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Case study

Prolymphocytic transformation of lymphoplasmacytic lymphoma: an extremely unusual event☆

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Summary Although rare cases of prolymphocytic transformation from splenic B-cell lymphomas and follicular lymphoma have been reported, prolymphocytic transformation from lymphoplasmacytic lymphoma has not been previously reported. We report a case of 76-year-old-male patient with a history of Waldenström macroglobulinemia diagnosed in 2010 and treated with infusion chemotherapy. He was in clinical remission for 5 years. In 2016, he presented with diffuse lymphadenopathy, and a head and neck lymph node biopsy showed lymphoplasmacytic lymphoma. MYD88 mutation was detected by polymerase chain reaction. A subsequent bone marrow biopsy showed B-cell lymphoma with increased prolymphocytes. Peripheral blood showed numerous circulating prolymphocytes. MYD88 was detected by polymerase chain reaction in the bone marrow. Cerebrospinal fluid was positive for lymphoma cells with prolymphocytic morphology. An IgM κ paraprotein was noted by immunofixation performed on the patient's serum, urine, and cerebrospinal fluid. The patient was resistant to chemotherapy, developed multi-organ failure, and died shortly thereafter.

1. Introduction

B-cell prolymphocytic leukemia (B-PLL) is a rare neoplasm of mature B cells observed in elderly individuals with a median age of 65 years, with an equal male-to-female predilection [1]. The term "prolymphocytic" is a misnomer because the neoplastic lymphocytes represent mature B cells, although the postulated normal counterpart is largely unknown. The clinicopathological features of B-PLL were originally described in 1974 as a variant of chronic lymphocytic leukemia (CLL) [2] but was subsequently recognized as a distinct entity in the different iterations of the World Health Organization classifications [1]. The debate still continues, though, about the distinction of B-PLL as an entity, and some data indicate that B-PLL represents a heterogenous group of disorders ranging from CLL-like PLL to leukemic mantle cell lymphoma to nodal mantle cell lymphoma [3,4]. Although rare cases of

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prolymphocytic transformation from follicular lymphoma and splenic B-cell lymphomas, including marginal zone lymphoma, have been reported [5,6], prolymphocytic transformation from lymphoplasmacytic lymphoma has not been previously reported, to the best of our knowledge.

2. Case report

Our patient is a 76-year-old man with a history of Waldenström macroglobulinemia diagnosed in 2010 at an outside facility. He received 1 dose of rituxan, which was stopped because of infusion reaction, and then he was treated with 3 cycles of fludarabine/cytoxan in 2011. He was in remission until October 2015 when he developed generalized lymphadenopathy. Abdominal and pelvic scans showed splenomegaly and retroperitoneal masses. The patient had 3 biopsies on June 2016: right periauricular mass, right submandibular mass, and right trapezius mass. The periauricular specimen showed moderately differentiated invasive squamous cell carcinoma. In addition, all 3 specimens showed scattered reactive germinal centers surrounded by expanding marginal zone layers and few clusters of κ-restricted plasma cells around the marginal zone cells (Fig. 1). Slightly increased numbers of large cells were noted, but no confluent sheets of large calls were seen. Ki-67 denoted an overall low proliferative activity (Fig. 1). Flow cytometry showed a κ-restricted B-cell population that express CD20, CD19, and CD22, but negative for CD5, CD10, and CD23. The case was signed out as low-grade B-cell lymphoma with clonal plasmacytic differentiation, and a differential diagnosis of marginal zone lymphoma and lymphoplasmacytic lymphoma, favoring marginal zone lymphoma. Subsequent MYD88 L265D mutation was detected by polymerase chain reaction (PCR). Lymphoplasmacytic lymphoma was then favored after the receipt of MYD88 results and the concurrent IgM κ paraproteinemia.

