CASE REPORT

Crystal-storing histiocytosis and Bing-Neel-like syndrome revealing a small B-cell lymphoma with plasmacytic differentiation, presumed to be a marginal zone lymphoma

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Abstract
Crystal-storing histiocytosis and Bing-Neel syndrome are two diseases induced by paraproteins. Herein, we report a rare case of crystal-storing histiocytosis associated with Bing-Neel-like neurological manifestations in the context of a small B-cell lymphoma with plasmacytic differentiation, presumed to be a marginal zone lymphoma.

KEYWORDS
Bing-Neel syndrome, crystal Storing histiocytosis, marginal zone lymphoma

1 | INTRODUCTION

Crystal-storing histiocytosis (CSH) is a rare disease characterized by the intra-lysosomal accumulation of monoclonal immunoglobulin light chains within histiocytes.[1] The pathophysiology of CSH seems to be influenced more by the type of light rather than that of heavy chains.[2] Some mutations in the variable regions may induce crystallization of Ig and resistance from lysosome clearance, leading to the formation of crystal-storing inclusions and secondary granulomatous lesions. In 90% of CSH cases, an underlying B lymphoproliferative or plasma cell disorder is present.[3]

Bing-Neel syndrome (BNS) is a rare and probably underdiagnosed neurological complication of Waldenström macroglobulinemia (WM) with infiltration of the central nervous system (CNS) by malignant lymphoplasmacytic cells.[4-6]

Herein, we report the case of a 69-year-old Caucasian male patient presenting atypical manifestations of a small B-cell lymphoma, presumed to be a marginal zone lymphoma with plasmacytic differentiation and IgM

paraprotein, complicated by CSH and neurological impairment similar to BNS.

2 | CASE REPORT

A 69-year-old Caucasian male patient presented with anorexia, asthenia, and weight loss, as well as abdominal pain. His neurological state gradually degraded; he experienced confusion, headache, hearing loss, and aphasia. Physical examination found a static cerebellar syndrome associated with major ataxia and pyramidal syndrome.

Computed tomography scan found enlarged spleen and liver, and an infra- and supradiaphragmatic polyadenopathy. Blood test results were the following: hemoglobin at 10 g/dl, monoclonal gammopathy (IgM lambda 8 g/L) with cryoglobulinemia type I activity, and a serum-free kappa/lambda light chain ratio at 0.08. The urine test found Bence Jones proteinuria; 4.5 g/24 h composed of 78% light chain lambda. The cerebral MRI found FLAIR hyperintensity in the supratentorial white matter with hyperintensity on diffusion sequence without restriction in apparent diffusion coefficient (ADC) induced by vasogenic edema. There was also a leptomeningeal contrast enhancement in gadolinium sequences (Figure 1). The lumbar puncture found mild elevated cerebrospinal fluid (CSF) protein (0.53 g/L; norm <0.4 g/L), 4 cells/mm^3 (lymphocytes and plasma cells), and a pathological elevation of IgM (14 mg/L) with an IgM index at 0.42. Flow cytometry failed to detect a monotypic B-cell population in the CSF.

