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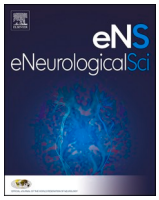

Case report

Bing Neel syndrome presenting as isolated cranial nerve palsies – a case report

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ABSTRACT

Background and aims: Waldenstroms macroglobulinemia (WM) is a low-grade B cell neoplasm. Bing Neel syndrome is a rare manifestation of WM characterized by infiltrative involvement of the central nervous system.
Case report: 64-year-old man, presented with 4 years history of slowly progressive diplopia and ptosis of eyes. Examination showed left oculomotor (internal and external ophthalmoplegia), with trochlear, abducens, and right partial oculomotor and abducens nerve involvement. Evaluation showed anemia of hemoglobin 10.7 g/dL, raised erythrocyte sedimentation rate of 120 mm/h and plasma albumin:globulin reversal. Serum protein electrophoresis showed a paraprotein peak in the early gamma region with elevated IgM level (3810 mg/dL) and elevated free kappa light chain level (70.1 mg/L). Bone marrow aspiration from posterior iliac crest revealed mature small lymphocytes with positive immunohistochemical markers of CD5, CD10 negativity and MYD88 mutation positivity suggestive of WM. Patient was treated with bendamustine and rituximab regimen, with no neurological improvement at the end of one year.
Conclusion: This case expands spectrum of paraproteinemic neuropathy to include cranial nerve palsy. Thus, plasma cell dyscrasias have to be considered in patients with isolated ophthalmoparesis especially in elderly patients, even with other comorbidities such as diabetes mellitus.

1. Introduction

Waldenstrom's macroglobulinemia (WM) is a rare lymphoproliferative disorder of the B-cell lineage defined by the presence of elevated serum IgM paraprotein and lymphoplasmacytic infiltration of the bone marrow. WM consists of only 1–2% of hematologic malignancies and usually affects men in the 6th to 8th decades. The clinical manifestations are mainly due to IgM paraproteinemia including hyperviscosity, hemolytic anemia and peripheral neuropathy. Extramedullary manifestations of WM are noted in 15–20% of cases which includes lymphadenopathies and splenomegaly. Extranodal involvement is very rare. Central nervous system involvement of WM due to infiltration of lymphoplasmacytic cells is called as Bing Neel syndrome (BNS). The clinical manifestations of BNS is slowly progressive over weeks or months. The phenotype of BNS is varied with the most common being cerebral / cerebellar syndrome and cranial nerve involvement [1]. BNS as the presenting feature of WM is noted in 15–36% of cases [2]. Here we document an interesting report on an elderly man with BNS presenting with only isolated cranial neve palsies evolving over years.

1.1. Case report

A 64-year-old man was evaluated during the year 2022. He presented with a 4-year history of progressive ptosis of the left eyelid, and horizontal binocular diplopia more on looking at far objects. He also developed ptosis of the right eye for the last 6 months. There was no history of fatigability/fluctuation of ocular symptoms. He had no bulbar symptoms, headache or vomiting. He had diabetes mellitus and hypertension for ten years. Examination showed left oculomotor (internal and external opthalmoplegia with pupillary sizes of right eye: 8 mm and left

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eye: 11 mm), with trochlear, abducens, and right partial oculomotor and abducens nerve involvement **(Fig. 1) (Supplementary video)**. Other cranial nerves and motor system examination were unremarkable.

