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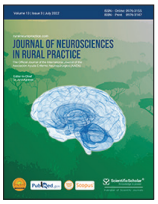
Journal of Neurosciences in Rural Practice



Case Report

Primary central nervous system Hodgkin's lymphoma – A case report and review of literature

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ABSTRACT

Hodgkin's lymphoma (HL) is primarily a disease affecting the lymph nodes. Extranodal involvement is rare. Primary central nervous system involvement in HL is extremely rare. The diagnosis is established by morphology and distinct immune-histochemical staining of the biopsies. A 76-year-old male patient presented with speech disturbance and weakness of the right upper and lower limbs. Magnetic resonance imaging of the brain showed an intraparenchymal mass lesion in the left frontal lobe with features of a high-grade tumor. Craniotomy and complete excision of the mass lesion were done. With histopathological examination and immunohistochemistry, the diagnosis of HL was made. Whole-body positron emission tomography did not reveal any other focus. The patient is being followed up with further oncological management. Only 26 cases of primary HL have been reported in the literature. Hence, this case is presented for its rarity. The previously reported cases and the recent concepts in the pathogenesis and treatment have also been reviewed.

Keywords: Central nervous system lymphoma, Hodgkin's lymphoma of central nervous system, Primary central nervous system Hodgkin's lymphoma

INTRODUCTION

Hodgkin's lymphoma (HL) commonly affects the lymph nodes. Central nervous system (CNS) lymphoma can present either as secondary CNS involvement by systemic lymphoma which is more common or rarely as primary CNS lymphoma which is restricted to the brain, leptomeninges, spinal cord, or eyes.[1-4] CNS involvement in HL is shown to occur in <0.2–0.5% of HL patients when compared to 5–30% CNS involvement in NHL patients.[5,6] Primary CNS lymphoma of CNS is NHL and is usually secondary to an immunocompromised state and HL has secondary CNS involvement usually in the leptomeninges. Primary CNS involvement is extremely rare and only about 26 cases have been reported so far. Due to its rarity, the exact pathogenesis, its relation to the immune status of the patient, the exact role of Epstein-Barr Virus, its activation of regulator T (T_{reg}) cells, and the role of programmed cell death ligand (PD-L) 1 in the genesis of primary CNS HL are yet to be investigated fully.

CASE REPORT

A 76-year-old male presented to the Department of Neurosurgery with behavioral change, speech disturbance, with weakness of the right upper and lower limbs for two weeks. The patient was conscious, disoriented, and confused and responded slowly to commands. He had right hemiparesis with Grade 3 power. He had no lymphadenopathy or hepatosplenomegaly. He was not immunocompromised magnetic resonance imaging Brain showed evidence of an irregular heterogeneous contrast-enhancing lesion in the left frontal lobe with surrounding edema and massive midline shift. The features were suggestive of high-grade glioma [Figure 1]. The patient underwent craniotomy and complete excision of the left frontal lobe mass lesion. Intraoperatively, the tumor was well defined with firm margins, moderate vascularity with a good plane of cleavage from the surrounding brain and could be excised *en masse*. The squash smears showed predominantly histiocytes with emperipolesis. The background showed numerous lymphocytes, histiocytes, occasional neutrophils, and atypical large cells. Scattered glial and neuronal cells are also shown [Figure 2]. Differential diagnosis of Rosai–Dorfman disease, histiocytic neoplasms, lymphoma, and melanoma were considered. Histopathological examination (hematoxylin and eosin-stained sections) showed brain

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Received: 25 October 2024 **Accepted:** 09 November 2024 **Epub ahead of print:** 04 January 2025 **Published:** 05 March 2025 **DOI:** 10.25259/JNRP_402_2024

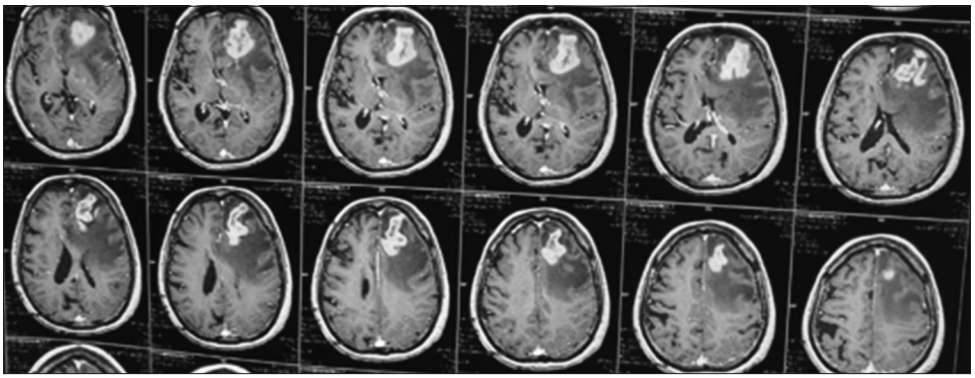

Figure 1: MRI Brain (T1 contrast) showing irregular contrast enhancing mass lesion in the left frontal lobe with mass effect.

