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Intracranial extranodal marginal zone lymphoma mimicking meningioma: A rare but insidious entity

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Magnetic resonance imaging (MRI) has revolutionized the treatment of central nervous systems (CNSs) diseases, becoming the gold-standard technique for the diagnosis of many conditions, as in the case of brain meningiomas.[1] However, in some cases, histological examination can still upset the radiological findings, providing a different diagnosis that can change the following therapeutic decisions. We present the case of a patient with intracranial lesions initially misdiagnosed as meningiomas but ultimately revealed to be extranodal marginal zone lymphoma (EMZL). This case highlights the importance of considering a broader differential diagnosis when interpreting radiological findings, as similar imaging characteristics can be observed in various neurological conditions.

The patient, a 58-year-old woman, presented with complaints of bilateral fluctuating vision disturbances. Her medical history included arterial hypertension, recovered tuberculous lymphadenitis, a recent episode of chronic pneumonia, follicular thyroid cancer, IgG-Lambda monoclonal gammopathy of uncertain significance, and infiltrating ductal breast carcinoma (Her2+, hormone receptor-negative, T2N0M0), treated 3 years prior with surgery, radiotherapy, and cytotoxic chemotherapy.

A brain MRI revealed two extra-axial lesions: one en plaque on the right frontal-parietal convexity, and another on the right anterior clinoidal process. The tumor board concluded that these were incidental multiple meningiomas, recommending clinical and neuro-radiological follow-up (Figure 1).

Twelve months later, the patient experienced a left focal seizure. A new MRI showed the growth of the right fronto-parietal lesion, the development of vasogenic edema, and the appearance of a new en plaque lesion in the left parietal convexity. Surgical intervention was advised to remove the right-sided en plaque lesion but was delayed for 5 months due to systemic inflammation and chronic pneumonia, managed with oral corticosteroids and antibiotics.

Given the increase in size of the right lesion and associated edema, surgery was performed, achieving a radical resection. Intraoperatively, the tumor appeared as a vascularized, fibrous red-gray mass, highly adherent to brain parenchyma. Interestingly, the lesion was easily dissected from the dura, but no arachnoidal plane could be identified, as the tumor extended into the subarachnoidal space. Complete tumor removal was achieved using a high-selective ultrasound aspirator. Postoperative recovery was uneventful, with a 72-h MRI showing no residual tumor. The contralateral lesion was not visible on the postoperative MRI, likely due to steroid treatment (Figure 2).

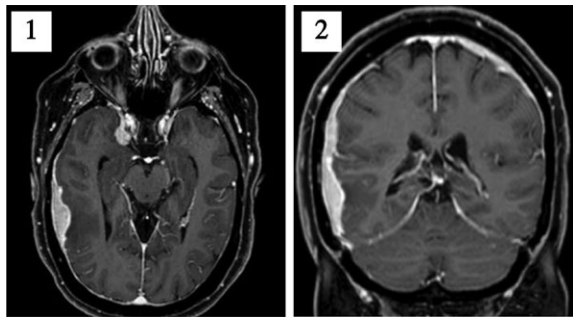

Figure 1. Preoperative axial and coronal MRI T1w CE of PR showing three extra-axial *en plaque* lesions with homogeneous contrast uptake, located in fronto-parieto-temporal right side (1,2), right clinoidal process (1), and fronto-parietal left side (2).

Unexpectedly, histological examination revealed meningeal tissue with dense, partially nodular, and partially diffuse infiltration of small mature lymphoid cells with condensed chromatin, plasmacytoid elements, and well-differentiated plasma cells around lymphoid nodules (Figure 3). The lymphoid component was immunopositive for CD20, while the plasmacytoid component was CD138+ (Figure 4). Cyclin D1, CD5, and CD23 were negative, and the plasmacytoid and plasmacellular components showed clonal λ light chain restriction (Figure 5). Differential diagnosis included EMZL, lymphoplasmacytic lymphoma, and plasmacytoma/plasma cell myeloma. However, no MYD88 mutation was observed (performed by PCR as described by Argentou et al.[2] and sequenced on 3500 Dx Genetic

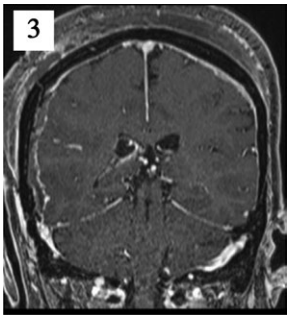

Figure 2. Immediate postoperative MRI T1w CE showing complete surgical removal of the right fronto-parieto-temporal lesion and the spontaneous regression of the left fronto-parietal lesion in the coronal plane.