Investigations showed reduced blood hemoglobin level of 10.7 g/dL with elevated erythrocyte sedimentation rate (120 mm/h) and normal platelet count (3,34,000/microL). Liver function tests showed raised total proteins (9.70 g/dL) with albumin:globulin reversal (0.80). The glycosylated hemoglobin (HbA1C) was 9.2%. Cerebrospinal fluid (CSF) analysis showed 5 cells (2 lymphocytes) with raised protein level (228.2 mg/dL). CSF cytospin analysis was negative for abnormal / atypical cells. The possibilities of inflammatory/ granulomatous disorders and neoplastic disorders were considered. Anti NuclearAntibody (ANA) profile, Antineutrophil cytoplasmic antibodies (ANCAs) and Anti-ganglioside antibodies were negative. Brain MRI revealed thickened bulky bilateral cavernous sinus with bilateral thickened oculomotor nerves **(Fig. 2 a-d)**.Whole body ^{18}F-FDG - Positron Emission Tomography (PET) MRI did not show any abnormal metabolic lesion. The peripheral nerve conduction study was normal. Serum protein electrophoresis showed a paraprotein peak in the early gamma region. Immunofixation showed elevated IgM levels (3810 mg/dL). Free kappa light chain level was elevated (70.1 mg/L, normal - 2.2 to 19.40 mg/L) and raised kappa lambda ratio of 8.549 (normal - 0.26 to 1.65). Bone marrow aspiration done from posterior iliac crest showed mature small lymphocytes, and IHC testing (CD5, CD10 negative) revealed mature B cell type, low-grade non-Hodgkin's lymphoma with MYD88 mutation positivity. Thus, a diagnosis of Waldenstrom's macroglobulinemia was made. Patient was referred to an oncology center and received chemotherapy consisting of Bendamustine and Rituximab regimen. Patient was reviewed after the fifth cycle of chemotherapy but did not show any significant neurological improvement.

2. Discussion

Bing Neel syndrome (BNS) is a rare disease manifestation of WM characterized by malignant lymphoplasmacytic infiltration of the central nervous system. Rarely, in 15–36% of cases, BNS can be the presenting feature of WM [1]. Better prognosis is noted in these patients than those with previous history of WM [1]. Since its first description by Bing and Neel in 1936, more than 100 cases have been reported. BNS being a very rare syndrome, its prevalence based on previous case series is 0.3–1% of WM cases.The median age at diagnosis of WM is 61 years [3], similar to our patient. In an earlier report, the median time from onset of symptoms to diagnosis was 4 months with maximum duration reported being 3 years (20% of cases had interval of more than one year) [2]. The diagnosis of BNS is challenging in a given patient with CNS manifestations without prior history of WM due various causes such as absence of other systemic symptoms, non-specific neurological symptoms, coexistent disorders such as diabetes mellitus as noted in this report. The most common manifestations of BNS based on previous large retrospective studies include ataxia (12–48%), encephalopathy (27–35%), motor deficits of limbs (14–35%), and cranial nerve involvement (29–36%) [1,2]. Simon et al., reported that the most common cranial nerves involved include facial and oculomotor nerves [2]. Our patient had complete ophthalmoparesis which has not been reported previously. There are two types of BNS described by Fintellmann et al., [4]. BNS type A is noted in 75% of cases with presence of lymphoplasmacytic cells (LPC) in brain tissue or CSF, whereas type B has very low LPC counts in CSF with symptoms of BNS alone. Our patient had isolated ophthalmoparesis with bulky enlargement cavernous sinus and thickened oculomotor nerves on MRI with evidence of WM on protein electrophoresis and bone marrow aspiration. The pathogenesis leading to nerve damage can be attributed to various mechanisms, like nonspecific IgM tissue deposition, antibody-mediated damage to nerves or vessels, and direct infiltration of the neuraxis by the lymphoplasmacytic clone or transformation to high-grade lymphoma [5]. In our case the possible etiology is IgM deposits in the cranial nerves rather than direct cellular infiltration as in type 2 BNS [1]. Kuang et al., have described a case of an elderly female with acute diplopia with trochlear nerve involvement due to WM [6]. Case reports of patients developing cranial neuropathies during treatment or many years into the illness have been described, probably due to different pathogenic mechanisms involved. Sutter et al., have documented a case of WM with double vision, and bulbar palsy, and attributed it to the progression of disease due to meningeal infiltration [7]. Klokkevold et al., have reported a 43 years old lady with 7 years of WM on treatment with mental nerve involvement [8]. In a retrospective study done by Viala et al., one patient out of 40 had presented with 4 years history of multiple cranial nerve involvement (CNs, 3,5,7,9,10,11) similar to our case, but despite treatment, the neurological symptoms did not improve and their patient had succumbed [9].