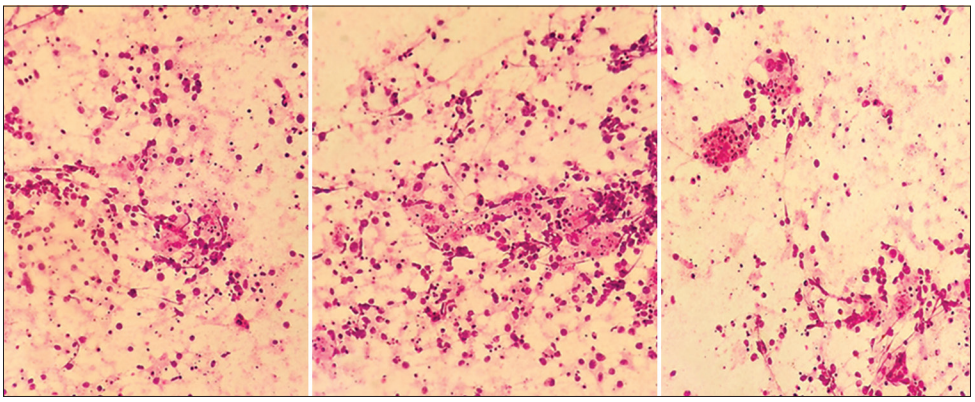

Figure 2: Squash smears predominantly showing histiocytes with emperipolesis, H&E, 40X. H&E: Hematoxylin and eosin.

tissue with an infiltrating tumor composed of scattered large cells showing large vesicular nuclei, prominent eosinophilic nucleoli resembling mononuclear Hodgkin's cells, Reed Sternberg (RS) cells, and popcorn cells [Figure 3]. Atypical mitosis was noted with 7–10 mitotic figures per 10 high-powered fields. Other cells include lymphocytes and histiocytes with active phagocytosis. Large areas of necrosis and broad bands of fibrosis were seen. Immunohistochemical staining CD 45 was positive in all the hematopoietic cells and negative in the large tumor cells. The large cells expressed CD 15, CD30, nuclear positivity of PAX-5, and membranous positivity of CD79a. Ki-67 was 70%. GFAP, PAN CK, and HMB 45 were negative in the tumor cells [Figure 4]. Whole-body positron emission tomography (PET) computed tomography did not reveal any extra-cranial Hodgkin's disease. Hence, this is a case of primary CNS HL in the left frontal lobe. Postoperatively, the patient made an uneventful recovery. Speech, power, right upper and lower limbs, and behavioral disturbance improved during the postoperative period. The patient was referred for further oncological treatment. The patient had improved completely at the review at two months.

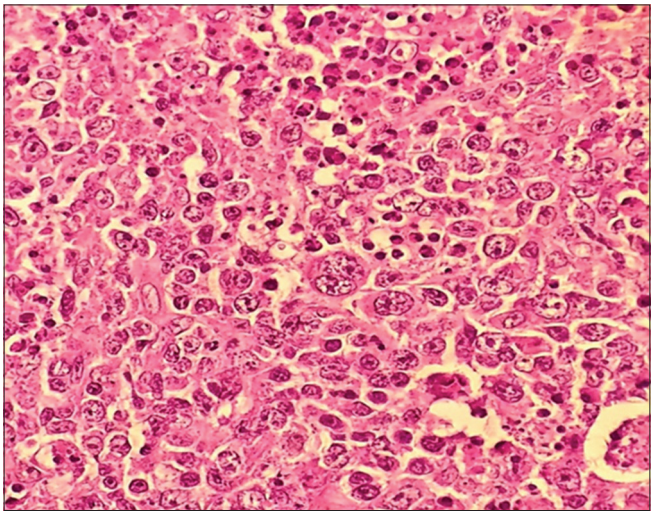

Figure 3: Histopathological images of Hodgkin's lymphoma with Reed-Sternberg cells, H&E, 40X. H&E: Hematoxylin and eosin.

