CASE REPORT

Lymphoplasmacytic Lymphoma with Paraprotein IgG

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ABSTRACT

Lymphoplasmacytic lymphoma (LPL) is a rare indolent mature B-cell lymphoma. LPL secreting immunoglobulins other than IgM are rare. There are very few case series on non-IgM LPL, and little is known about the clinical features and outcomes of patients with this disease. We report the case of a 65-year-old-male who was referred to our hospital for further investigations of persistent chronic anaemia and was diagnosed with IgG-LPL based on the presence of M protein from serum electrophoresis. Bone marrow morphology exhibit a spectrum of B-cell differentiation ranging from small mature lymphocytes to plasma cells. The patient underwent treatment with a combination of bortezomib, dexamethasone and rituximab and showed positive response. LPL with paraprotein IgG is a rare indolent disease and has a heterogeneous clinicopathological presentation with limited literature reviews. Our case report and literature review provide insights and knowledge in the description of the clinicopathological features of IgG LPL.
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INTRODUCTION

According to the latest World Health Organization (WHO) classification revised in 2016, lymphoplasmacytic lymphoma (LPL) is a low grade monoclonal expansion of B-lymphocytes characterized by various degrees of B-cell differentiation from small B lymphocytes, plasmacytoid lymphocytes to plasma cells(1). Waldenstrum's macroglobulinemia (WM) is a subset of LPL with bone marrow involvement and the presence of circulating immunoglobulin M (IgM) paraprotein(1). Non-IgM LPL presenting with IgG or IgA is rare and accounts for <5% of all LPL cases(2). Epidemiologically, LPL occur mainly amongst the adult population with a slight male preponderance in their seventh decade of life.

Diagnosis of non-IgM LPL is often difficult and can be challenging due to its morphologic and immunophenotype overlap with other low-grade B-cell lymphomas. The diagnosis of LPL is typically made by exclusion of other small B-cell lymphoid neoplasms with plasmacytic differentiation e.g., multiple myeloma, chronic lymphocytic leukaemia, splenic or nodal marginal zone lymphomas and follicular lymphoma.

Recently, a mutation in MYD88 (MYD88 L265P) has been recognized in most patients with IgM LPL/WM, accounting for >90% of tumour samples from patients with LPL(3). MYD88 L265P genetic mutation analysis may be helpful in making a diagnosis even though it is not LPL-specific and can also be found in other B-cell lymphomas. This mutation plays a crucial role in the pathogenesis of LPL/WM and can help to differentiate B-cell lymphomas and plasma cell myeloma, both of which warrant further investigations(3).

The purpose of this article is to describe a rare case of LPL with paraprotein IgG which was diagnosed recently in the haematology laboratory of Hospital Tuanku Ja'afar, Seremban. This patient presented with nonspecific symptoms highlighting that proper and thorough haematological investigation is crucial in making early diagnosis thus avoiding serious complications.

CASE REPORT

A 65-year-old man with underlying diabetes, hypertension, and end stage renal failure (ESRF) on regular haemodialysis; was referred to our hospital for further investigation in view of persistent anaemia. He initially presented with a week history of productive cough, loss of appetite and reduced effort tolerance for the past two months. Otherwise, he was free of fever, night sweats, weight loss and bone pain. Besides, the patient did not show any signs nor symptoms of hyperviscosity syndrome, such as bleeding, blurring or loss of vision, dizziness, headache, or neurologic symptoms. Physical examination revealed pallor without lymphadenopathy

or hepatosplenomegaly.

Peripheral count demonstrated bicytopenia with severe anaemia (6.5 g/dL), normal white blood cell count (5.3 x 10^9/L) and mild thrombocytopenia (142 x 10^9/L). Peripheral smear revealed normocytic normochromic anaemia with mild rouleaux formation. The bone marrow (BM) aspirate smear was suboptimal with presence of mainly circulating plasma cells and lymphocytes in the trephine roll. The plasma cells were mainly homogenous in size, with eccentric nucleus, clumped chromatin, and perinuclear halo. A few plasma cells were binucleated. The bone marrow (BM) trephine biopsy showed hypercellular marrow (>90% cellularity) with diffuse infiltration of predominantly small lymphocytes admixed with plasma cells and plasmacytoid lymphocytes. These cells were positive (60%) for CD20, CD79a, CD138, CD45 with kappa light chain restriction and negative for CD56, CD10, CD23 and cyclin D1. Other haematopoietic cell lines were markedly suppressed. Hence, the diagnosis of lymphoplasmacytic lymphoma was made.
Biochemical profile showed normal liver function

