Crystal Storing Histiocytosis and Bing-Neel-like syndrome revealing a marginal zone lymphoma with plasmacytic differentiation.

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Abstract

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Abstract:

Crystal Storing Histiocytosis and Bing Neel Syndrome are two diseases induced by paraprotein. Herein, we report a rare case of Crystal Storing Histiocytosis associated with Bing-Neel-like neurological manifestations in the context of marginal zone lymphoma with plasmacytic differentiation.

Keywords: **Crystal Storing Histiocytosis, Marginal zone lymphoma, Bing Neel syndrome.**

Key message:

This case shows the need to search for a B lymphoproliferative disorder after a Crystal Storing Histiocytosis diagnosis and to hypothesize that a B-lymphoproliferative disorder other than Waldenström Macroglobulinemia can induce Bing-Neel Syndrome

Introduction:

Crystal storing histiocytosis (CSH) is a rare entity characterized by the intra-lysosomal accumulation of crystals composed of immunoglobulin light and/or heavy chain fragments enriched in Ig variable regions within histiocytes [1]. In 90% of CSH, an underlying B lymphoproliferative or plasma cell disorder is present [2]. The pathophysiology of CSH seemed to be associated with the type of light chain rather than the heavy chain [3]. Some mutations in variable sequences may induce crystallization of immunoglobulins and resistance from lysosome clearance leading to the formation of crystal storing inclusions and secondary granulomatous lesions. Bing-Neel syndrome is a rare and probably underdiagnosed neurologic complication of Waldenström macroglobulinemia (WM) with infiltration of central nervous system (CNS) by malignant lymphoplasmacytic cells [4-5-6].

Herein, we report the case of a 69-year-old Caucasian male presenting atypical manifestations of a marginal zone lymphoma with plasmacytic differentiation and IgM paraprotein complicated by CSH and neurological impairment similar to BNS which is known as a complication of Waldenstöm macroglobulinemia.

Case report:

A 69-year-old Caucasian male presented with an impaired general condition with abdominal pain. He gradually exhibited a degradation of his neurological state with confusion, headache, hearing loss, and aphasia. His physical examination showed a static cerebellar syndrome associated with major ataxia and pyramidal syndrome.

An abdominal-chest computed tomography revealed enlarged spleen and liver, and an upper and under diaphragmatic polyadenopathy. Laboratory findings were the following: haemoglobin 10g/dL, a monoclonal gammopathy (IgM lambda 8g/L) with cryoglobulinemia type I activity and a serum free light chain ratio kappa/lambda at 0.08. The urine test found a Bence Jones proteinuria at 4.5 g/24h composed of 78% light chain lambda.

The cerebral MRI found hypersignal FLAIR in the supra-tentorial white matter with hypersignal on diffusion sequence without restriction in ADC induced by vasogenic edema. Moreover, there was a leptomeningeal contrast enhancement in Gadolinium sequences (Figure 1).

The lumbar puncture found a mild hyperproteinorachia (0.53 g/L; norm $<$ 0,4 g/L) and 4 cells/mm^3 composed of lymphocytes and plasma cells, with a pathological elevation of IgM at 14 mg/L and an IgM index at 0,42. Flow cytometry analysis failed to detect a monotypic B cell population in the cerebro-spinal fluid, but cellularity was very low.

Several histological specimens were studied:

1/ A colonoscopy was performed because of abdominal pain and showed a mild colitis with multiple small whitish lesions. The colonic biopsies showed submucosal clusters of histiocytes with abundant crystalline eosinophilic cytoplasm inclusions (Figure 2).

2/ The bone marrow biopsy was hypercellular, with a normal representation of the three hematopoietic lineages. There was a discrete lymphoid infiltrate, made of small B and T lymphocytes. The plasma cells represented 5 to 10% of the bone marrow cellularity and showed an inversion of their kappa/lambda ratio (Figure 3). A monoclonal B-cell population was found by polymerase chain reaction (PCR). Any mutation was detected by Next Generation Sequencing (NGS), in particular no MYD88 L265P mutation. Some clusters of histiocytes with abundant crystalline eosinophilic cytoplasmic inclusions were also identified.

3/ A cervical lymph node biopsy showed a massive infiltration by the same histiocytes as observed in colon biopsy and bone marrow (Figure 4). It was associated with small lymphoid B-cell nodules, lacking a specific phenotype by immunohistochemistry, and numerous monotypic lambda plasma cells. The PCR identified the same monoclonal B-cell population than in the bone marrow. No mutation was found by NGS, in particular no MYD88 L265P mutation. Cytogenetic analyses of the lymph node showed a complex caryotype with 2q, 3p, 10q, 17p deletions and 9p addition, any of these anomalies being specific of a B lymphoproliferative syndrome.