DISCUSSION

Classical HL is primarily affecting the lymph nodes and CNS involvement is rare with HL, accounting for 0.2–0.5% of all

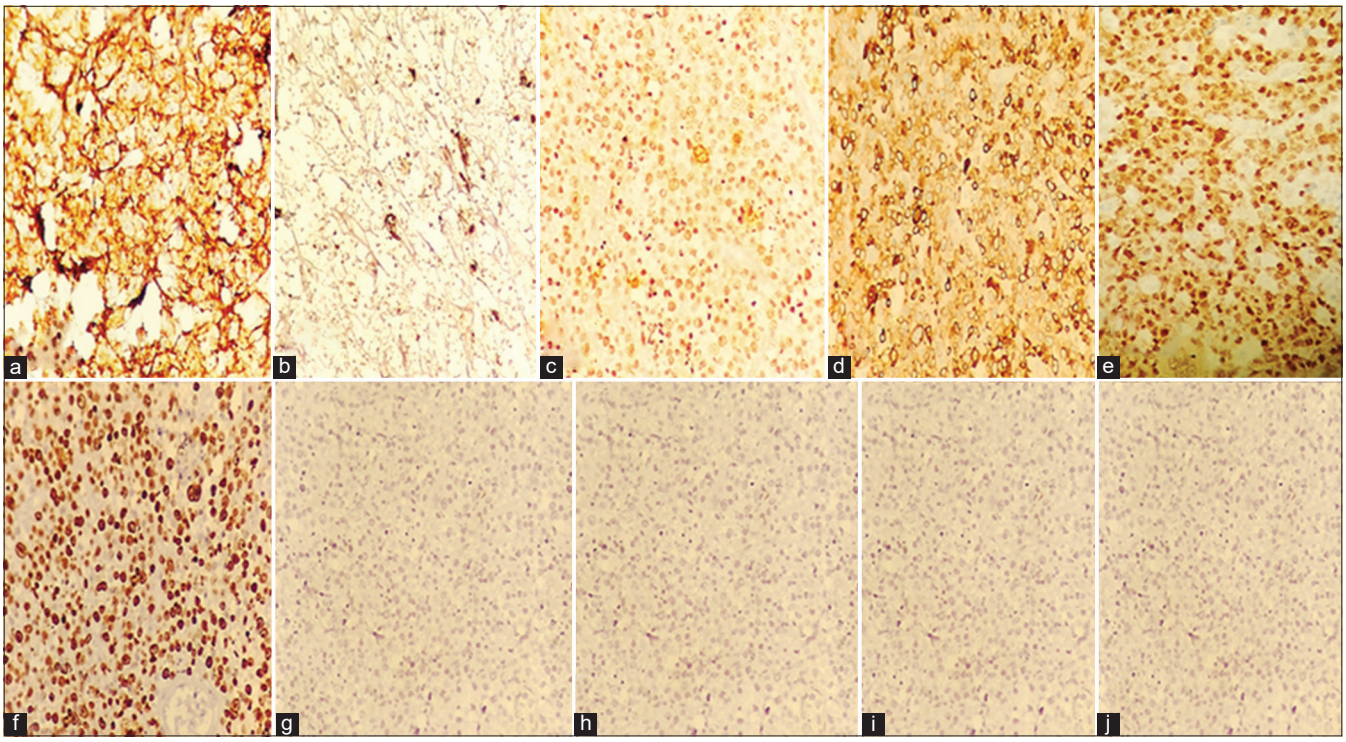

Figure 4: (a) CD45 - Positive in all the hematopoietic elements, (b) CD15 - Cytoplasmic and membranous positivity of large cells, (c) CD30- Cytoplasmic and membranous positivity of large cells, (d) CD79a- Membranous positivity of large cells, (e) PAX-5- Weak nuclear positivity of large cells, (f) Ki-67: 70%, (g) HMB – 45: Negative in the tumor cells, (h) GFAP: Negative in the tumor cells, (i) Pan CK: Negative in the tumor cells, (j) EBV: Negative in the tumor cells.

cases.[5] The incidence of HL in CNS remains exceedingly rare in the literature with only 26 cases reported so far. The first 22 cases have been summarized by Cecyn *et al*. and five more cases (including the present case) have been added since then [Table 1].[7-11] There have been 18 males and nine females, showing a male preponderance. In 17 cases, the lesion was in the supratentorial compartment and the rest in the posterior cranial fossa. In four patients, the lesion was dura-based mimicking a meningioma. Twenty-two patients had normal immunological status and only five had some form of immune deficiency. The most common histological type has been reported as "Classical HL – not otherwise specified" (11 cases), followed by nodular sclerosis type (seven cases) and mixed cellularity (seven cases). The Epstein-Barr virus (EBV) status has been investigated only in 13 patients, and 10 patients have been reported positive for EBV. There has been no consensus on adjuvant therapy after surgery, with varying radiotherapy and/or chemotherapy regimens. The longest reported disease-free survival has been 10 years.

