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MYD88L265P mutated IgA Lymphoplasmacytic Lymphoma.

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ABSTRACT

Here we report two new cases of IgA-Lymphoplasmacytic Lymphoma (LPL) with diverse clinical presentation and performed a review of the three cohorts of patients with non-IgM LPL published in the literature. IgA LPL is rare and affects patients with a mean age at diagnosis of 67-year-old, with male predominance. Hyper viscosity related symptoms are extremely uncommon in comparison with LPL/WM and reported in unique cases. Extramedullary involvement includes lymph node disease (6/14, 42%) and rarely splenomegaly (3 cases, 21%). Associated amyloid deposition has been found in 21% of the cases. Histopathological features in the bone marrow if IgA-LPL are equivalent to IgM-LPL/WM. IgA LPL are positive for MYD88L265P mutation in 83% of the cases (10/12 cases). 6 q deletion is rarely found. In conclusion, the available evidence about the biological features of IgA-LPL supports the inclusion of these cases in the lymphoplasmacytic lymphoma spectrum. This is relevant for therapeutic reasons, mainly due to the availability of novel highly effective regimens for the treatment of LPL/WM.

Lymphoplasmacytic Lymphoma (LPL)/ Waldestrom Macroglobulinemia is a neoplasm of small B lymphocytes, plasmacytoid lymphocytes and plasma cells, usually involving the bone marrow and sometimes lymph node and spleen[1] with an associated IgM monoclonal component[2]. MYD88L265P somatic mutation is the driver mutation in most cases[3-6]. Patients with IgG or IgA monoclonal proteins and those with non-secretory LPL exist and show clinical and pathological heterogeneity[7,8].

Here we describe two cases of IgA LPL diagnosed and treated in our institution. These two cases accounted for 7% of all LPL patients managed in our center in a 5 years period.

Both patients were elderly men (71 and 75-year-old). Patient 1 presented with constitutional symptoms. On CT scan retroperitoneal pathological lymph nodes were identified. Case 2 presented with asthenia and bone pain. After CT no pathological lymph nodes were identified. Neither of the patients had hepatosplenomegaly, CNS involvement, bone lesions nor hyper viscosity related symptoms at diagnosis. Both patients had anemia, elevated β2-microglobulin, Bence-Jones proteinuria and IgA positive M component of 1.54 g/dL and 5.82 g/dL, respectively. Case 1 had, by FCM a 0.98% population of clonal B cells with kappa light chain restriction in the peripheral blood without increased lymphocytes, plasma cells, nor atypical cells in the PB smear.

In both cases bone marrow core biopsy established the diagnosis of LPL, based on the unequivocal infiltration of the marrow space (Figure). Bone marrow aspirate in case 1 showed 18.5% lymphocytes (4.5% clonal by FCM) and 2% plasma cells. Case 2 had 25% lymphocytes in the BM aspirate (13% clonal by FCM) and 3.5% plasma cells. Dutcher bodies were not identified, and mast cells were within normal limits. Case 2 had increased histiocytes in the marrow core biopsy. Case 1 had associated AL-k amyloid deposits in both bone marrow and retroperitoneal lymph node tissues. Both cases showed a clonal B cell population with plasma cell differentiation and IgA expression in the lymphoid and plasma cell population as demonstrated by IHC. Molecular testing demonstrated the presence of MYD88L265P mutation by Allele Specific-PCR in the bone marrow clot material from both cases. In both cases FISH was performed in the bone marrow aspirate and was found positive for 6q deletion (17% of the nuclei) in case number 2.

Case number 1 was treated with immunochemotherapy with Rituximab, Bortezomib and Dexamethasone. After 6 cycles the patient achieved partial response. The second patient was treated with Rituximab, cyclophosphamide and dexamethasone. After 2 cycles the patient developed a cutaneous rash and hyper viscosity related symptoms. A second line treatment with Ibrutinib is now ongoing.

We reviewed the clinical, morphological, phenotypical and molecular features in comparison with the cases described in the three larger cohorts of patients with non-IgM LPL so far published[7,8,10] (Table). Including the two cases here reported IgA-LPL affects patients with a mean age at diagnosis of 67-year-old (range 51-80) and male predominance (9 out of 14 cases). Mean serum IgA M component was 3 g/dL (0.74-5.75 g/dL). 42% of the cases presented with anemia and with B symptoms. Hyper viscosity related symptoms such as impaired vision are not reported in IgA-LPL except in very unique cases[9].

Extramedullary involvement in these patients usually includes lymphadenopathy (6/14, 42%) and rarely splenomegaly (3 cases, 21%). CNS involvement by IgA-LPL has not been reported. Associated amyloid deposition has been described in two previously published cases (3 out of 14 cases, 21%, including our case number 1).

Histopathological features in the bone marrow of IgA-LPL are equivalent to IgM-LPL/WM, including paratrabecular and interstitial clonal B cell infiltrates with plasma cell differentiation. IgA expression by neoplastic cells confirms the production by the neoplastic cells.

