W26: Novel phenotypically distinct small B cell lymphoma clones may be associated with IgM paraprotein-associated peripheral neuropathy

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BACKGROUND

IgM paraprotein-associated peripheral neuropathy (PN) is an uncommon phenomenon that can cause disability. Progressive PN in patients with WM is an indication for haematological treatment with chemo-immunotherapy. Those with IgM MGUS only occasionally receive immunomodulatory therapy if they have evidence of a causal antibody to a neural target, such as anti-myelin associated glycoprotein (MAG) antibodies. Patients with IgM MGUS-related PN do not typically undergo bone marrow examination, unless there are features suggestive of malignant progression and therefore the cell of origin of the IgM paraprotein in these patients is often not identified.

Following the introduction of an extended multi-parameter flow cytometry (MFC) lymphoma panel in our laboratory, we identified five patients seen at our tertiary haematology-neurology referral centre with IgM paraprotein-associated neuropathy who were found to have small, histopathologically distinct abnormal B-cell clones without evidence of MGUS, lymphoma or WM. This led us to postulate that this finding may be instrumental in the aetiology of the PN.

METHODS

Ninety-eight patients were seen at our joint haematology-neurology referral clinic between January 2015 and May 2018. Fifty-two were new to the service. Sixty-six patients had IgM paraproteinaemia and neuropathy. Recorded clinical features, laboratory, neurophysiology and radiology results were reviewed retrospectively. Twenty of the 66 patients with IgM paraproteinaemia and peripheral neuropathy underwent bone marrow examination including extended MFC using a panel of 18 antigens.

RESULTS

Out of the 20 patients who underwent bone marrow examination, five were found to have abnormal small B-cell clones (see Table 1 also for MAG status). Median age of these patients was 62 years (range 45 to 78 years; 3 M and 2 F). All patients presented with chronic progressive sensorimotor neuropathy causing disability, with a median duration of symptoms of four years (range 2 to 13 years) and median Overall Neuropathy Limitations Scale (ONLS) score of 3 (range 3 to 5) pre-treatment.

MFC showed small abnormal mature B-cell clones (see Table 1), all <3% total cellularity. All patients were positive for the MYD88 L265P mutation. All clones were positive for CD19, CD20, CD79b, and sIg, but showed variable expression of CD5, 10 and 23. In all cases, there was no clinical, radiological or bone marrow trephine evidence of lymphoma.

Four of the five patients have received rituximab monotherapy. All have responded to therapy in terms of improvement of neuropathy symptoms, but to varying degrees.

CONCLUSION

This is a new clinicopathological entity of PN, IgM paraproteinemia, with low-level phenotypically abnormal mature B-cell clones in the bone marrow and the MYD88 L265P mutation, without evidence of overt lymphoplasmacytic lymphoma, and histopathologically distinct from MGUS. The presence of abnormal B-cell clones in these patients could be associated with the pathophysiology of IgM paraprotein-associated neuropathy, and may guide treatment decisions in the future. Further studies are required to validate these findings in larger patient cohorts, and investigate the relationship between these abnormal B-cells and IgM paraprotein-associated neuropathy.

Table 1. Summary of patient characteristics, results and treatment

Patient	Age/Sex	Previous failed therapy	Duration of neuropathy symptoms when referred (years)	Pre-treatment ONLS score	Paraprotein isotype	Pre-treatment SPEP (g/L)	MYD88 L265P	Anti-MAG antibodies	Flow cytometry (% Total cellularity)	Treatment	Response
1	45/ F	Steroids	2	3	IgM-kappa	4	Positive	Strong positive	CD19+ CD10+ CD20+ CD23+ small B-cell clone (2.1%)	None	
2	62/ F	IVIG	2	n/a	IgM-kappa	3	Positive	Not available	CD19+ CD10+ small B-cell clone (0.75%)	Rituximab monotherapy	Resolution of neuropathy symptoms
3	50/ M	Simple analgesia	4	4	IgM-kappa	6	Positive	Strong positive	CD19+ CD5+ CD79b+ small B-cell clone (0.12%)	Rituximab monotherapy	Post-treatment ONLS = 3
4	78/ M	IVIG	4	5	IgM-kappa	<3	Positive	Positive	CD 19+ CD23+ small B-cell clone (1.15%)	Rituximab monotherapy	Slowed progression of symptoms
5	62/ M	None	13	3	IgM-kappa	n/a	Positive	Strong positive	CD19+ CD79b+ sIg+ small B-cell clone (2.47%)	Rituximab monotherapy	Significant improvement

IVIG: intravenous immunoglobulin; SPEP: serum protein electrophoresis, anti-MAG antibodies: anti-myelin associated glycoprotein antibodies; ONLS: overall neuropathy limitations scale