Finally, these clinical, biological, histological and imaging presentation were consistent with the diagnosis of a CNS involvement similar to BNS which usually occurs in the setting of WM, associated with CSH. However, in our case, underlying lymphoma was more accurately diagnosed as a marginal zone lymphoma (MZL) with plasmacytic differentiation.

The patient was first treated as a BNS by 3 cures of Rituximab-Bendamustine and intrathecal Methotrexate – Methylprednisolone - Aracytine. This treatment allowed an improvement of his clinical and cognitive state, with disappearance of cerebellar ataxia and pyramidal signs. An MRI realized after treatment find a stabilization of white matter lesions and a disappearance of the leptomeningeal contrast enhancement (Figure 1).

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.

Here we present a generalized form of CSH which represents 42% of clinical presentation of this disease, whereas the localized pattern is more frequent and often localized in the head and neck region [2]. CSH do not usually impair CNS: Dogan S. et al. report only 3% of dura and pia mater involvement in patients with generalized CSH, and Flanagan ME et al. report one case of CSH involving cerebellum and caudal brain stem [2, 7].

In our case, neurological manifestations and MRI findings were highly suggestive of BNS with signs of parenchymal and leptomeningeal involvement. The lumbar puncture cellularity was consistent with a type B BNS according to the Fintelmann's proposed classification [8]. Type B BNS represents 25% of total BNS and is defined by a very low cells rate (<5 cells/mm^3) in the cerebrospinal fluid. This suggested neurological manifestations being associated with IgM deposition with an intrathecal secretion, as the pathological CSF IgM index indicates, rather than lymphoplasmacytic infiltration [8].

There is no clear causal link between CSH and BNS. We consider that they are just two manifestations of an abnormal circulation of immunoglobulins in quantity and quality.

In our case, definitive classification of the underlying small B-cell lymphoma, which shows a striking plasmacytic differentiation, remains difficult. Lymphoplasmacytic lymphoma (LPL) usually involves bone marrow and sometimes lymph nodes 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 all, if not all (this is a point of debate) LPL/WM, associated with a CXCR4 mutation in approximately 30% of cases. Conversely, this MYD88 L265P mutation is rarely (˜5% of cases) present in MZL. So, in our case, polyadenopathy with minimal bone marrow involvement and 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 in literature, our patient was considered as having WM complicated by a BNS for therapeutic decision. 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 cells infiltration.

The patient was treated as a BNS with R-Bendamustine associated and intrathecal treatment allowing a clinical and radiological improvement. Ibrutinib appears to be a good alternative as an oral treatment for this disease [9]. CSH treatment depends of the causal pathology. There is little information concerning specific response of CSH after chimiotherapy but the histologic lesions persist in available observations [10].

Conclusion:

This unique case associate two complications of a marginal zone lymphoma with plasmacytic differentiation and IgM paraprotein. This observation underlines the need to search for a B lymphoproliferative disorder after an 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.

Fig1 Cerebral MRI. Leptomeningeal contrast enhancement in T1 Gadolinium sequence before treatment (arrow) (1A). Disappearance of the leptomeningeal contrast enhancement in T1 Gadolinium sequence after treatment (1B). Hypersignal lesions in the supra-tentorial white matter in T2 FLAIR sequence before treatment (arrow) (1C). Stabilization of hypersignal lesions in the supra-tentorial white matter in T2 FLAIR sequence after treatment (arrow) (1D).

Fig2 Colon biopsy. Submucosal clusters of histiocytes with crystalline eosinophilic cytoplasm inclusions (2A: HPS x 2.5, 2B: HPS x 40)

Fig3 Bone marrow biopsy. Hypercellular bone marrow with a discret lymphoid infiltrat (arrow) (3A: HPS x 2.5). Histiocytes with abundant crystalline eosinophilic cytoplasmic inclusions were identified, scattered or in clusters (3B: HPS x 40). The lymphoid infiltrate is made of a mixture of a B and T lymphocytes (3C: CD20 x 5, 3D: CD3 x 5). The plasma cells represented 5 to 10% of the bone marrow cellularity (3E: CD138 x 5).

Fig4 Lymph node biopsy. Massive infiltration by the same crystalline histiocytes as observed in colon biopsy and bone marrow, associated with small lymphoid nodules at the periphery of the lymph node (4A: HPS x 2.5). The crystalline histiocytes are admixed with numerous plasma cells (4B: HPS x 40).

Conflict of Interest:

The authors declare that they have no conflict of interest.

Author contributions:

HL, PS, MGV, PG and EF: Clinical diagnosis, treatment of the patient and described clinical part of the manuscript.

JF and ATG: Anatomopathological diagnosis and described anatomopathological part of the manuscript.

YJ: Revised the manuscript.

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