2.1 | Several histological specimens were studied

A colonoscopy was performed because of the abdominal pain and found a mild colitis with multiple small whitish lesions. The colonic biopsies found submucosal clusters of histiocytes with abundant crystalline eosinophilic
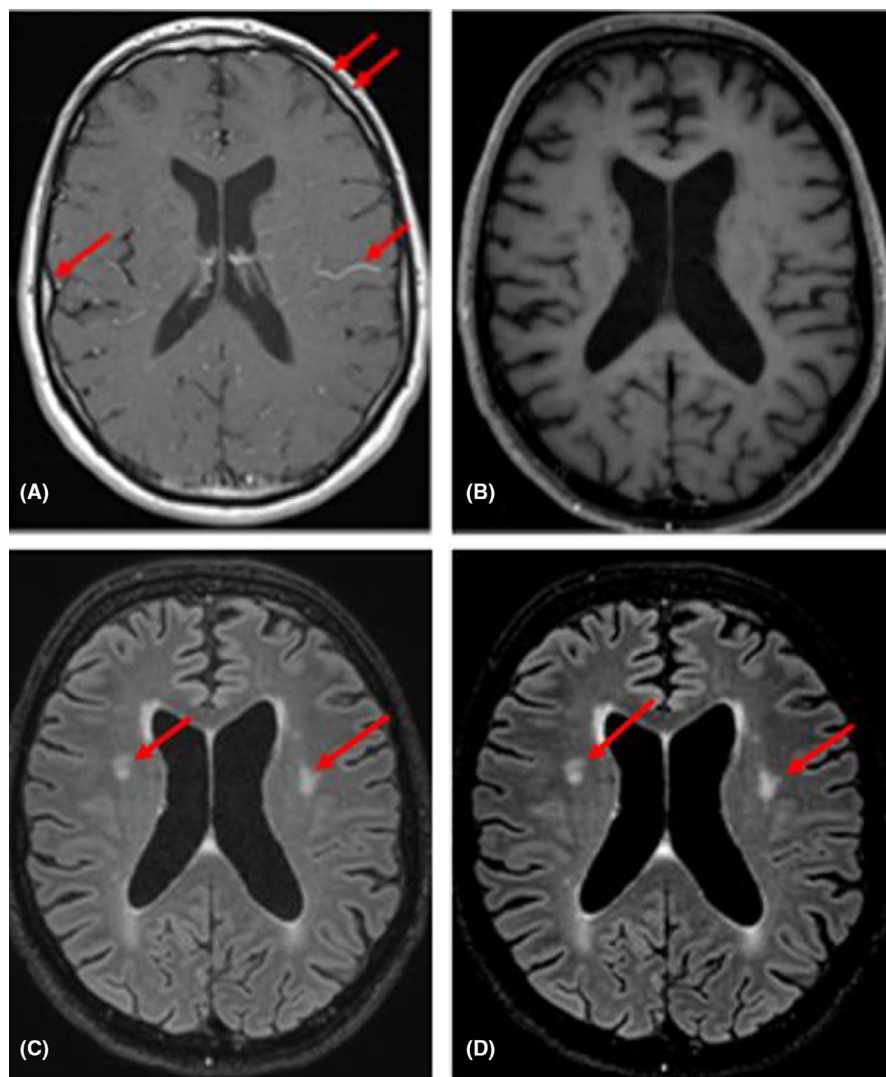

FIGURE 1 Cerebral MRI. Leptomeningeal contrast enhancement in T1 gadolinium sequence before treatment (arrow; A). Disappearance of the leptomeningeal contrast enhancement in T1 gadolinium sequence after treatment (B). Hyperintensity lesions in the supratentorial white matter in T2 FLAIR sequence before treatment (arrow; C). Stabilization of hyperintensity lesions in the supratentorial white matter in T2 FLAIR sequence after treatment (arrow; D)

cytoplasmic inclusions. These were associated with a lymphoid infiltrate, in the form of a nodule of small cells. The mucosa was composed of normal lieberkühn crypts, and plasma cells were found within the lamina propria (Figure 2). A bone marrow biopsy was also performed; this was hypercellular, and there was a normal representation of the three hematopoietic lineages. There was a discrete lymphoid infiltrate, composed of small B and T lymphocytes. The plasma cells represented 5%–10% of the bone marrow cellularity and displayed an inversion of the kappa/lambda ratio (Figure 3). A monoclonal B-cell population was detected by polymerase chain reaction (PCR). No mutation was detected by next generation sequencing (NGS); in particular, MYD88 L265P was not found. Some clusters of histiocytes with abundant crystalline eosinophilic cytoplasmic inclusions were also identified. In addition, a cervical lymph node biopsy was performed, which found a massive infiltration by the same histiocytes as observed in the colon and bone marrow (Figure 4). The histiocytes were admixed with numerous monotypic lambda plasma cells and were associated with small lymphoid nodules at the periphery of the lymph node. Immunohistochemistry found that lymphoid nodules were predominantly composed of B cells, which did not express BCL6, CD10, CD5, cyclin D1, nor CD23. Small atrophic dendritic meshworks were identified in the B-cell nodules using anti-CD23 antibody. The mast cell population was not elevated, and there was no hemosiderin. The same monoclonal B-cell population as that found in the bone marrow was identified by PCR. No mutation was found by NGS; in particular, MYD88 L265P was not found. Cytogenetic analyses of the lymph node found a complex karyotype with 2q, 3p, 10q, and 17p deletions and 9p addition, none of these anomalies being specific of a B lymphoproliferative syndrome. Given the presence of a small B-cell lymphoma with plasmacytic differentiation in the lymph node biopsy, additional techniques were then used on the colonic biopsy sample. Lymphoid infiltrate in the submucosa was composed of a mixture of small B and T cells, but B cells were predominant. Plasma cells in the lamina propria were monotypic lambda. PCR identified the same monoclonal B-cell population as that found in the bone marrow and the lymph node.

