

Primary Central Nervous System Hodgkin Lymphoma versus Lymphoproliferative Disorder in an Asymptomatic Immunocompromised Patient – A Case Report and Review of the Current Literature

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Abstract

Primary central nervous system (CNS) Hodgkin's lymphoma is extremely rare. An 82 year old female presented to the Emergency Department after she tripped and hit her head, resulting in a head laceration with no other apparent injuries. Head CT revealed a hyperdense area consistent with either a parieto-occipital hemorrhage or mass. She was transferred to a tertiary care institution, where head MRI revealed a parieto-occipital mass concerning for metastatic disease. No primary source or evidence of metastatic disease were found. The tumor was resected and identified to be a classical Hodgkin's lymphoma, mixed cellularity type. The patient had no complications and was discharged home. Recommendations for patient's future treatment included a PET scan and radiotherapy. After a consultation with a lymphoma expert at the NIH, the patient's diagnosis was changed to an atypical lymphoproliferative disorder with Reed-Sternberg/Hodgkin like cells based on the patient's history of rheumatoid arthritis treated with an immunosuppressant. A review of the literature revealed several primary CNS Hodgkin's lymphoma cases that were extremely similar to the patient in this study. This case's diagnosis as an atypical lymphoproliferative disorder casts doubt on if previously reported cases of CNS primary Hodgkin's disease were misclassified as the pathological staining of this patient and the immunosuppressant history are extremely similar.

Keywords: Primary CNS tumor; Lymphoma; Hodgkin; Lymphoproliferative disorder

Abbreviations: CNS: Central Nervous System; HL: Hodgkin Lymphoma; LPD: Lymphoproliferative Disorder, EBV: Epstein Barr Virus

Introduction

Hodgkin Lymphoma (HL) is a systemic disease typically involving the lymph nodes. When systemic Hodgkin disease is present, the incidence of central nervous system (CNS) involvement is less than 0.2% (and has been reported as low as 0.02%) [1,2]. Most of the cases with intracranial involvement of Hodgkin's disease present at relapse, with several at initial presentation as part of systemic disease. Intracranial HL very rarely presents as a primary lesion [1,2]. As of January 2019, there have only been 23 cases of primary CNS HL reported in the literature [3,4]. Common presentations of CNS involvement of Hodgkin's includes cranial nerve palsies, motor and/or sensory deficits, headaches, papilledema, coma, and seizures [5,6]. In this case report, we describe a patient diagnosed initially with isolated primary CNS HL. After consultation with the NIH, the diagnosis was changed to an atypical lymphoproliferative disorder (LPD) with Reed-Sternberg/Hodgkin like cells.

Risk factors for HL include previous infection by Epstein Barr virus (EBV) and immunosuppression, although the full underlying etiology is not yet understood [7]. The incidence of HL increases in patients with a history of autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus [7]. For LPDs, risk factors include immunosuppressant use, length of use, underlying disease type, infection by Epstein-Barr virus (EBV), and a patient's genetic predisposition [8]. The immunosuppressants most associated with increasing the risk of a lymphoproliferative disorder are methotrexate and azathioprine (although patient's using azathioprine are at less risk than those using methotrexate) [8]. The risk of the medication hydroxychloroquine on LPDs was not found in the literature at this time.

Classical HL has Reed-Sternberg cells in a reactive inflammatory background with CD 30(+), CD15(+), and CD45/LCA(-) [8]. Comparatively, Hodgkin-like LPDs have large cells that are CD20(+), CD30(+), CD45/LCA(+), and CD15(-) [8]. It is difficult to differentiate HL from HL LPDs due to the similar aforementioned risk factors and staining, especially if the LPD is CD15(+).