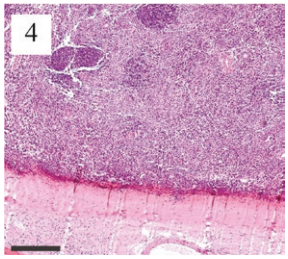

Figure 3. Histological picture demonstrates meningeal fibrous tissue (in the lower part) with dense, partially nodular, and partially diffuse infiltration by small mature lymphoid cells associated with plasmacytoid elements and well-differentiated plasma cells (Hematoxylin-eosin (H&E), original magnification 40×, bar 1000 µm).

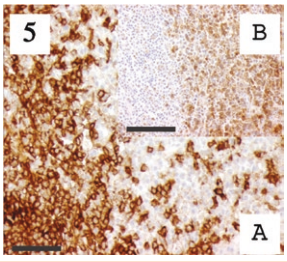

Figure 4. Immunohistochemical analyses highlight the lymphoid component immunopositive for CD20 (A, CD20, original magnification 200×, bar 200 µm) and, as demonstrated in the top righthand corner, the plasmacellular component CD138 + (B, CD138, original magnification 200×, bar 400 µm).

analyser, ThermoFisher Scientific, Life technologies) so lymphoplasmacytic lymphoma diagnosis was unlikely; moreover, the presence of lymphoid nodules and the positivity of clonally restricted plasma cells for CD19 excluded plasmocytoma/plasma cell myeloma. The final diagnosis was meningeal localization of peripheral B-cell lymphoma with plasmacytoid differentiation, classified as EMZL.

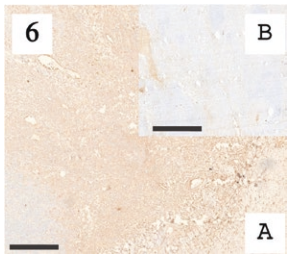

Figure 5. The plasmacytoid and plasmacellular components present clonal λ light chain restriction (A, lambda light chain, original magnification 100×, bar 400 µm). In the top righthand corner, kappa light chain staining is showed (B, kappa light chain, original magnification 100×, bar 400 µm).

Staging was then performed. Cerebrospinal fluid analysis showed slightly elevated protein levels (73.2 mg/dL) and 20 cells, without MYD88 mutations (the molecular analysis aimed at identifying the main variants of the MYD88 gene was performed by sequencing part of exon 5 (from residue G259 to residue I284) on genomic DNA extracted from paraffin material, through PCR amplification and direct sequencing). Cytological examination revealed atypical lymphocytes with irregular nuclei and moderately basophilic cytoplasm. An IGH biclonal gene rearrangement was identified in serum and cerebrospinal B lymphocytes. A total-body CT scan revealed multiple lymphadenopathies in the inguinal and hilar (mediastinal) regions. No lymph nodes were sampled, and the patient was subsequently referred to a hematologist for treatment initiation with methotrexate and cytarabine.

Discussion

Extranodal marginal zone lymphoma is an indolent B-cell non-Hodgkin lymphoma that rarely involves the CNS, where it typically adheres to the dural layer. The pathogenesis of mucosa-associated lymphoid tissue lymphoma generally begins with an inflammatory phase, leading to the formation of a lymphoepithelial lesion, usually within mucosal surfaces.[3] In the CNS, this process is replaced by meningothelial cells, which facilitate the adhesion of B cells that expose surface antigens and promote cell proliferation through cytokine release.[4] These B cells are found in the arachnoid layer, the arachnoid villi of the dural sinuses, and the choroid plexus of the lateral ventricles.[4,5] Indeed, EMZL have been previously described to involve these sites of the CNS.[6]

Clinical presentation depends on the site of tumor development, and it frequently includes headaches, focal motor and sensory impairment, seizures, visual alterations, gait disturbances, and hearing loss.[7]

Radiologically, meningeal EMZL mimic meningioma appearance, presenting as extra-axial lesions with well-defined tumor margins and homogeneous contrast-enhancement uptake.[7] More frequently than meningioma, EMZL can present with *en plaque* presentation.