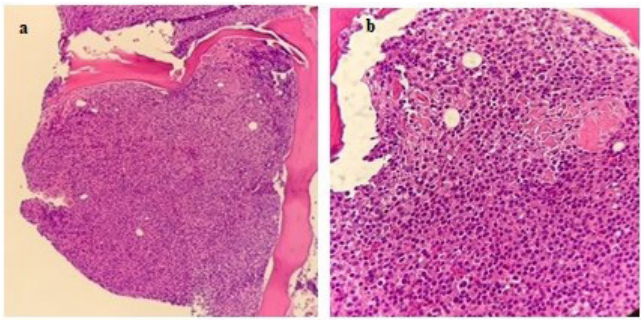

Figure 1 (a) (H&E,40X) and 1 (b)(H&E,100X): Trephine biopsy showed hypercellular marrow with diffuse infiltration of predominantly small lymphocytes admixed with plasma cells and plasmacytoid lymphocytes).

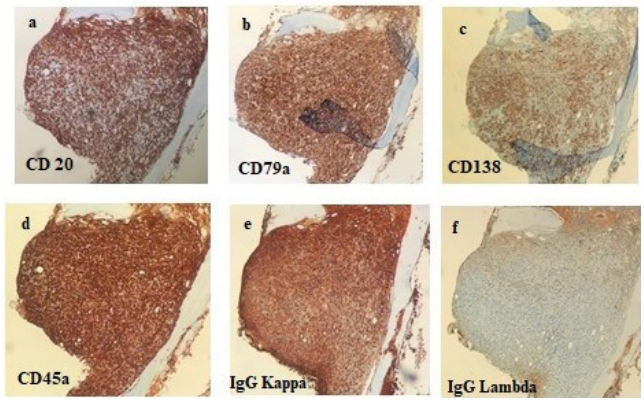

Figure 2 (a)-2(f): Immunohistochemistry stain (40X) showed these cells are positive for CD20, CD79a, CD138, and CD45 with kappa light chain restriction

test with reversed A/G ratio; albumin 19 g/L, globulin 82.0 g/L and A/G ratio 0.2. Other laboratory findings include deranged renal profile with urea 16.7 mmol/l and creatinine 563.0 µmol/L, corrected calcium 1.61 mmol/L, high serum beta-2-microglobulin (β-2-MG) 28.3 mg/L and an increased 24 hour urine total protein of 2.90 g/24hr. Viral screening and anti-hepatitis B core were non-reactive. ANA, ANCA, rheumatoid factor, anti-MPO and anti-proteinase 3 (PR3) were all negative. The ESR was 98 mm/1hr. CA19-9, serum AFP and CEA were all negative. Serum protein electrophoresis and immunofixation showed IgG kappa with excess kappa light chain paraproteinemia to a total of 63.1 g/L in the gamma region with severe immunoparesis. The skeletal survey did not reveal any osteolytic lesions. Neither a CT scan nor a positron emission tomography (PET) scan were performed for this patient. Apart from that, neither FISH nor conventional cytogenetic karyotyping were carried out. MYD88 mutation analysis was not done due to financial constraint.

Based on the above findings, this patient had an intermediate-risk LPL, IgG kappa, according to WM specific IPSS (haemoglobin ≤11.5 g/L, and high β-2-microglobulin >3 mg/L). He received 5 cycles of bortezomib, dexamethasone, rituximab (BDR) regimen chemotherapy. This patient responded to treatment as evidenced by bone marrow (BM) aspirate and trephine biopsy after completed chemotherapy revealed 15% residual plasma cells with very occasional plasmacytoid lymphocytes. Additionally, IgG level has decreased from 63.1 g/L at diagnosis to 31.0 g/L after he completed chemotherapy.

Patient has been followed up on a regular basis with no active intervention as he had no disease related symptoms; B symptoms and signs of marrow failure (no significant cytopenia). There were no subsequent or additional laboratory investigations (bone marrow examination and serial paraprotein level) performed after that.

DISCUSSION

Lymphoplasmacytic lymphoma (LPL) is an uncommon low-grade B-cell neoplasm exhibiting a spectrum of B-cell differentiation ranging from small lymphocytes to plasma cells(1). LPL accounts for approximately less than 2% of non-Hodgkin's lymphoma(2). Ninety to ninety five percent of LPL patients have clinical syndrome of Waldenstrom macroglobulinemia which is defined as LPL with bone marrow involvement and IgM monoclonal gammopathy of any concentration(1). Patients with LPL associated with IgA or IgG paraprotein are rare and seen in less than 5% of the LPL cases(2). The non-IgM LPL are uncommon and poorly defined; thus, the precise diagnosis could be challenging. Combination of the clinical presentation, lymph node biopsy, bone marrow examination and molecular/cytogenetic findings are important to establish the right diagnosis.

