone marrow biopsy demonstrated few plasma cells, particularly outside the lymphoid aggregates; further

immunohistochemical stains of CD138 confirmed their presence. It has been reported that some CLL cells can present with extensive plasmacytoid differentiation with expression of CD138. However, the expression of Cyclin D1 in these plasma cells suggests that these plasma cells might be a different neoplastic process. Furthermore, *in situ* hybridization for kappa and lambda light chains was performed and also supported the presence of separate diseases processes (**Figure 3**). These pathological findings, in conjunction with the patient's clinical presentation, substantiate the diagnoses of concomitant CLL and plasma cell myeloma.

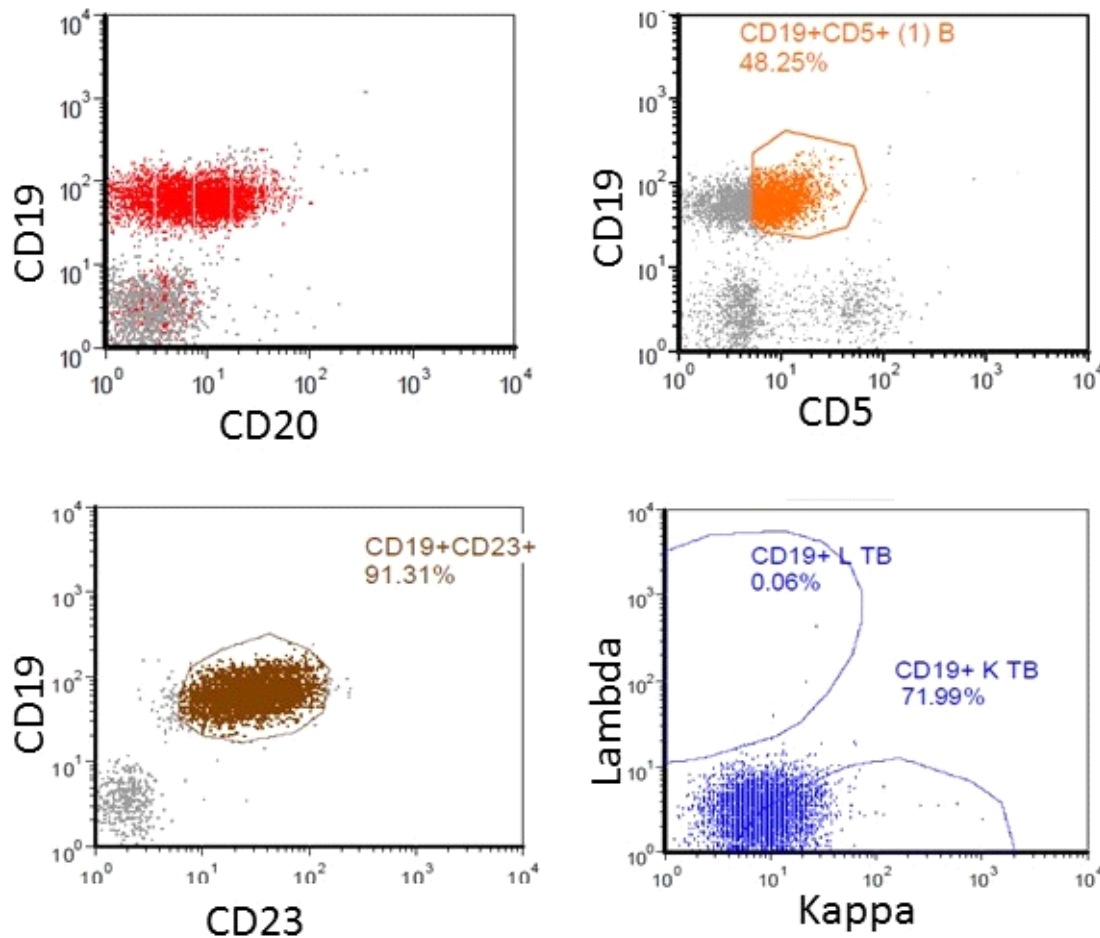


Figure 2. flow cytometry shows a CD5+, CD19+, CD20+(dim), CD23+, kappa+(dim) monoclonal B cellpopulation.