Case Report

An 82-year-old female with a history of HTN, hyperlipidemia, rheumatoid arthritis, chronic kidney disease, and an unknown type of skin cancer was admitted to a rural hospital after she sustained a head injury. She has no family history of cancer. Patient was treated for her rheumatoid arthritis with Plaquenil, but has been off of this medication for two years. The patient stated she slipped on a tree root while walking up a bank and fell forward, striking her head on a root. Patient did not lose consciousness and proceeded to the Emergency Department at a local hospital where she was treated for a head laceration and underwent head CT. The CT showed a hyper-dense parieto-occipital lesion, either hemorrhage or mass. The patient was then transferred to a tertiary care institution. Upon arrival, no other injuries were identified on physical exam and the patient denied neck pain, nausea, and vomiting although she did admit to intermittent headaches for the past few months.

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A repeat CT brain without contrast showed a small focal hyper-density in the left parieto-occipital region with surrounding edema (Figure 1). There was no midline shift. MRI was recommended to further evaluate for an underlying mass lesion. The MRI showed an enhancing lesion on the inferior aspect of the left parietal lobe measuring 1.4 cm with adjacent white matter edema but without significant local mass-effect (Figure 2). No other lesions were identified, but the findings were worrisome for underlying metastatic disease in a patient of her age group. A CT chest, abdomen, pelvis found no primary sources for the brain lesion, and no evidence of metastatic disease (Figure 3) [9-15].

The neurosurgery team started the patient on Decadron and Keppra. The patient remained stable without neurologic defects over the next few days.

On hospital day 5, she underwent a left parieto-occipital craniotomy for tumor resection. Patient had 75 cc of blood loss and was stable post procedure. Patient was AAOx4 with 5/5 motor strength and sensation intact. Her pain was controlled with prn acetaminophen, oxycodone, and fentanyl. Her blood pressure was 176/57 with an elevated BUN and creatinine due to her other medical conditions. Other laboratory findings were within normal limits [16-26].

On day 6, the patient was recovering well with stable lab values other than a low Hemoglobin and an increase in WBC count thought to be stress/steroid induced leukocytosis. Physical exam was within normal limits, and patient started physical therapy. The patient started occupational therapy on day 7. Patient functioned near baseline with physical components of mobility and activities of daily living but below



Figure 1: CT head/brain angled axial view with small focal hyper-density in left parieto-occipital region.

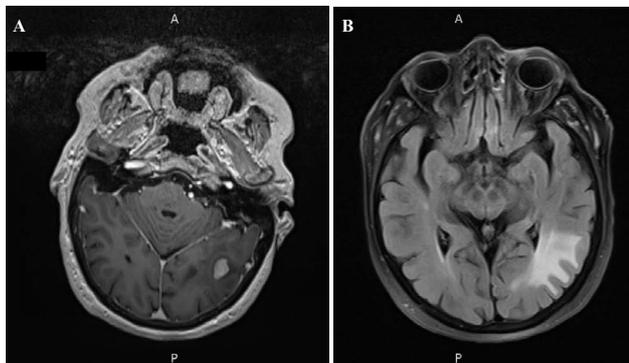


Figure 2: MRI brain w/wo contrast. Enhancing lesion on inferior aspect of left parietal lobe with adjacent white matter edema but no significant local mass-effect. (A) Axial T1 Post Contrast (B) T2 Flare.

