CLINICAL HETEROGENEITY OF BING-NEEL SYNDROME. A SINGLE-CENTER EXPERIENCE

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Introduction

Bing Neel syndrome (BNS) is **a rare form of Waldenström's macroglobulinemia** (WM) resulting from direct **infiltration of central nervous system by tumoral lymphoplasmacytic cells**.

It includes a **diffuse form** (lymphoid cell infiltration of leptomeninges and perivascular spaces) and a **tumoral form** (uni- or multifocal parenchymal infiltration, usually in the deep hemispheric white matter)[1].

BNS is mostly diagnosed in patients with a progressing WM, but it may occur during systemic remission or even be the presenting symptom in patients without history of WM[2,3]. Diagnosis can be established on a direct **biopsy** or **CSF analysis** with evidence of **B-cell clonality** and/or **MYD88 mutation**[1,4].

Here we report four cases of Bing Neel syndrome from our center experience.

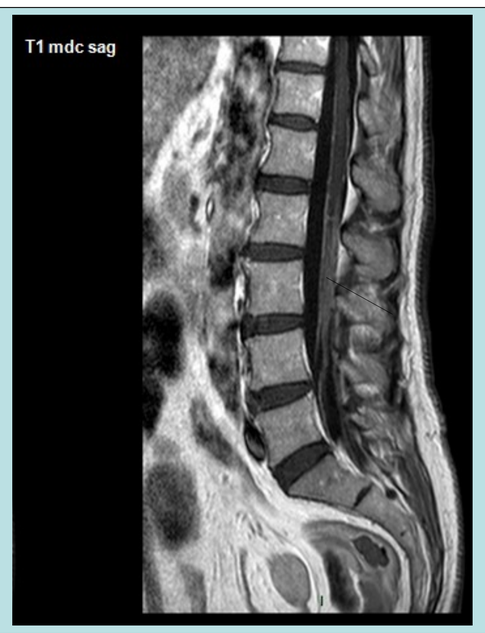

Fig. A: T1 sagittal post Gd shows thickening and enhancement of spinal leptomeninges and cauda equina roots

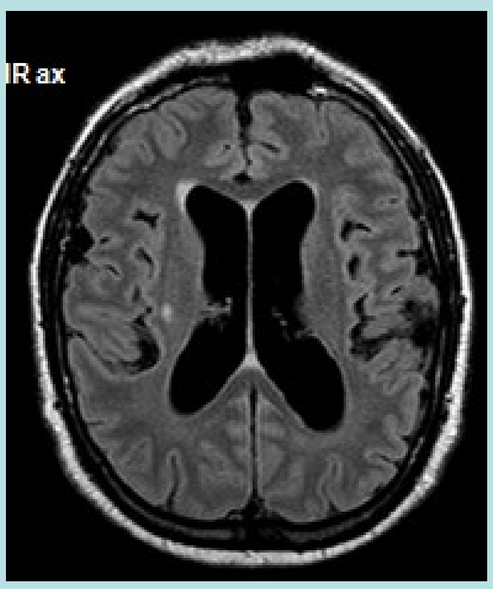

Fig. B: FLAIR axial shows marked ventricular dilatation, disproportioned to sulcal enlargement

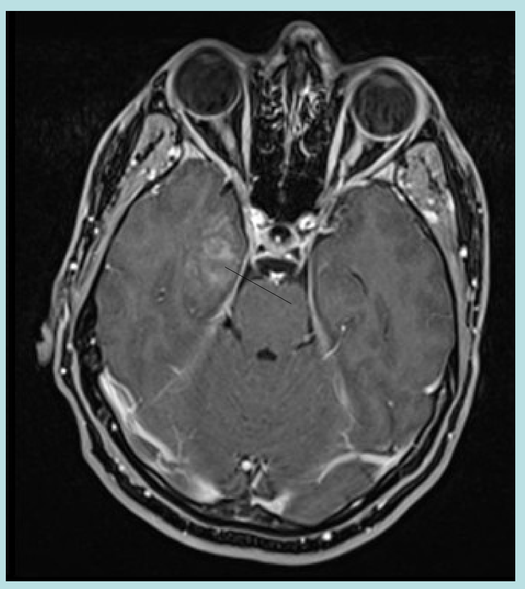

Fig. C: T1 axial post Gd shows cortico-subcortical right mesial temporal lesion with inhomogeneous enhancement

Results

In **Table 1** are summarized patients' characteristics. Male sex was predominant and mean age was 58 years. Clinical presentation was heterogeneous. Only one patient had a diagnosis of lymphoplasmocytic lymphoma at symptoms onset. In MRI, diffuse pattern was the most common. Of note, in one patient leptomeningeal carcinomatosis manifested as normal pressure hydrocephalus.

