Pearls and Oysters: Non-motor Seizures as Presenting Feature of Hodgkin Lymphoma

CNS Involvement

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Pearls

- CNS involvement in Hodgkin Lymphoma (HL) is extremely rare, and it usually presents with focal weakness, non-specific sensitive symptoms, headache, altered mental status, and seizures.

Oy-sters

- CNS involvement usually presents during advanced stages, most commonly within the first two years after the initial diagnosis.
- CSF findings are unspecific with low positivity rates on flow cytometry, which makes essential the need for tissue sampling.

Case Presentation

A 43-year-old woman hospitalized for acute bacterial cholangitis treated with piperacillin/tazobactam and meropenem developed on day 10 of in-hospital stay an episode of abrupt headache followed by paresthesia of the right arm and a speech impairment lasting more than 15 minutes. Her medical history was relevant for a high-risk (international prognostic score of 4 points) stage IVB classical (mixed cellularity) Hodgkin lymphoma (HL) with lymphatic, gastrointestinal, hepatic, and bone marrow involvement diagnosed four months before admission. She was receiving treatment with AVDB (adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy and had received the fourth cycle one-month before admission.

Upon examination, vital signs were within the normal range. She was alert but unable to communicate correctly; speech was fluent with impaired comprehension, being able to repeat simple phrases with semantic paraphasias and echolalia, findings consistent with sensitive transcortical aphasia, the rest of the examination was unremarkable. Blood workup was relevant for mild anemia of 10.2 g/dL (reference: 14.5–17.7) with a normal white blood cell and platelet
count. Serum electrolytes, coagulation, liver, and renal function tests were normal. To approach a neurovascular cause, we performed an urgent brain MRI, which showed an ill-defined, contrast-enhancing lesion on the left parietal lobe with mixed pachymeningeal and leptomeningeal involvement, and prominent vasogenic perilesional edema (figure 1, A-E).

Right after finishing the MRI, the aphasia had resolved spontaneously. On interrogation, the patient referred to having experienced a similar event, which lasted 10–15 minutes two months before. She also complained of a progressive mild to moderate daily headache, exacerbated by daily life activities, without nausea or vomiting for the past three months. While being prepared for an EEG one hour after the first episode, she developed another similar event. Under suspicion of focal onset, non-motor seizures, we performed a benzodiazepine test with 10 mg of IV diazepam, which resolved the symptoms. An EEG performed after the administration of benzodiazepines revealed slow background rhythm within theta range on the left temporal and parietal lobes without epileptiform activity. Then, we started treatment with IV levetiracetam.

A whole-body $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET/CT showed resolution of the initial hepatic and gastrointestinal involvement with partial response of the lymphadenopathies (Deauville score of 2), and brain PET/MRI fused images showed a decreased $^{18}$F-FDG uptake of the CNS lesion. CSF analysis showed only mildly elevated proteins in 68 mg/dL (reference: 15–45) with normal white cells (3 cells/µl [reference: 0–10]), glucose (68 mg/dL [range: 50-80]) and CSF/serum glucose ratio. Gram and acid-fast bacilli stains were negative as well as PCR for herpes simplex viruses 1 and 2, varicella-zoster virus, Epstein-Barr virus, toxoplasma gondii, and Mycobacterium tuberculosis. CSF was also negative for malignancy, by morphology and flow cytometry.
Because of the inconclusive neuroimaging findings, under suspicion of HL progression to the CNS, we performed a complete surgical removal of the lesion. Histopathological analysis showed lymphocytic infiltration and Reed-Sternberg cells, with positive immunohistochemistry staining for CD30, CD15 (figure G-I), latent membrane protein-1 (LMP-1) and paired box 5 (PAX5) antibody, consistent with a diagnosis of HL. After confirming progression to the CNS, we started local treatment with whole-brain radiation plus systemic therapy with monthly brentuximab vedotin (1.8 mg/kg). She was discharged 25 days after admission on levetiracetam 500 mg twice a day. On follow-up four months after discharge, the patient remains asymptomatic without any further seizures.

Discussion
HL is a hematological neoplasm that arises from B-cells, accounting for 10% of all newly diagnosed lymphoma cases. In the early stages, it is usually limited to the lymph nodes, although it can also involve extranodal sites. On Histopathological analysis, the neoplastic cells appear as multinucleated giant cells or large mononuclear cells, better known as the pathognomonic Reed-Sternberg cells. CNS involvement of HL is rare, with a frequency of 0.02–0.07%, usually presenting in advanced stages, but can occur at the time of diagnosis or during a relapse. Furthermore, it can also have other neurological manifestations, such as paraneoplastic syndromes (e.g., cerebellar degeneration) and treatment-related complications. Because of the rarity of CNS involvement, the knowledge of these patients’ clinical characteristics derives from a few case reports and small case series.