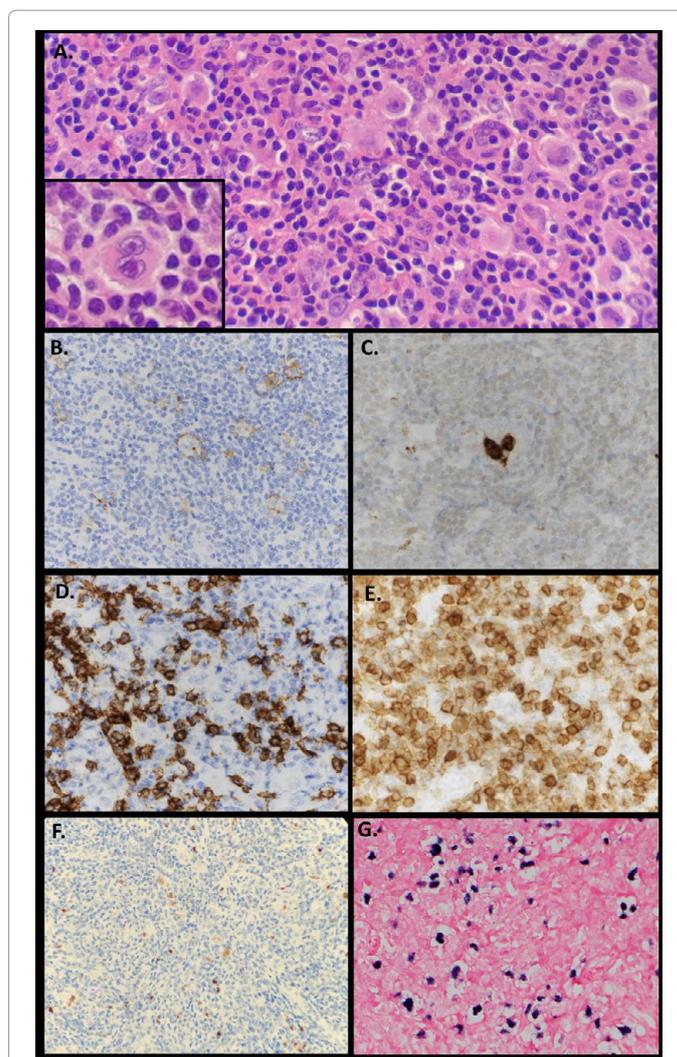


Figure 3: (A) H&E stain, inset with Reed Sternberg cell. (B) Large cells stained for CD30. (C) CD15 positive. (D) CD20 negative in large cells (E) CD45 negative in large cells. (F) Pax5 dim nuclear staining. (G) EBV by ISH positive. Images were acquired using an Olympus BX41 microscope and Pixel 2XL camera.

baseline with vision, memory, and cognitive components of activities of daily living.

The pathology report originally indicated the left occipital brain mass to be a classical Hodgkin's lymphoma, mixed cellularity subtype. Scattered small clusters of large atypical cells with abundant slightly eosinophilic cytoplasm and regular nuclei were present, some with multiple nuclei and prominent nucleoli consistent with Reed-Sternberg cells (CD30 positive in large cells, CD45 negative in large cells). A consult with a lymphoma expert NIH disagreed with this interpretation and the diagnosis was changed to EBV-positive atypical lymphoproliferative disorder with Reed-Sternberg/Hodgkin like cells.

As patient was stable (other than relatively poor blood pressure control), discharge planning was initiated. Patient was discharged on post-operative day 3 (day 9 of hospital stay). Recommendations for patient's future treatment included a PET scan and radiation treatment (36 Gy). The patient is now being followed by Med/Onc.

Discussion

The main differentials for this patient included an intracerebral hemorrhage (due to patient’s fall), or a metastatic lesion due to her demographic. HL was not originally on the differential list as, in addition to a primary CNS lesion being uncommon, the patient is older than the reported age of other patients with Primary CNS HL (average age at onset is 56 years with a range of 34-84 years [4]) and lacks the common presentation of cranial nerve palsies or deficits [1]. Once this rare diagnosis was made, the specimens were sent to the NIH for a second opinion. A lymphoma expert at the NIH disagreed with the original diagnosis based on the patient’s history of immunosuppression and EBV positivity. The diagnosis was changed to an EBV-positive B-cell lymphoproliferative disorder with Hodgkin/ Reed-Sternberg-like cells.

A review of the literature found 23 cases of primary CNS HL. The cases are tabulated in Figure 4. Interestingly, the patient in case 21 was treated with methotrexate while the patients in case 19 and 20 were both treated with azathioprine (medications strongly associated with LPDs). Additionally, cases 19 and 20 were EBV positive (not investigated in case 21). Case 19, 20, and 21 had similar staining to the patient discussed in this report. Based on their history and staining profile, these three cases may actually represent HL-like LPDs. The similar risk factors and stains cast doubt on how to make a true diagnosis of primary CNS Hodgkin’s lymphoma.