Additionally, the presence of dural attachment and dural tail sign is frequently described (90%).[8]

Among lower grade lymphoproliferative disorders, those histopathologically appearing with high content of plasma cells encompass differential diagnostic hypothesis, particularly including lymphoplasmacytic Lymphoma/Waldenström macroglobulinemia. Although immunophenotype profile of these different entities may overlap (CD19+, CD20+, CD45/LCA+, CD138+, Bcl2+, MNDA+/–, but Cyclin D1–, CD5–, CD23–), common laboratory abnormalities encountered in lymphoplasmacytic/Waldenstrom lymphoma were missing in our case, including MYD88 mutation and IgM monoclonal component. Instead, our patient presented with a tenuous IgG monoclonal component (lambda). Similarly to our case, extramedullary solitary plasmacytoma typically shows light chain restriction at immunostaining, but it is characterized by a single lesion, without clonal lymphoplasmacytic cells on bone marrow biopsy, generally without an unrelated IgM monoclonal gammopathy.

The analysis of immunoglobulin gene rearrangements is an important diagnostic tool in assessment of B-cell clonality in suspected B-cell proliferations, and immunoglobulin heavy chain gene (IGH) rearrangements are the most frequent target for clonality analysis by polymerase chain reaction. A clonal IGH gene rearrangement, which is a poor prognostic factor in patients with acute myelogenous leukemia, would have oriented us toward the previously described hematological disorders. Biclonal IGH gene rearrangement in a B-cell chronic lymphoproliferative disorder may be due to two immunophenotypically distinct B-cell subsets or to a single disease displaying subclonal evolution. Indeed, oligoclonal IGH gene rearrangement could also be found in case of immunosuppressive or autoimmune disorders, conditions additionally reported by our patient.

The diagnosis of meningeal EMZL usually comes unexpectedly with the histological examination performed after surgical resection. Surgery is more challenging and insidious in case of EMZL because of the lack of a dissection plane within the arachnoid and the infiltrative behavior.[9]

Notably, treatment of EMZL is based on radiotherapy, chemotherapy, immunotherapy, and corticosteroid with optimal responses.[10]

The prognosis for primary CSN EMZL is generally favorable, with most patients achieving complete remission after treatment combinations of surgery, radiotherapy, and chemotherapy. Long-term survival is high, but short follow-up periods in reported cases limit the understanding of potential late recurrences and iatrogenic effects.[11]

With this report, we would raise awareness on the chance of different diagnoses in case of suspected meningioma, especially if there is a history of chronic inflammatory disease and the mass presents *en plaque* with atypical response to corticosteroids. Different strategies to rule out EMZL before performing a complete surgical resection should be considered to reduce surgery-related risks. In some cases, a biopsy was retained more adequate to investigate the nature of the disease,[12] as in case of lymphadenopathies. An alternative approach could contemplate the intraoperative execution of an extemporaneous histological exam before attempting a complete surgical resection.

Less invasive diagnostic strategies for EMZL have not yet been established, although certain clinical and radiological features, such as a history of chronic inflammation and en plaque presentation on MRI, are common indicators. In such cases, repeated MRI after corticosteroid administration could help assess the response and guide the diagnosis toward lymphoma.

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Conflict of interest statement

None of the authors have a conflict to declare related to the work in this manuscript.

Authorship statement

Conceptualization: M.D.B., M.B. Contributed to acquisition of clinical, histological, and imaging data: G.B., A.S., D.L., G.M. Prepared manuscript text and created figure: M.B., G.B., M.D.B., G.M., D.L. Supervision: M.D.B., F.D.M., A.S., G.M. Edited manuscript text, figures, and/or tables: all authors.

Data availability

All data are available through reasonable request.

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