The characteristic MRI findings includes thickening and contrast enhancement of meningeal sheaths, brain parenchyma, cranial and spinal nerves. Our patient showed bulky enlargement of cavernous sinus and oculomotor nerves reflecting an immune mediated chronic inflammatory process. WM has a long indolent course with a median survival of 7–12 years [10]. A retroscpective study by Simon et al., on BNS showed a survival rate of 71% at 5 years and 59% at 10 years [2]. Another study bt Castillo et al., showed a 3 year survival rate of 59% [1]. However, our patient had a chronic slowly progressive history of ocular symptoms without any other neurological or systemic symptoms at the time of diagnosis.

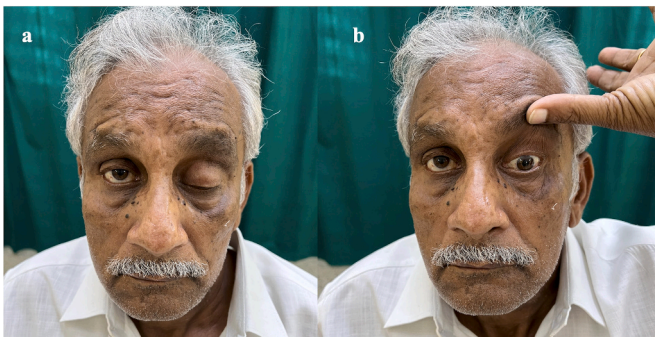

Fig. 1. Clinical images of the patient
a-Left eye ptosis.
b-Restricted upward eye mobility of left eye along with dilated pupil.

3. Conclusion

We report an interesting case of Bing-Neel syndrome (BNS) with isolated cranial nerve involvement due to WM. The salient features noted were long duration of illness, extremely slow progression, isolated cranial nerve involvement without systemic involvement even after several years and oculomotor nerve thickening on MRI. This expands the phenotypic manifestion of BNS with an indolent course and has to be considered in appropriate clinical context especially in the elderly.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2024.100505.

CRediT authorship contribution statement

Dipti Baskar: Writing – original draft, Methodology, Formal analysis, Data curation. **Davuluri Durga Srinivas Anudeep:** Methodology, Data curation. **Seena Vengalil:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Preetham Patavaradhan:** Investigation. **Karthik Kulanthaivelu:** Investigation. **Ravindu Tiwari:** Data curation. **Bevinahalli Nanjegowda Nandeesh:** Writing – review & editing, Investigation, Data curation. **Keerti Sitani:** Investigation. **Pritam Raja:** Data curation. **Ravindranadh C. Mundlamuri:** Writing – review & editing. **Ravi Yadav:** Writing – review & editing. **Atchayaram**