This clinical, laboratory, histological, and imaging presentation was consistent with the diagnosis of a CNS involvement similar to BNS, which usually occurs in the setting of WM, associated with CSH. However, in the present case, because of the clinical presentation (polyadenopathy with colon involvement coupled with only minimal bone marrow involvement) and molecular data (absence of MYD88 L265P mutation), the underlying lymphoma was more accurately diagnosed as a marginal zone
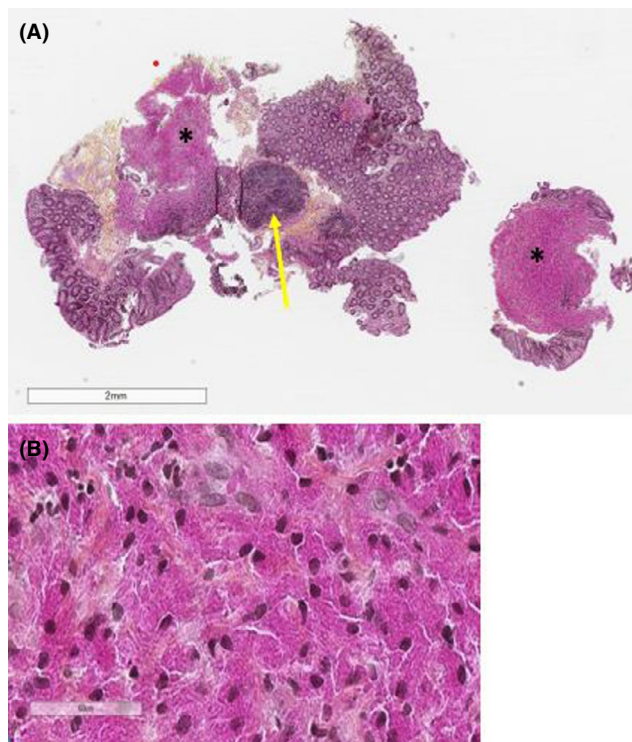

FIGURE 2 Colon biopsy. Submucosal clusters of histiocytes with crystalline eosinophilic cytoplatic inclusions (*) associated with a lymphoid infiltrate (↑) (A; HPS × 1.2). Submucosal clusters of histiocytes with crystalline eosinophilic cytoplasmic inclusions at higher magnification (B; HPS × 40)

lymphoma (MZL) with plasmacytic differentiation rather than a lymphoplasmacytic lymphoma (LPL)/WM.

The patient was first treated for a BNS by 3 cycles of rituximab-bendamustine and intrathecal methotrexate-methylprednisolone-cytarabine. This treatment led to the improvement of his clinical and cognitive state, and the cerebellar ataxia and pyramidal signs disappeared. An MRI performed after treatment found a stabilization of white matter lesions and the disappearance of the leptomeningeal contrast enhancement (Figure 1).

3 | DISCUSSION

To the best of our knowledge, this is the first reported case of a CNS involvement similar to BNS associated with a generalized CSH in the setting of a MZL.

