CASE REPORT

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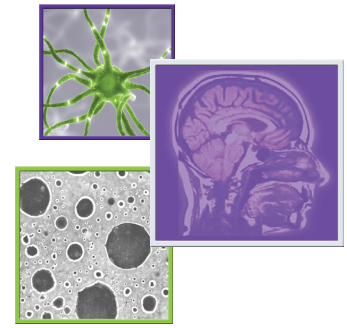
CNS Oncology



Isolated CNS Hodgkin's lymphoma: implications for tissue diagnosis

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Practice points

- Specific, accurate tissue diagnosis is essential for appropriate therapy regimen implementation in the treatment of lymphoma involving the CNS given that chemotherapy or radiation therapy are often tailored to the specific lymphoid neoplasm involved.
- Immunocompromised patients with atypical lesions require thorough evaluation as they may harbor unexpected or rare neoplasms. In this case, lymphoma was suspected even in the absence of systemic manifestations but Hodgkin's lymphoma was not expected.
- Cerebrospinal fluid testing including flow cytometry is helpful in lymphoma diagnosis but is often not sufficiently specific to guide treatment decisions.
- Open biopsy of primary CNS lesions may be necessary to establish a precise diagnosis and tailor treatment regimens when lymphoma is suspected in the absence of metastatic or leptomeningeal disease.
- Rare intramedullary stage 1AE Hodgkin's lymphoma of the CNS can respond to appropriate treatment. In this case, the patient achieved good recovery of neurologic function.

SUMMARY CNS involvement in the setting of lymphoid neoplasia is a clinical situation that requires specific diagnosis due to the disparate treatment regimens recommended for neoplasms of specific lymphoid cell types. Cerebrospinal fluid (CSF) sampling may provide sufficient information to determine the presence of abnormal lymphoid cells but may not be able to further specify the malignant cellular population. In cases where abnormal clinical or radiographic features are present, accurate tissue diagnosis is essential. In this report, we define a rare case of primary CNS intramedullary Hodgkin's lymphoma without leptomeningeal dissemination diagnosed via resectional biopsy of a conus medullaris lesion. The patient received post-resection radiation therapy and subsequently demonstrated radiographic and clinical improvement. Lymphoid neoplasia within the CNS comprises a diverse group with varying response and survival rates. Treatment hinges upon accurate diagnosis as chemotherapy varies widely among Hodgkin's and non-Hodgkin's lymphoma. While CSF sampling may yield a positive result with sufficiency to diagnose an abnormal lymphoid cell population, tissue is necessary for further defining cellular pathology. In this

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report, we define a rare case of primary CNS intramedullary Hodgkin's lymphoma without leptomeningeal dissemination via resectional biopsy of a conus medullaris lesion. In cases where abnormal enhancement is found in eloquent CNS regions and lymphoid neoplasia is suspected, management often entails either stereotactic biopsy or CSF sampling. While CSF analysis may differentiate malignancy at a low rate, tissue diagnosis via paraffin block immunohistochemistry is necessary to further classify malignancy as primary or peripheral, Hodgkin's or non-Hodgkin's lymphoma, or other such as metastatic leptomeningeal dissemination and glioma. Within the subtypes of lymphoid neoplasms, treatment regimens vastly differ and thus accurate tissue diagnosis is paramount. We therefore present a rare case of primary CNS intramedullary Hodgkin's lymphoma without leptomeningeal disease in the setting of immunocompromise diagnosed via open resectional biopsy of the conus medullaris.

KEYWORDS
• absent leptomeningeal dissemination
• cerebrospinal fluid sampling • open biopsy
• primary intramedullary Hodgkin's lymphoma
• radiation therapy
• Reed–Sternberg cells

Presentation of the case

• Clinical presentation

The patient is a 74-year-old female with long-standing history of rheumatoid arthritis for which she had been treated with infliximab and methotrexate. Over the course of several weeks, she noticed she was falling with increasing frequency and then developed neuropathy and left upper and lower limb paresis. At the time of admission to the hospital, she had left leg weakness (motor grade 4/5 all major muscle groups) and left deltoid weakness (motor grade 4/5) with increased reflexes at the biceps but without ankle clonus. Contrasted MRIs of her neuraxis were obtained during the course of her neurological workup.