CSF immunophenotyping showing B-cells clonality and presence of MYD88 mutation confirmed diagnosis in patients without history of hematological malignancy. One patient also showed anti-MAG antibodies positivity. Patient#1 also had amiloidosis.

3 patients out of 4 had 6 cycles of rituximab-bendamustine plus intrathecal methotrexate as first line therapy. The remaining patient showed refractority to different polychemotherapy lines before starting the bendamustine - methotrexate scheme. All of them showed at least a partial response, but 3 patients relapsed. Patient #4 had a distant tumoral progression (involvement of the thalamus). Three patients are currently on second-line treatment with BTK inhibitor Ibrutinib.

	Sex and age	Known WM at onset	Symptoms at onset	Pattern	Brain MRI	Spine MRI	M protein (g/dL)	CSF albumin (mg/dl)	CSF cells (/mm3)	CSF immuno-phenotyping	MYD88 mut	Anti-MAG Ab	EMG / ENG	First-line therapy	Response	Relapse	Second-line therapies
#1	M, 69	No	Fatigue, four-limbs paresthesias, abdominal pain, gait impairment	diffuse	No evidence of infiltration	Leptomeningeal infiltration with CE	IgM k (17.5)	291	11	presence of clonal B-cell population	yes	no	Mixed demyelinating-axonal sensorimotor polineuropathy	R-bendamustine + intrathecal MTX 6 cycles	CR	No	n/a
#2	F, 60	No	Sensitive ataxia, four-limbs paresthesias	diffuse	Shaded peritruncal and internal auditory meatus leptomeningeal CE	Leptomeningeal thickening and CE of conus and cauda equina (Fig. A)	IgM k (7.3)	68	107	presence of clonal B-cell population	yes	yes	Mixed demyelinating-axonal sensorimotor polineuropathy	R-bendamustine + intrathecal MTX 6 cycles	PR	yes (CNS only)	Ibrutinib
#3	M, 64	No	Cognitive and balance impairment	diffuse	Tetraventricular hydrocephalus (Fig. B)	n/p	IgM k (3.0)	95	101	presence of clonal B-cell population	yes	no	Normal	R-HyperCVAD (not tolerated) → R-bendamustine 6 cycles + intrathecal MTX 9 cycles	CR	yes (CNS only)	Ibrutinib
#4	M, 39	Yes	Seizures	tumoral	Temporomesial CE lesion, optic nerves CE, leptomeningeal CE (Fig. C)	n/p	IgG k	n/a	n/a	No detectable lymphoid cells	n/p	n/p	Normal	R-ICE → HyperCVAD → bendamustine + intrathecal MTX 6 cycles	CR	yes (CNS only)	Ara-C → WBR (24 Gy) → ibrutinib

Table 1. Ab=antibodies, CE=contrast enhancement, R=rituximab, MTX=methotrexate, CR=complete response, PR=partial response, CNS=central nervous system, Ara-C=cytarabine, WBR=whole brain radiation, n/p=not performed, n/a=not available

Conclusions

Bing-Neel Syndrome (BNS) is uncommon, but it should always be considered when **neurological symptoms** appear in patients with **diagnosis of WM**. Nevertheless, it should be investigated even in patients without a known hematological malignancy, when symptoms are associated with a **serum IgM monoclonal component**.

MRI imaging and **CSF analysis** with flow cytometric immunophenotyping and search for MYD88 mutation can confirm diagnosis. Differential diagnosis include anti-MAG polyneuropathy, but they can coexist.

Systemic **rituximab - bendamustine with intrathecal methotrexate** is an effective therapy, but patients tend to relapse. New therapies as **ibrutinib** seem promising[5] in relapsing patients and also for peripheral neuropathic symptoms.

Bibliography

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