We present herein a generalized form of CSH, which is found in 42% of reported cases.[2] CSH does not usually impair CNS, although Dogan et al. reported only 3% of dura and pia mater involvement in patients with generalized CSH, and Flanagan et al. reported one case of CSH involving the cerebellum and caudal brain stem.[2,7] In the present case, neurological manifestations and MRI findings were
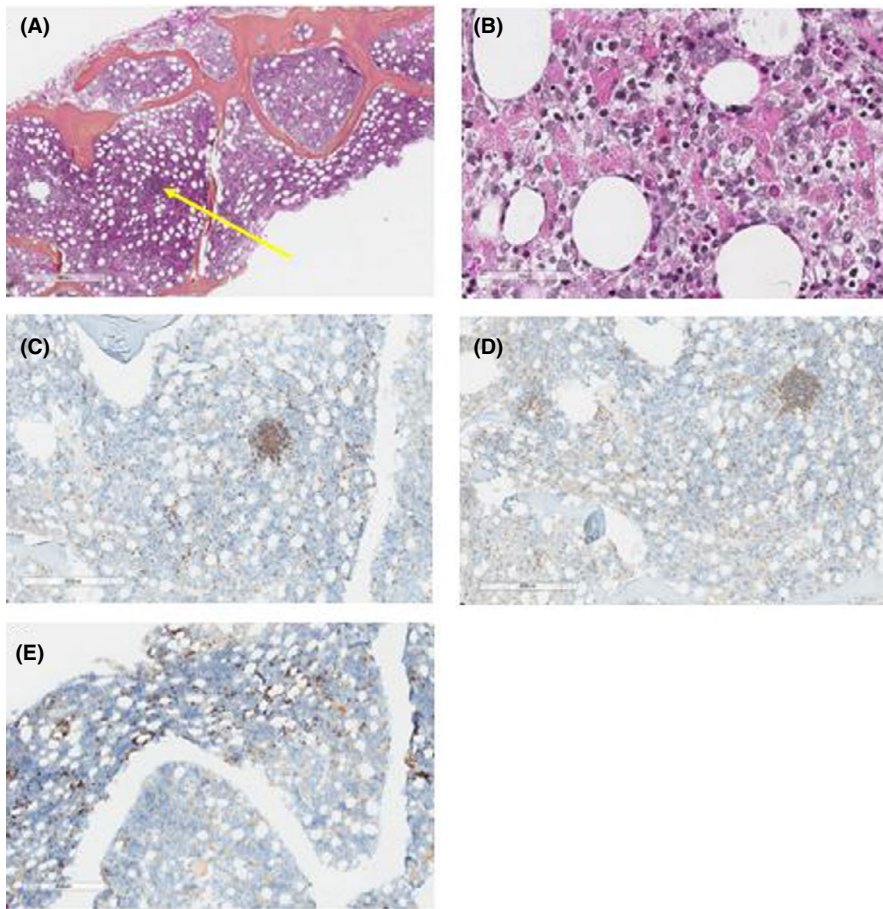
FIGURE 3 Bone marrow biopsy. Hypercellular bone marrow with a discrete lymphoid infiltrate (arrow; A; HPS × 2.5). Histiocytes with abundant crystalline eosinophilic cytoplasmic inclusions were identified, either scattered or in clusters (B; HPS × 40). The lymphoid infiltrate is composed of a mixture of B and T lymphocytes (C; CD20 × 5, D; CD3 × 5). The plasma cells represented 5 to 10% of the bone marrow cellularity (E; CD138 × 5)
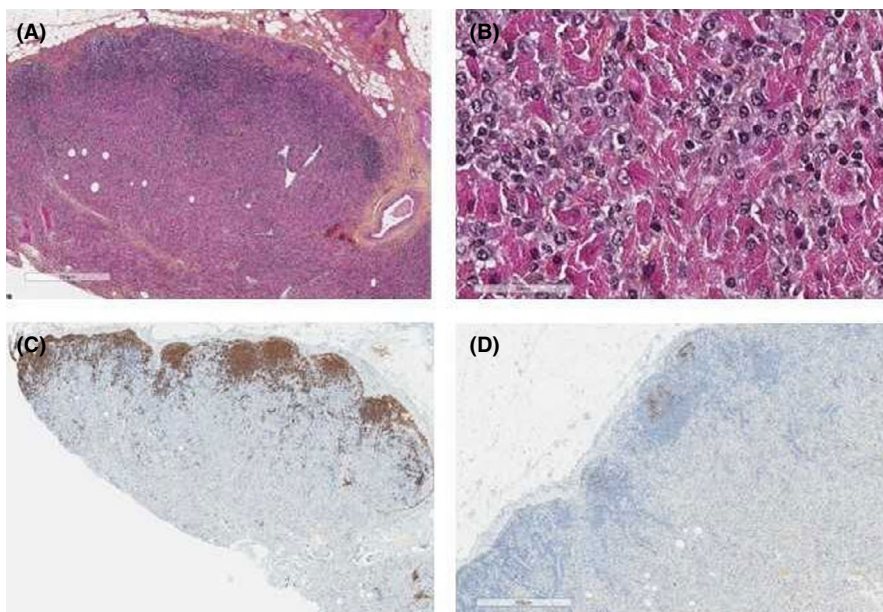