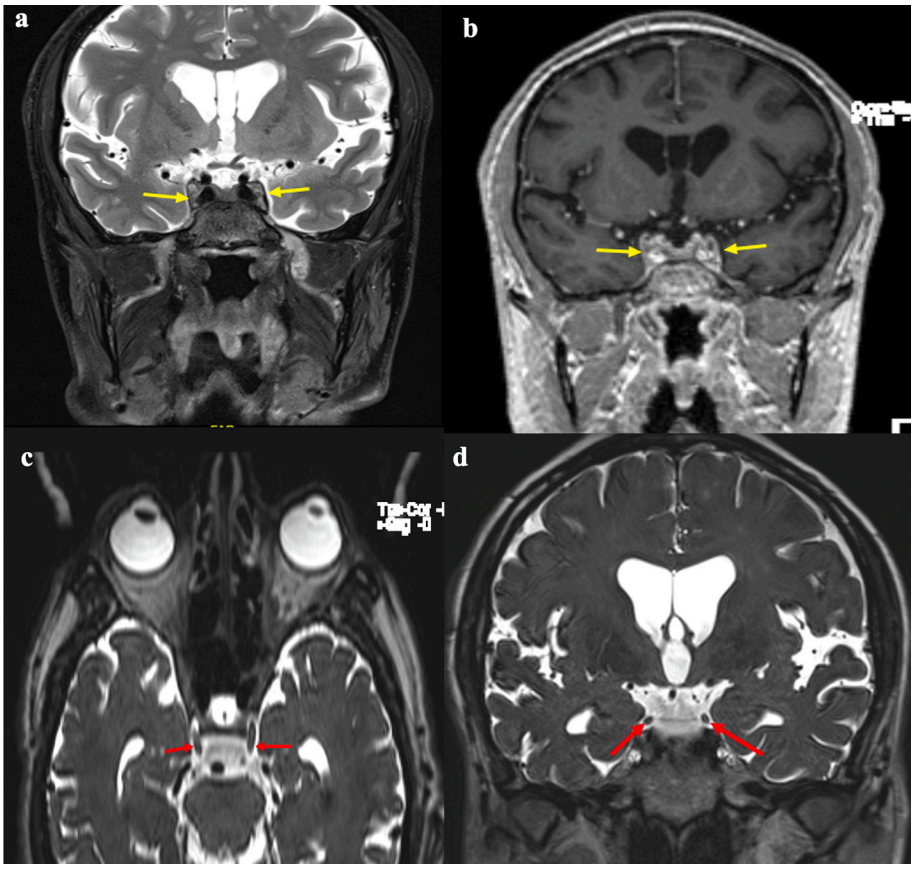

Fig. 2. MRI brain of the patient: **a)** Coronal STIR and **b)** post contrast T1 images depicting bulky cavernous sinuses bilaterally with convex margins (yellow arrows). **c)** Axial and **d)** Coronal heavily T2 weighted images showing enlarged oculomotor nerves (CN III) in interpeduncular cisterns (red arrows) just before their entry into the cavernous sinuses.

Nalini: Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

Nothing to disclose.

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Nil

References

[1] J.J. Castillo, S. D'Sa, M. Lunn, M.C. Minnema, A. Tedeschi, F. Lansigan, M. L. Palomba, M. Varettoni, R. Garcia-Sanz, L. Nayak, et al., Central nervous system involvement by Waldenströmmacroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study, Br J Haematol 172 (2015) 709–715.

[2] L. Simon, A. Fitsiori, R. Lemal, et al., Bing-Neel syndrome, a rare complication of Walden-ström's Macroglobulinemia: analysis of 44 cases and review of literature. A study on be-half of the French Innovative Leukemia Organization (FILO), Haematologica 100 (12) (2015) 1587–1594.

[3] A. Nanah, S. Al Hadidi, Bing-Neel syndrome: update on the diagnosis and treatment, Clin Lymphoma Myeloma Leuk 22 (2021) e213–e219.

[4] F. Fintelmann, R. Forghani, P.W. Schaefer, E.P. Hochberg, F.H. Hochberg, Bing-Neel Syndrome revisited, Clin Lymphoma Myeloma 9 (1) (2009) 104–106.

[5] J.M. Baehring, E.P. Hochberg, N. Raje, M. Ulrickson, F.H. Hochberg, Neurological manifestations of Waldenström macroglobulinemia, Nat Clin Pract Neurol 4 (10) (2008 Oct) 547–556.

[6] Q. Kuang, J. Yu, X. Zhang, F. Yang, X. Chen, W. Xiao, et al., Trochlear nerve damage resulting from Waldenstrom's macroglobulinemia: a case report and literature review, Rev Neurol (Paris) 177 (3) (2021 Mar) 317–319.

[7] R. Sutter, C. Arber, A. Tichelli, A.J. Steck, A. Czaplinski, Cranial and peripheral neuropathy due to leptomeningeal infiltration in a patient with Waldenstrom's macroglobulinemia, J Neurol 254 (8) (2007 Aug) 1122–1123.

[8] P.R. Klokkevold, D.A. Miller, A.H. Friedlander, Mental nerve neuropathy: a symptom of Waldenström's macroglobulinemia, Oral Surg Oral Med Oral Pathol 67 (6) (1989 Jun) 689–693.

[9] K. Viala, T. Stojkovic, A.V. Doncker, T. Maisonobe, T. Lenglet, G. Bruneteau, L. Musset, J. Neil, J.M. Léger, V. Leblond, Heterogeneous spectrum of neuropathies in Waldenström's macroglobulinemia: a diagnostic strategy to optimize their management, J PeripherNerv Syst 17 (1) (2012 Mar) 90–101.

[10] S.Y. Kristinsson, M. Bjorkholm, O. Landgren, Survival in monoclonal gammopathy of undetermined significance and Waldenstrom macroglobulinemia, Clin Lymphoma Myeloma Leuk 13 (2) (2013) 187–190.