• Imaging

The MRI of brain demonstrated abnormal signal enhancement of the left medulla and mild mass effect and expansion of the pontomedullary junction including left and middle cerebellar peduncles (Figure 1). MRI of lumbar spine demonstrated a 1.4 cm cranial–caudal diameter, homogenous, intensely enhancing intramedullary mass causing expansion of the cord diameter and cord signal change (Figure 2). Neither the thoracic nor cervical regions had any abnormalities. None of the MRIs demonstrated involvement of the leptomeninges. Contrasted computed tomography of her chest, abdomen and pelvis did not reveal mass lesions or lymphadenopathy.

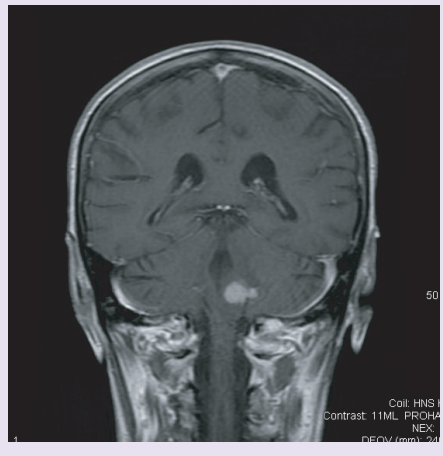

Figure 1. Coronal contrast-enhanced T1-weighted MRI of the brain demonstrating an enhancing lesion at the pontomedullary junction and involving the left middle and inferior cerebellar peduncles.

• Pathology

Biopsy of the conus medullaris lesion in the lumbar spine was undertaken. Upon intraoperative gross inspection of the tumor it was poorly delineated and firm with a grayish color and an avascular appearance. Multiple specimens were sent for pathological and microbiological analysis. Frozen sections at the time of surgery suggested lymphoma or possibly an inflammatory process. Subsequent analysis of the lesion showed Epstein–Barr virus-positive tissue and multinucleated Reed–Sternberg cells consistent with classical Hodgkin's lymphoma (HL) (Figures 3 & 4). Flow cytometry of cerebrospinal fluid demonstrated no abnormal cell population.

• Postoperative course

With two isolated lesions confined to one organ system the diagnosis was determined to be stage IAE nodular sclerosing HL. Radiation treatment of the lesions was initiated and consisted of 3600 cGy to the posterior fossa and thoracolumbar spine. The remainder of the spinal axis was treated with 2160 cGy. At 3-month follow-up MRI evaluation showed radiographic resolution of the lesions but the patient still required minor assistive devices to ambulate. She continued to

improve and at 6-month follow-up she was able to ambulate without assistance.

Discussion

Primary CNS intramedullary HL is exceedingly uncommon. A recent review by the Mayo Clinic found 14 cases of primary spinal cord HL treated at their institution over a 14-year period. Three of those patients were immunosuppressed (one due to HIV, two as a result of post-transplant treatment) and one of these three had Epstein–Barr virus-positive lymphoma [1]. A previously published review of CNS HL reported only 16 adult cases treated by a multinational collaborative group. The finding of atypical site involvement or advanced disease at presentation is usually found in the situation of immunocompromise [2]. In general, lymphoma with CNS involvement in the setting of immunocompromise is poorly understood other than recognition of immunodeficiency as a risk factor. There is some evidence that the molecular characteristics of lymphomas found in the CNS may differ from their similarly named systemic counterparts even if their histology overlaps. Whether the combination of the relative immune-privileged status of the CNS in combination with a weakened immune system results in susceptibility or if the poorly understood neuro-immunological milieu is more susceptible to certain subtypes of lymphoid cells is not known. However, CNS involvement is still rarely documented and may range from only 0.5 to 3% in all cases of HL [3]. Furthermore, the few cases of CNS intramedullary disease in HL are reported within the context of disseminated/metastatic disease or leptomeningeal disease (LMD) [4]. Thus, primary intramedullary HL without LMD as described in this case report is exceedingly rare.

The differentiation of tissue type in oncological treatment is of utmost importance. For classical HL, treatment is based upon excisional or core needle biopsy. It is highly recommended that immunohistochemistry be obtained [5]. Chemotherapy treatment, with or without accompanying radiation therapy, consists of two to four cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) for early-stage disease or six to eight cycles for advanced-stage disease or, alternatively as a second-line option, Stanford V regimen [6–8]. Given the isolated enhancement in the neuraxis, primary CNS lymphoma could also be entertained for which treatment vastly differs. In these cases,