The patient was treated with 2 cycles of oxaliplatin, cytarabine, and ibrutinib for 6 months followed by chlorambucil for 1 month with no apparent remission. His absolute neutrophil count was persistently zero despite daily doses of filgrastim after chemotherapy. He was also transfusion dependent to both platelet and red blood cells. The patient was then transferred to our facility in August 2016, where a bone marrow biopsy was performed that showed significant involvement by B-cell lymphoma in nodular and interstitial patterns of

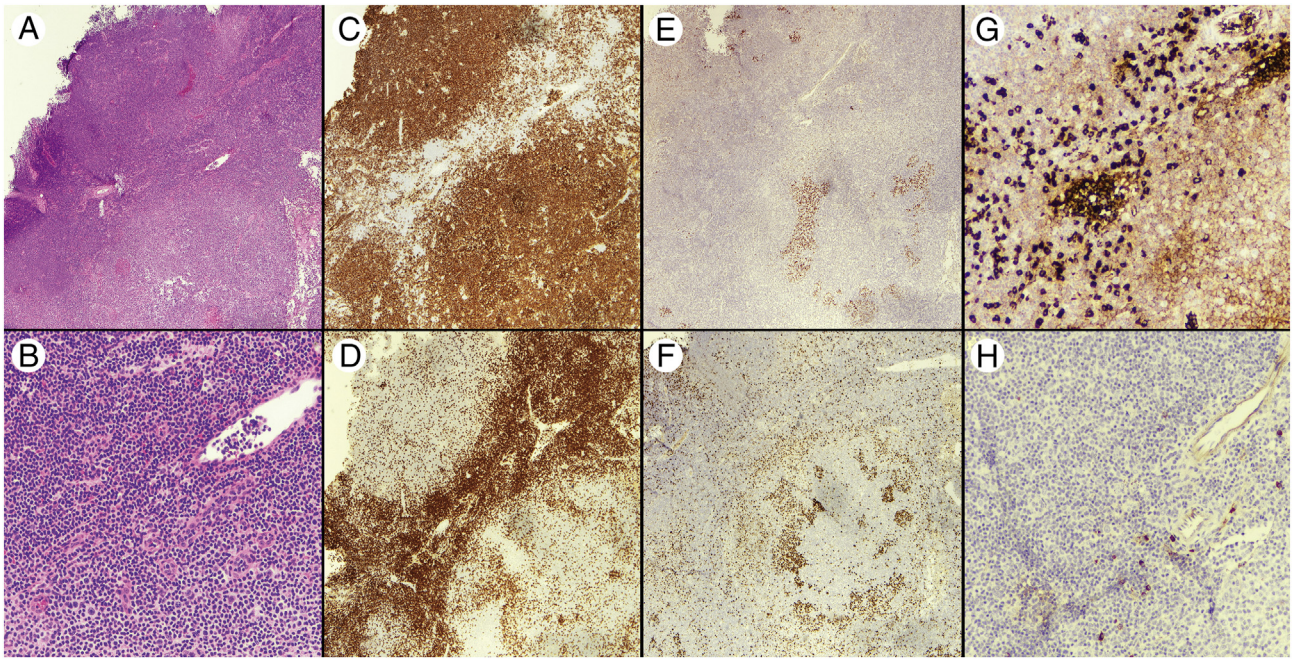

Fig. 1 The composite picture is from a submandibular mass biopsy performed in 2016. A, Hematoxylin and eosin stain at low magnification (×4) shows effacement of the nodal architecture by a vaguely nodular process. Few open sinuses are noted. B, At high magnification (×40), most of the lymphocytes are small with scattered interspersed large cells. Slightly increased number of plasma cells is noted. C, CD20 stain at ×4 magnification highlights the B cells in a nodular fashion. Tiny clusters of darker staining cells are noted in the lower nodule corresponding to residual germinal center cells. D, CD3 stain at ×4 magnification highlights the T cells. E, Bcl-6 stain at ×4 magnification highlights the tiny clusters of residual germinal center cells, suggestive of follicular colonization of the follicles by the lymphoma cells. F, Ki-67 at ×4 magnification shows high proliferative index within the residual germinal center cells. Despite the presence of slightly increased proliferative activity outside the germinal centers, no confluent clusters of proliferating cells are noted. G, kappa Stain at high magnification (×40) highlights small clusters of plasma cells indicative of kappa restriction. The adjacent lymphoma cells also show faint kappa positivity. H, lambda Stain at high magnification (×40) highlights rare positive plasma cells with a significantly increased kappa-to-lambda ratio.