FIGURE 4 Lymph node biopsy. Massive infiltration by the same crystalline histiocytes as observed in the colon and bone marrow, associated with small lymphoid nodules at the periphery of the lymph node (A; HPS × 2.5). The crystalline histiocytes are admixed with numerous plasma cells (B; HPS × 40). Small lymphoid B-cell nodules are present at the periphery of the lymph node (C; CD20 × 1.5). Small atrophic dendritic meshworks were found in the nodules with anti-CD23 antibody (D; CD23 × 4)

highly suggestive of BNS with signs of parenchymal and leptomeningeal involvement. Furthermore, the lumbar puncture cellularity was consistent with a type B BNS according to Fintelmann's proposed classification[8]; this type represents 25% of all BNS cases and is characterized by a very low cell count (<5 cells/mm^3) in the cerebrospinal fluid. This, and the pathological CSF IgM index, suggested neurological manifestations associated with IgM deposition with an intrathecal secretion, rather than lymphoplasmacytic infiltration.[8] Taken together, we consider that

CSH and BNS in the case presented are simply two manifestations of an abnormal circulation of immunoglobulins in terms of quantity and quality.

In the present case, the definitive classification of the underlying small B-cell lymphoma, which displayed a striking plasmacytic differentiation, remains difficult. LPL usually involves bone marrow and sometimes lymph nodes, extranodal sites, and spleen. WM is defined as a LPL with bone marrow involvement and an IgM monoclonal gammopathy. MYD88 L265P mutation has been described in almost if not all (this remains debated) LPL/WM cases and associated with a CXCR4 mutation in approximately 30% of cases. Conversely, this MYD88 L265P mutation is rarely (~5% of cases) present in MZL. Therefore, in the case presented herein, polyadenopathy with extranodal involvement (colon) and only minimal bone marrow involvement, coupled with the absence of MYD88 L265P mutation, would favor MZL with plasmacytic differentiation rather than LPL/WM. However, because this neurological presentation similar to BNS, which is, to our knowledge, exclusively described as a complication of WM, the patient was treated as a case of WM complicated by a BNS. Nevertheless, one can legitimately wonder why BNS could not also complicate a MZL with plasmacytic differentiation and IgM paraprotein, knowing that neurological manifestations in BNS type B are probably related to IgM rather than to lymphoma cell infiltration.

The patient was treated as a BNS case with rituximab-bendamustine and intrathecal treatment leading to a clinical and radiological improvement, but more recently, ibrutinib appears to be a good alternative as an oral treatment for this disease.[9] CSH is treated according to the causal pathology; there is little information concerning the specific response of CSH after chemotherapy but the histological lesions do persist after treatment in the available observations.[10]

4 | CONCLUSION

This unique case associates two complications of a marginal zone lymphoma with plasmacytic differentiation and IgM paraprotein. It underlines the need to search for a B lymphoproliferative disorder after a histological CSH diagnosis and to hypothesize that a B lymphoproliferative disorder with plasmacytic differentiation and paraprotein secretion other than WM can induce neurological presentations similar to BNS.

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AUTHOR CONTRIBUTIONS
HL, PS, MGV, PG, and EF contributed to clinical diagnosis, treatment of the patient, and description of the clinical part of the manuscript. JF and ATG contributed to anatomopathological diagnosis and description of the anatomopathological part of the manuscript. YJ revised the manuscript. All authors approved the final version of the submission.

ETHICS APPROVAL
The study protocol was conducted according to the declaration of Helsinki.

CONSENT
Written informed consent was obtained from the patient for the publication of this case report and any associated images.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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