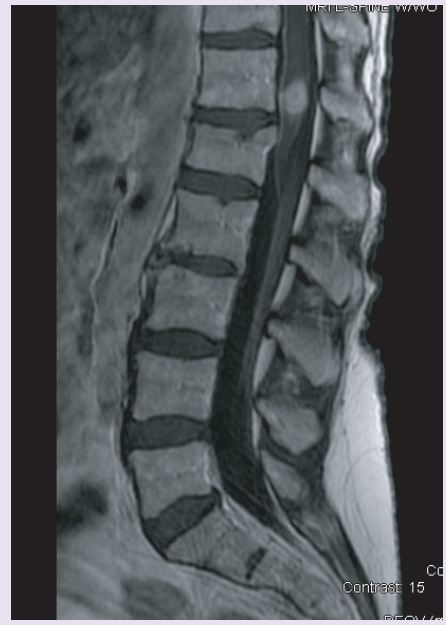

Figure 2. Sagittal contrast-enhanced T1-weighted MRI of the lumbar spine demonstrating an enhancing lesion within the conus medullaris.

cerebrospinal fluid (CSF) sampling is often sufficient for diagnosis and is followed by high-dose methotrexate based regimens [9,10]. Multifocal CNS enhancement is also a manifestation of diffuse large B-cell lymphoma (DLBCL). It is recommended that paraffin block review be conducted as opposed to core biopsy or fine-needle aspiration alone for DLBCL. First-line treatment is combination therapy with rituximab,

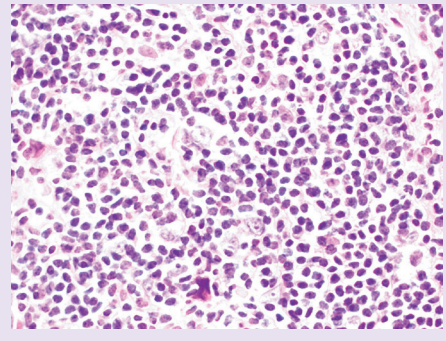

Figure 3. Histological micrograph of biopsy specimen with hematoxylin and eosin stain demonstrating lymphocyte population.
Magnification 400×.

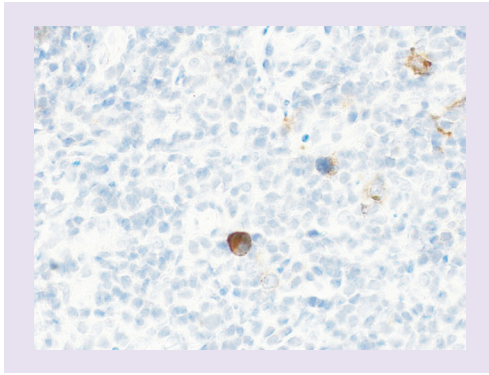

Figure 4. Histological micrograph of biopsy specimen with CD30 stain for Reed–Sternberg cells. Magnification 400×.

cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for three to six cycles [11]. Lastly, metastatic disease and malignant glioma with either primary spinal involvement or CSF seeding must be considered.

While CSF analysis alone may be positive to differentiate malignancy at a low rate of approximately 12–18% of CNS lymphoma cases, and on occasion may define metastatic disease or glioma pathology [12], as outlined above, treatment regimens are vastly different and accurate diagnosis is imperative. In situations where diagnoses through other methods are unsuccessful definitive diagnosis requires tissue analysis. In the case of HL diagnosis, the rate of not only determining the lymphoma diagnosis, but with further identification of the classical Reed–Sternberg cell in the CSF would be expected to be extremely low thereby precluding accurate diagnosis. Furthermore, without LMD, the likelihood of obtaining a positive CSF sample is theoretically very low and in the presented case the flow cytometry studies were negative for lymphocytes.

For this patient, radiation treatment alone was selected as appropriate postsurgical therapy based upon the lack of widespread systemic involvement and the few similar reports of isolated HL within the CNS. The general HL treatment guidelines are not specifically applicable to this case but had the patient not improved, appropriate chemotherapy could have been selected based upon the clear histological evidence of HL. Had further treatment been necessary a bone marrow biopsy would likely have been performed as part of an ongoing systemic treatment plan.

Tissue was thus of critical importance in this case as immunohistochemistry of the paraffin block defined the classical Reed–Sternberg cell necessary for the HL diagnosis. In non-standard cases where lymphoma is suspected in the setting of a negative systemic computed tomography or PET computed tomography, particularly in those with immunocompromise or atypical isolated site involvement, CSF sampling may not be sufficient as cytology and/or flow cytometry may define a cell population adequate for a lymphoma diagnosis, however, not specific enough to differentiate among DLBCL, HL or primary CNS lymphoma. We advocate surgical biopsy in these uncommonly encountered situations.

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