Assuming that all currently reported cases of primary CNS HL are indeed HL rather than a LPD, there are more cases in males (15) than in females (8). Of the 23 cases, 60.9% (14) are immunocompetent, 26.1% (6) have an unknown immune status, while 13.0% (3) are immunocompromised. These are the same three cases that may be LPDs rather than primary HL. No patient has a history of HIV. A 2008 study found that 37.5% of patients with systemic HL including the CNS (n=16) were immunocompromised [1]. This is greater than the

13.0% of immunocompromised patients making up all reported cases of primary CNS HL. Perhaps the link between immunodeficiency is not as strong between systemic HL and primary CNS HL. Or perhaps when the patient is immunocompromised in the case of a CNS lesion the disease is classified as HL-like LPD.

Out of the current count of primary CNS HL cases 72% of cases were EBV positive (eight cases were positive, three that are negative, and twelve cases that were not investigated). A study examining the EBV association in systemic HL with CNS involvement found only 44% of cases were EBV positive. This is another interesting difference between primary CNS HL and systemic HL with CNS involvement. It is important to note that the sample size in these comparisons are low due to the rarity of both presentations. It is also important to note that LPDs are also strongly associated with EBV positivity.

Of the four main subtypes of Hodgkin’s lymphoma, only nodular sclerosing and mixed cellularity have been reported as primary CNS lesions. Five cases are mixed cellularity, while seven are nodular sclerosing with the rest remaining unspecified.

Primary CNS HL has a good prognosis, with no evidence of recurrence as long as ten years after initial diagnosis. The LPDs similarly have good prognosis – spontaneous regression of the lesion in response to drug withdrawal has been recorded in most EBV positive cases [27]. The patient discussed in this report was already off of her immunosuppressive therapy for two years when her diagnosis was made. Treatment for CNS HL typically consists of radiation therapy with 30-45 Gy after resection (if possible), as was recommended for the case discussed in this report. Patients have also been treated successfully with chemotherapy and combination therapy in the past. This report casts doubt upon need for radiation and chemotherapy was indeed necessary for cases 19, 20, and 21 if the diagnosis was a HL-like LPD.