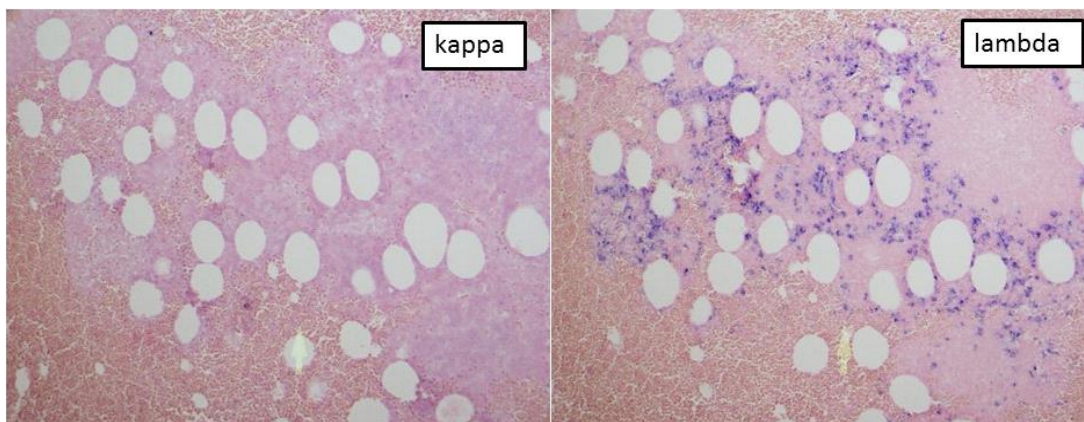


Figure 3. In situ hybridization of kappa and lambda light chain.

As CLL and PCM both originate from the B-cell maturation pathway, the question has been raised as to whether the two diseases arise from the same progenitor cell or are of biclonal derivation. Since plasma cells have the ability to develop from follicular B-cells, marginal-zone B-cells, B-1 cells, and memory B- cells.⁵ it is theoretically possible that malignant plasma cells may originate from a B-CLL clone. Several

authors have attempted to address this issue by analyzing the immunoglobulin light chains produced by the two types of cells.⁶⁻⁹ Femand et al conducted a study using the cells of a patient who, similar to our patient, was initially diagnosed with CLL, and was then found to have concomitant PCM ten years later. Their work supported a monoclonal origin for both diseases by demonstrating that the patient's B-CLL cells

and malignant plasma cells synthesized IgG κ and IgA κ molecules, respectively, with shared idiotypic determinants. Furthermore, when the B-CLL cells were cultured *in vitro* and then stimulated to differentiate into immunoblasts and plasma cells, a switch from IgG to IgA occurred, suggesting that conserved immunoglobulins may be evidence of PCM originating from B-CLL cells.⁷ Novak et al used the same idea and supported a biclonal origin based on the contrasting expressions of kappa and lambda light chains in the CLL and PCM populations, respectively, in a single patient.⁹ Relationships between immunoglobulin gene rearrangement analyses and FISH chromosomal abnormalities have also been studied in the lymphocytes and plasma cells of patients harboring both diseases.¹⁰⁻¹²

In patients with CLL, treatment with alkylating agents, such as chlorambucil, may be a potential factor linked to the concomitant development of multiple myeloma.^{7,13,14} Patriarca et al reported a case in which PCM of clonal origin which was separate and distinct from the patient's original B-CLL, occurred after treatment with fludarabine, based on the detection of two different heavy chain rearrangements in the bone marrow.¹¹ Development of PCM in a CLL patient has also been reported after experimental immunotherapy with IL-4, which has shown to stimulate B-cell growth and maturation *in vitro*.¹⁵ These are important considerations when treating patients with CLL, although the majority of reported patients in the literature affected by both diseases, including ours, had not been previously treated for CLL.^{8,9,16}

The rarity of concomitant PCM and CLL in a patient has the potential to delay proper diagnosis and treatment. Our patient's series of orthopedic injuries were initially thought to be due to her CLL, despite the fact that the disease does not characteristically involve bone. In the years leading up to her clavicular fractures, the patient's white count had doubled, however her serum calcium and kidney function remained normal. Her hemoglobin was slightly decreased from prior, though this could have also been easily attributed to her CLL. To date, there are no established risk factors or immunophenotypic or chromosomal patterns that contribute to the development of PCM in a patient with CLL and vice versa. Even in patients who harbor matching light chain restrictions among the malignant CLL and PCM cells, this finding is not necessarily diagnostic of monoclonality.⁴

CONCLUSION

CLL and PCM are both commonly occurring hematologic malignancies, however their coexistence in a single patient is rare. Clinicians should be aware that these two B-cell disorders have been reported to occur together and not be quick to dismiss the possibility of a simultaneous diagnosis if the proper clinical and laboratory findings are present. Concurrent CLL and PCM arising from monoclonal and biclonal origin have both been reported in the literature.

Future investigations on the transformation events would shed light on the oncogenesis behind these B-cell disorders.

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CONFLICT OF INTEREST

There is no commercial, financial or other association that poses a conflict of interest in connection with the article.

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