Molecular features of IgA-LPL include the frequent detection of MYD88L265P mutation. Including our two cases, IgA LPL are reported to be positive in 83% of the cases (10/12 cases [7,8,10]). The identification of MYD88L265P mutation in IgA-LPL aids in the differential diagnosis with multiple myeloma and marginal zone lymphoma, since it is never found in multiple myeloma and appears only in roughly 15% of marginal zone lymphoma cases (mostly splenic type)[11-13].

The prevalence of other genetic features found in WM such as 6q deletion is poorly defined in the non-IgM LPL group of cases [9]. 6q deletion in WM has been found to be associated with features of poor prognosis[14,15] and upregulation of BCR pathway[16]. The clinical significance of this alteration in IgA-LPL is however not well stablished.

In conclusion here we report two cases of IgA-LPL with diverse clinical presentation. Bone marrow histopathological findings and demonstration of MYD88L265P mutation were essential for the diagnosis. The available evidence about the biological features of IgA-LPL supports the inclusion of these cases in the lymphoplasmacytic lymphoma spectrum. This is critical for therapeutic reasons, mainly due to the availability of novel highly effective regimens for the treatment of LPL/WM[17].

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Figure. Case 1. **IgA lymphoplasmacytic lymphoma, involving bone marrow and lymph nodes with amyloid deposits.** (A,B, H&E). The bone marrow core biopsy shows paratrabecular and interstitial infiltration of small lymphocytes some with plasmacytoid features and plasma cells (20% of marrow cellularity). Interstitial deposits of amyloid were also identified. IHC shows positivity for CD20 (C), CD138 (D) and IgA (E). There was kappa light chain restriction (F). The pink amorphous material was positive for P protein (G). HE from the retroperitoneal LN biopsy discloses the same combination of lymphoid and plasmacytoid infiltrates with amyloid material, positive with Congo red staining under polarized light (H, I). **Case 2. IgA kappa lymphoplasmacytic lymphoma involving bone marrow** (J, K, H&E). The bone marrow core biopsy shows a diffuse-solid interstitial infiltrate of small lymphocytes, plasmacytoid lymphocytes and plasma cells (80% of the marrow cellularity). IHC shows positivity for CD20 (L), CD138 (M) and IgA (N). There was kappa light chain restriction (O).

Table. Clinicopathological features of patients with IgA Lymphoplasmacytic Lymphoma. A summary of the clinical and pathologic features of the IgA LPL cases described in the three larger cohorts of patients so far published is shown, together with the results of the two cases here reported[7,8,10].

Clinicopathological features of patients with IgA lymphoplasmacytic lymphoma

	Cao et al. Leukemia & Lymphoma 2016	King et al. AJCP, 2016	Tursz et al. Am J Med, 1977	Urquieta Lam et al.	TOTAL
n	8	2	2	2	14
Clinical features					
Age (years)	65 (51-80)	62 (54-70)	69 (58-80)	73 (71-75)	67 (51-80)
Male (n, %)	5 (62)	2 (100)	0 (0)	2 (100)	9 (64.28)
Female (n, %)	3 (38)	0 (0)	2 (100)	0 (0)	5 (35.72)
Serum IgA (in mg/dL; mean, range)	2475 (747-5260)	1750 (1000-2500)	4550 (3800-5300)	3575 (1400-5750)	3087 (747-5750)
Anemia (n, %)	2 (16%)	2 (100)	—	2 (100)	6 (42)
B symptoms (n, %)	5 (62)	—	—	1 (50)	6 (42.85)
Visual impairment (n, %)	0 (0)	0 (0)	—	0 (0)	0 (0)
Hyperviscosity (n, %)	0 (0)	0 (0)	0 (0)	1 (50)	1 (7)
Amyloidosis (n, %)	1 (12.5)	1 (50)	—	1 (50)	3 (21.42)
Neuropathy (n, %)	1 (12.5)	0 (0)	—	1 (50)	2 (14.29)
Bence-Jones proteinuria (n, %)	—	—	0 (0)	2 (100)	2 (14.29)
Pathological features					
BM involvement (n, %)	8 (100)	2 (100)	2 (100)	2 (100)	14 (100)
Extramedullary involvement (n, %)*	6 (75)	0 (0)	0 (0)	1 (50)	7 (50)
Splenomegaly (n, %)	1 (12.5)	0 (0)	2 (100)	0 (0)	3 (21.42)
Hepatomegaly (n, %)	0 (0)	0 (0)	1 (50)	0 (0)	1 (7.14)
Lymphadenopaty (n, %)	5 (62.5)	0 (0)	0 (0)	1 (50)	6 (42.85)
CNS involvement (n, %)	0 (0)	0 (0)	—	0 (0)	0 (0)
Molecular feaures					
FISH/Karyotype 6qdel (%)	0/8 (0)	0 (0) **	—	1/2 (50)	1
MYD88 L265P mutation, positive (%)	6 (75)	2 (100)	—	2 (100)	10 (83)
Therapy					
Treatment ***	8 (100)	1 (50)	1 (50)	2 (100)	12 (92)
Watch and wait	0	1 (50)	0 (0)	0 (0)	1 (8)

* 5 cases with LN involvement and 1 case with renal and nasopharinx involvement.
** Karyotype performed on 18 of 23 lymphoma cases
*** R+/- diverse chemotherapy regimens +/- ASCT