A case series of 16 patients with intracranial involvement of HL reported that 56% of patients were males with a mean age at presentation of 45 years. Median time from initial diagnosis of HL to CNS involvement was 11.7 (6.9–18.9) months, and 9 out of 13 (69%) patients were in complete response at the time of diagnosis. Another case series that included
patients from an international multicenter study of 30,781 patients with HL found only 21 (0.07%) histologically confirmed cases. In this study, 52% were males with a median age at onset of 40 years (range 18–84). The median time from the initial diagnosis of HL to CNS involvement was 1.9 years (range 0.4–6.6) with an overall response rate of 65% and median overall survival of 29 months during a 3.6 years follow-up. From these findings, we can partially conclude that CNS involvement in HL is slightly more frequent in males during the fifth decade of life and that it usually develops within the first two years after the initial diagnosis of HL.

The clinical presentation reported within these series was as follows: pyramidal weakness (18–35%), non-specific sensitive manifestations including pain (20–31%), headache (18–25%), altered mental status (15–18%), seizures (5–18%), aphasia (5%) and ataxia (5%). Our patient clinical presentation included headache, paresthesia, and focal seizures. Pathophysiological mechanisms of intracranial involvement in HL remains incompletely understood; the proposed hypotheses include hematogenous dissemination of the neoplastic cells to the meninges or surrounding bony structures with subsequent brain involvement or direct parenchymal dissemination. Those hypotheses could explain the neuroimaging findings, with isolated parenchyma involvement in 58-83% of cases, leptomeningeal involvement in 15–31% or both in 5–26%.

The reported locations within the parenchyma are highly variable, and there are no specific neuroimaging findings for distinguishing HL infiltration from other etiologies, such as a brain abscess. Also, CSF findings are unspecific, being the most common finding an elevation of proteins in a wide range, varying from 0 to 245 mg/dL. CSF flow cytometry is positive only in 22 to 45% of cases, making even harder the diagnosis without a brain biopsy. Nevertheless, when possible, CSF analysis with flow cytometry constitutes a feasible way to approach these patients.
There is a wide variation of treatment modalities that can be used, including guided radiotherapy alone, whole-brain radiation, multiagent systemic chemotherapy, and total or subtotal surgical resection. The most constant reported treatment is a combination of whole-brain radiation with systemic chemotherapy. Recently, in a phase 3 trial, a combination of brentuximab vedotin (an anti-CD30 antibody-drug conjugate) plus standard chemotherapy showed to improve the risk of progression, death, or noncomplete response in patients with advance stages of HL during a 2-year follow-up. Regarding its use in patients with CNS involvement, there is only one case report in which the patient received brentuximab vedotin plus standard chemotherapy and consolidation with autologous stem cell transplantation followed by brentuximab vedotin maintenance. In this report, the authors showed a durable partial response of 18 months in a highly refractory HL with CNS involvement. However, the patient died six months after the last dose of brentuximab vedotin.

Because of the rarity of CNS involvement, screening for any new neurological symptoms in patients with a known history of HL is mandatory. Any brain space-occupying lesion in these patients should be thoroughly investigated to rule out secondary causes such as a brain abscess, making essential the need for tissue sampling as it can prompt the diagnosis of a progressive or relapsing disease, which may improve the prognosis of these patients.
# Appendix 1: Authors

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References:


Figure 1. Brain MRI and histopathological analysis

(A) Axial T1 weighted image (T1WI) shows an ill-defined lesion in the left parietal lobe. (B) Axial fluid-attenuated inversion recovery (FLAIR) image shows perilesional edema. (C) Axial diffusion-weighted image (DWI) demonstrates the lesion with peripheral restriction. (D) Axial and (E) sagittal contrast-enhanced T1WI shows a heterogenous enhancing lesion with a central necrotic component associated with mixed pachymeningeal and leptomeningeal enhancement. (F) Axial fused 18FDG PET and contrast-enhanced T1WI shows regional parietal lobe hypometabolism. (G) Hematoxylin and Eosin (H&E) stain at 200x (arrow) shows a large binucleated with conspicuous nucleoli and prominent eosinophilic cytoplasm, which are the pathognomonic Hodgkin lymphoma Reed-Sternberg cells, with positive immunohistochemistry staining (arrows) for (H) CD15 and (I) CD30.
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