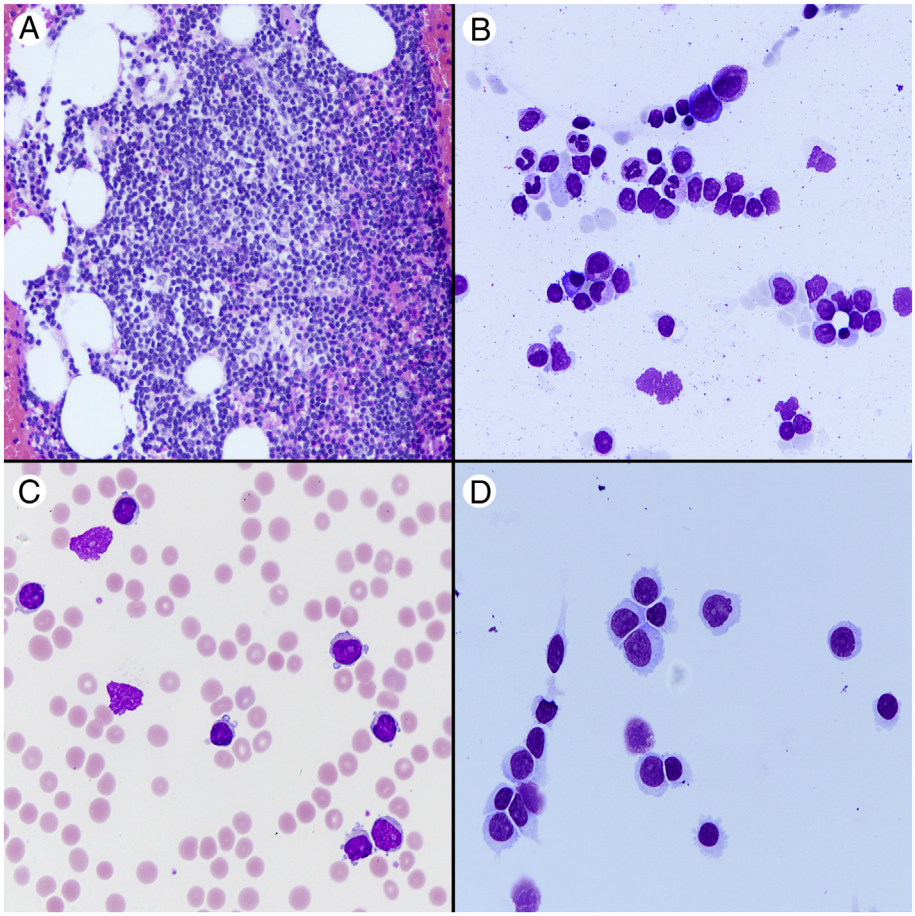

Fig. 2 A, In the composite picture, a hematoxylin and eosin stain from the bone marrow clot biopsy shows one of the lymphoid aggregates with increased number of large cells. B, Giemsa stain of the bone marrow aspirate smear shows evidence of hematopoiesis along with the presence of medium to large lymphoma cells with one prominent nucleoli, mainly concentrated on the right side of the picture. C, Giemsa stain of the peripheral blood smear shows circulating prolymphocytes with one centrally placed prominent nucleolus. D, Giemsa stain of the CSF cytospin shows few small lymphocytes along with large lymphoma cells with one prominent nucleoli and a similar morphology to those seen in the bone marrow aspirate smear and peripheral blood smear. All pictures were taken at a ×40 magnification.

infiltration (60%) (Fig. 2). Variable proliferative activity was detected within the lymphoid infiltrate, but areas with increased proliferation index were noted. The peripheral blood smear showed many circulating lymphoma cells, many of which have a centrally placed nucleolus suggestive of prolymphocytes and were estimated at greater than 55% of all cells (Fig. 2). No increased plasma cells or evidence of a monoclonal plasma cell population was detected. Flow cytometry on the bone marrow showed 47% κ-restricted B cells that express CD20, CD19, and CD22, but negative for CD5, CD10, CD38, and CD23. By immunohistochemistry, LEF-1, cyclin D1, and SOX-11 were negative within the neoplastic lymphocytes. MYD88 L265p mutation analysis by PCR was positive in the bone marrow sample. Fluorescence in situ hybridization (FISH) analysis showed loss of 1 copy of 13q14 signal in 17 (5.7%) of 300 cells examined and loss of 1 copy of the 17p13.1 signal in 127 (42.3%) of 300 cells examined. Cytogenetic studies showed a loss of Y chromosome (45, X, −Y) in 10 cells and normal male karyotype (46, XY) in the other 10 cells. The cerebrospinal fluid (CSF) was also involved by large lymphoma cells with a morphologic appearance consistent with prolymphocytes (Fig. 2). Flow cytometry on the CSF showed a κ-restricted B-cell population with a phenotype similar to that seen on the bone marrow.