Case	Author	Year	Age/Sex	Immunocompromised	Location of lesion	Type	EBV	Treatment	Outcome at last followup
1	Sparling et al.	1946	53/M	unknown	L frontal lobe	Hodgkin’s sarcoma	not investigated	none	Died 5 days post op
2	Scrickler et al.	1955	45/M	unknown	R temporal lobe	nonsarcomatous Hodgkin Granuloma	not investigated	RT 1500 r	NED- 36 months
3	Nagashima et al.	1980	60/M	unknown	Falk cerebri	Hodgkin’s lymphoma mixed cellularity type	not investigated	none	unknown
4	Bender and Mayernik	1986	34/M	unknown	R frontal lobe and dura	Hodgkin’s lymphoma nodular sclerosing type	not investigated	RT + CT	NED- 12 months
5	Doorly et al.	1987	51/M	no	L cerebellum	Hodgkin’s lymphoma mixed cellularity type	not investigated	WBRT, 30 Gy	NED- 12 months
6	Ashby et al.	1988	62/M	no	R frontoparietal region	Hodgkin’s lymphoma nodular sclerosing type	not investigated	RT, 40 Gy; +IT CT	NED- 14 months
7	Sickler et al.	1990	84/F	no	R parieto-occipital region	Classical Hodgkin’s lymphoma not otherwise specified	not investigated	RT 35 cGy	NED- 8 months
8	Clark et al.	1992	53/F	unknown	R cerebellum	Hodgkin’s lymphoma nodular sclerosing type	not investigated	RT 45 cGy	NED- 6 months
9	Klein et al.	1999	54/M	no	R occipital lobe	Hodgkin’s lymphoma nodular sclerosing type	positive	WBRT, 36 Gy + CT	NED- 16 months
10	Blagi et al.	2000	52/M	no	L temporoparietal region	Hodgkin’s lymphoma nodular sclerosing type	negative	RT 30 Gy + 5 Gy boost	NED- 21 months
11	Johnson et al.	2000	55/F	no	inferior aspect of tentorium cerebelli	Hodgkin’s lymphoma nodular sclerosing type	positive	RT: 36 Gy + 14 Gy boost	NED- 8 months
12	de Castro et al.	2007	63/M	no	L fronto-parietal region, L cerebellar hemisphere	Classical Hodgkin’s lymphoma not otherwise specified	positive	WBRT: 40 Gy	unknown
13	Hwang et al. [23]	2007	64/F	no	L cerebellar hemisphere	Hodgkin’s lymphoma mixed cellularity type	not investigated	WBRT, 30 Gy + 6Gy boost	NED- 16 months
14	Gerstner et al.	2008	58/F	no	unknown	Classical Hodgkin’s lymphoma not otherwise specified	positive	WBRT: 35 Gy	NED: 90.3 months
15	Gerstner et al.	2008	60/F	no	Cavernous sinus, Meckel’s cave, L mesial temporal lobe	Hodgkin’s lymphoma nodular sclerosing type	negative	WBRT	NED: 1 month
16	Foo et al.	2011	58/M	no	L temporal lobe	Classical Hodgkin’s lymphoma not otherwise specified	positive	WBRT: 45 Gy + CT	14 months recurrence
17	Kresak et al.	2013	70/M	HIV negative, h/o SCC and COPD, immune status not otherwise stated	L Cerebellum	Classical Hodgkin’s lymphoma not otherwise specified	not investigated	Local RT	NED: 10 years
18	Kresak et al.	2013	72/F	no	Cerebellum	Classical Hodgkin’s lymphoma not otherwise specified	positive	WBRT	NED: 6 months
19	Henkenberens et al.	2014	47/M	yes - 20 yr history of multiple sclerosis treated with azathioprine	Cerebellum	Hodgkin’s lymphoma mixed cellularity	positive	Local RT: 20 Gy + CT BEACOPP	NED: 9 months
20	Mercadal et al.	2015	59/M	yes - 20 yr history ulcerative colitis treated with azathioprine	R thalamic- mesencephalic and protuberantial regions	Classical Hodgkin’s lymphoma not otherwise specified	positive	CT: methotrexate and cytosine arabinoside	NED- 65 months
21	Szelemej et al.	2016	47/F	yes - 10 years dermatomyositis, methotrexate	L parietal lobe	Classical Hodgkin’s lymphoma not otherwise specified	not investigated	WBRT: 30 Gy + 6 Gy boost	NED- 110 months
22	Cecyn et al.	2017	46/M	no	R frontal lobe	Classical Hodgkin’s lymphoma not otherwise specified	negative	RT: 30 Gy + CT (ABVD)	NED- 87 months (died due to unrelated causes)
23	Alfaseh et al.	2019	38/M	no	intra axial lesion compressing 4th ventricle	Hodgkin’s lymphoma, mixed cellularity type	not investigated	WBRT: 40 Gy + 10 Gy boost + CT (ABVD)	NED - 7 years

Figure 4: Review of current literature of primary CNS Hodgkin lymphoma patients [1,3,4,9-26].

Conclusion

This case report and literature review addresses the ambiguity of diagnosing primary HL versus HL-like LPD. Both of these diagnoses have similar risk factors and similar good prognoses. The basis of diagnosis based the patient's medical history when pathological staining appears to fit both HL and HL-like LPD leads to question what guidelines might be created next to better differentiate these two disease processes. By better differentiating these two processes, we can aim to prevent unnecessary radiation to patients with HL-like LPD.

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