LPL is an indolent B-cell neoplasm and most patients are asymptomatic. The clinical presentation varies and may include symptoms related to bone marrow

infiltration or paraprotein-related features. Most patients experience anaemia-related symptoms, most notably fatigue, because of bone marrow involvement. Besides, some patients may have clinical manifestations related to spleen, liver, and other extra nodal sites, including the skin, and gastrointestinal system. Hyperviscosity syndrome can occur in up to 30% of IgM-LPL cases(1). In addition, some patients may present with B-related symptoms, including night sweats, recurrent fever, and weight loss. Several studies have shown that patients with non-IgM LPL have similar clinical and pathologic features with IgM LPL (WM). Cao et al compared the clinical data of 17 non-IgM patients and 312 typical WM patients and found similar clinical and biological characteristics (2).

According to various case reports, non-IgM LPL is difficult to diagnose and is frequently misdiagnosed as multiple myeloma. IgG and IgA are commonly seen in multiple myeloma while IgM gammopathy is associated with LPL(5). However, the clinical manifestation seen in multiple myeloma, with bone lesion, hypercalcemia, and renal insufficiency, are rarely observed in LPL(5). Less frequently, IgA or IgG gammopathy might be associated with other non-Hodgkin lymphomas such as splenic or nodal marginal zone lymphomas, and chronic lymphocytic leukaemia that needs to be excluded. Thus, the diagnosis of LPL is typically by exclusion of other small mature B-cell lymphomas.

In the present case, an expressive monoclonal peak of more than 3 g/dL in a patient with mild anaemia and no other multiple myeloma clinical features raised the suspicion of a non-IgM LPL. Bone marrow histopathological features with infiltration by small mature lymphocytes admixed with lymphoplasmacytoid lymphocytes and absence of excess plasma cells confirmed the diagnosis in our patient. Apart from the bone marrow morphological features, relevant immunohistochemistry also gave us a diagnostic clue.
LPLs typically express B-cell associated antigens (CD19, CD20, CD22 and CD79a) and are most typically negative for CD5, CD10, CD23 and CD103, with frequent CD25 and CD38 expression(1). CD138 are often expressed on the surface of monoclonal plasma cells; unlike in plasma cell myeloma, they are also positive for CD19 and often for CD45(1). In our present case, the bone marrow biopsy revealed tumour infiltration by B-cells positive (approximately 40%) for CD79a, CD20, CD45, and a small population of CD138+ plasma cells with kappa light chain restriction.

MYD88 L265P mutation is present in about 90% of WM and has become a new tool for diagnosis of LPL(1).. Besides, it is rarely found in marginal-zone lymphomas and is absent in multiple myeloma. Thus, testing for this mutation can be a useful diagnostic adjunct in these complicated cases. As for our patient, due to limited availability and financial constraint, the MYD88 mutation analysis was not performed.

LPL has the characteristic of low-grade malignant cell lymphoma with a typical indolent clinical course and a long-term survival. The treatment options for LPL are heterogeneous although there are no prospective studies regarding standard treatment regimens for patients with LPL. “Watch and wait” is the first-choice treatment strategy for LPL patients without systemic symptoms, vital organ impairment, bulky lesions or evident of disease progression(4). However, patients with symptoms require further treatment. In practice, Rituximab based regimens like R-CHOP and Bortezomib-Rituximab (BR) are commonly used. Among these, bortezomib-dexamethasone-rituximab (BDR regimen) combinations were associated with higher response rates and longer survival, and it was found to be effective in our case as well.

CONCLUSION

Non-IgM LPL poses diagnostic and therapeutic challenges as it is an extremely rare malignancy with a heterogeneous clinicopathological presentation and scarce literature. It is essential to distinguish LPL from other lymphoma by comprehensive clinical and haematological work up. The diagnosis of LPL is frequently complicated due to the scarcity of certain morphologic, immunophenotyping and chromosomal abnormalities, thus diagnosis was usually through exclusion. MYD88 L265P mutation analysis is a very valuable tool for a more precise diagnosis of LPL/WM. Our case report will be a valuable addition to the literature of this extremely rare entity and help guide the management of such cases in the future.

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