Serum immunoglobulin profile on August 2016 showed increased IgM at 3330 mg/dL (65-263 mg/dL), whereas IgA levels were at 10 mg/dL (68-378 mg/dL) and IgG levels were at 555 mg/dL (694-1618 mg/dL). The serum κ free light chains were 30.60 mg/L (3.30-19.40 mg/L), λ free light chains were 8.38 mg/L (5.71-26.30 mg/L), and the κ-to-λ ratio was increased at 3.65 (0.26-1.65). An IgM κ monoclonal paraprotein was consistently identified by electrophoresis, immunotyping, and immunofixation in serum, CSF, and urine specimens (Fig. 3). An additional free κ light-chain band was noted in the urine sample by immunofixation. On September 2016, the patient developed dysphagia, aspiration pneumonia, and subsequent candidemia. He died of multiorgan failure shortly thereafter.

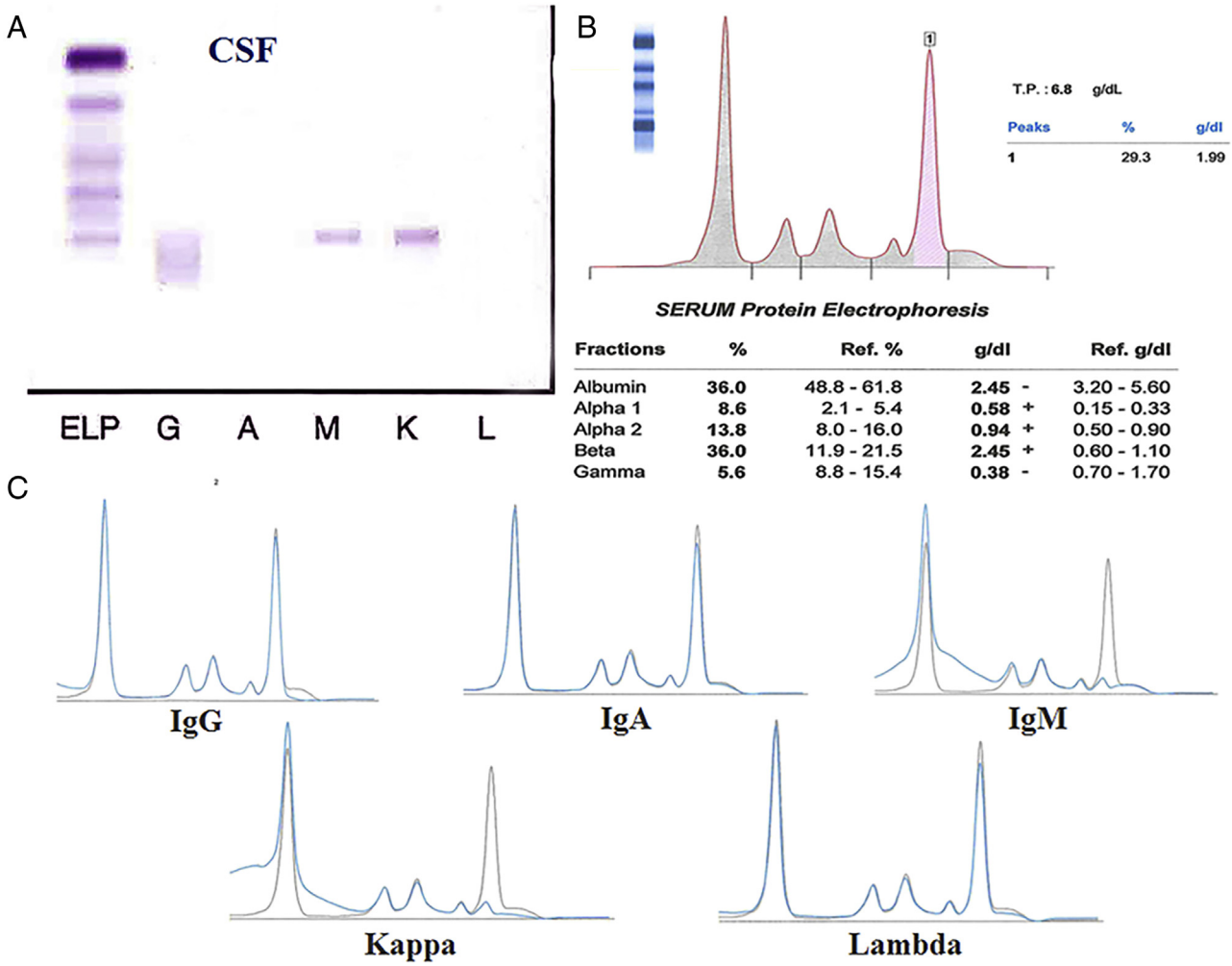

Fig. 3 A, In the composite picture, CSF immunofixation with IgM κ bands correlates with a band near the β region by gel electrophoresis. This portion was scanned from the Sebia Hydragel electrophoresis system. B, Serum protein electrophoresis shows a prominent peak in the β region. C, By immunotyping, an IgM κ paraprotein is clearly identified. The testing was performed using Sebia electrophoresis system.

3. Discussion

B-PLL is a rare neoplasm, where prolymphocytes comprise greater than 55% of the cells in the peripheral blood [1]. Prolymphocytes are large cells (twice the size of a normal lymphocyte) with round nucleus, moderately condensed chromatin, and one prominent centrally located nucleolus. Most patients present with B symptoms, massive splenomegaly with absent or minimal peripheral lymphadenopathy, anemia, thrombocytopenia, and rapidly increasing lymphocyte count (usually >100 × 10^9/L) [1]. By cytogenetics testing, deletion in 17p13 is detected in more than 50% of the cases and is associated with *TP53* mutations, which represents the highest reported rate in B-cell lymphomas and likely explains the progressive course and relative treatment resistance of B-PLL [1,7]. Deletions of 11q23 and 13q14 occur in about 30% of the cases, but trisomy 12 is uncommon [7,8]. In contrast to CLL, deletions of *RB1* are reported to be more frequent than deletion of *D13S25* on the long arm of chromosome 13 [9]. Aberrations of *MYC*, including gains, amplifications, and translocations, are seen in most cases, which may be suggestive of a potential role that the C-MYC pathway may play in the pathogenesis of B-PLL [7]. Cases previously reported to harbor t(11; 14) involving the *cyclin D1* gene are now reclassified as leukemic variants of mantle cell lymphoma.

For our patient, the head and neck biopsies showed evidence of lymphoplasmacytic lymphoma with supportive morphology and immunophenotype. Although marginal zone lymphoma with clonal plasmacytic differentiation cannot be ruled out, the detection of MYD88 mutation and the reported IgM paraproteinemia were more supportive of a diagnosis of lymphoplasmacytic lymphoma. No definitive evidence of prolymphocytic or large cell transformation was seen at the time. The subsequent examination of the bone marrow and peripheral blood showed involvement by a B-cell lymphoma but with evidence of prolymphocytic transformation. The peripheral smear shows greater than 55% circulating prolymphocytes. Although the identification of a low-grade component

in the bone marrow may have been suggestive of CLL in transformation, the detection of MYD88 mutation by PCR and the negativity for CD5 and LEF-1 by immunohistochemistry were consistent with lymphoplasmacytic lymphoma. The CSF showed involvement by many large cells with a morphologic appearance of prolymphocytes, similar to those seen in the peripheral blood. IgM κ paraprotein was detected by immunofixation on the CSF, serum, and urine samples. The loss of Y chromosome by cytogenetic studies is likely constitutional in origin, especially that it is seen in only 50% of the cells examined. The loss of 1 copy of 13q14 by FISH can be suggestive of CLL, but it was detected in only 5.7% of the cells examined and has been reported in B-PLL cases as well. Deletion in 17p13 by FISH seen in our patient is commonly detected in B-PLL cases.

In summary, very rare cases of prolymphocytic transformation from follicular lymphoma and splenic B-cell lymphomas, including marginal zone lymphoma, have been reported before, but to our knowledge, this is the first case reported of prolymphocytic transformation from lymphoplasmacytic lymphoma. Our case likely represents a proliferative/transformative phase with prolymphocytic morphology from lymphoplasmacytic lymphoma and not necessarily a transition to a new neoplasm. Moreover, central nervous system involvement in B-PLL is rare and limited to case reports regardless of the underlying disease process (de novo versus transformed) [10]. Our case showed symptomatic central nervous system involvement and predominance of prolymphocytes in the CSF similar to previously reported rare cases [10].

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