The primary CNS-HL is exceedingly rare and it is of interest to note that primary CNS-HL has not been included in the primary CNS (hematolymphoid tumors) lymphomas in the latest WHO Classification of tumors of the CNS (5th Edition). Immune compromised state, if present, may contribute to the development of primary CNS HL, though in the available literature, the majority of the patients had no evidence of immune deficiency. There has been male sex preponderance in the literature. The role of EBV has been of interest of late. The presence of EBV in the RS cells seems to correlate with the increased T_{reg} cells and may contribute to the development of this tumor.[9] However, further research is needed in this regard. This may lead to better modalities of treatment, like targeting the T_{reg} cells. About 82% of patients with classical HL have PD-L on the surface of tumor cells and EBV infection seems to increase the expression of PD-L on the RS cells.[9] It is of interest to note that anti-programmed cell death protein antibodies (anti-PD 1) have been used in the treatment of refractory HL. In the future anti-PD 1 antibody, like sintilimab, may form the first-line drug treatment in HL due to its relative safety compared to the potentially toxic first-line drugs used at present.

The present patient was a 76-year-old non-immunocompromised man presented with features of a rapidly growing malignant neoplasm in the left frontal lobe with imaging features suggestive of a high-grade parenchymal tumor possibly glioma. The histopathology and immunohistochemistry clinched the diagnosis of HL. We could not do the EBV DNA testing and PD-L staining which could have been very useful. The whole body PET did not reveal any focus elsewhere in the body. Hence, this is a rare case of primary CNS-HL.

Table 1: Details of the cases of primary CNS-HL reported in literature.

Case	Author	Year	Age/ sex	Immunocom promised	Location of the lesion	Type	EBV	Adjuvant treatment	Outcome
1.	Sparling *et al.*[9]	1946	53/M	Unknown	Lt frontal lobe	Hodgkin's sarcoma	Not investigated	None	Died 5 days after surgery
2.	Scricker *et al.*[10]	1955	45/M	Unknown	Rt temporal lobe	Non-sarcomatous Hodgkin's granuloma	Not investigated	RT 1500 r	NED 36 months
3.	Nagashima *et al.*[11]	1980	60/M	Unknown	Falx cerebri	HL mixed cellularity type	Not investigated	None	Unknown
4.	Bender and Mayernik[12]	1986	34/M	Unknown	Rt frontal lobe and dura	HL nodular sclerosing type	Not investigated	RT+CT	NED 12 months
5.	Doorly *et al.*[13]	1987	51/M	No	Lt cerebellum	HL mixed cellularity type	Not investigated	RT 30 Gy	NED 12 months
6.	Ashby *et al.*[14]	1988	62/M	No	Rt frontoparietal region	HL nodular sclerosing type	Not investigated	RT 40Gy+IT CT	NED 14 months
7.	Sickler *et al.*[15]	1990	84/M	No	Rt parietooccipital region	Classical HL NOS	Not investigated	RT 35cGy	NED 8 months
8.	Clark *et al.*[16]	1992	53/F	Unknown	Rt cerebellum	HL nodular sclerosing type	Not investigated	RT 45 Gy	NED 6 months
9.	Klein *et al.*[17]	1999	54/M	No	Rt occipital lobe	HL nodular sclerosing type	Positive	RT 36 Gy+CT	NED 16 months
10.	Blagi *et al.*[18]	2000	52/M	No	Lt temporoparietal region	HL nodular sclerosing type	Negative	RT 30 Gy+5 Gy boost	NED 21 months
11.	Johnson *et al.*[19]	2000	55/F	No	Inferior aspect of tentorium cerebelli	HL nodular sclerosing type	Positive	RT 36 Gy+14 Gy boost	NED 8 months
12.	de Castro *et al.*[20]	2007	63?M	No	Lt frontoparietal region; Lt cerebellar hemisphere	Classical HL NOS	Positive	RT 40 Gy	Unknown
13.	Hwang *et al.*[21]	2007	64/F	No	Lt cerebellar hemisphere	HL mixed cellularity type	Not investigated	RT 30 Gy+6 Gy boost	NED 16 months
14.	Gerstner *et al.*[22]	2008	58/F	No	Unknown	Classical HL NOS	Positive	RT 35 Gy	NED 90.3 months
15.	Gerstner *et al.*[22]	2008	60/F	No	Cavernous sinus, Meckel's cave, Lt mesial temporal lobe	HL nodular sclerosing type	Negative	RT	NED 1 month
16.	Foo *et al.*[23]	2011	58/M	No	Lt temporal lobe	Classical HL NOS	Positive	RT 45 GY+CT	Recurrence at 14 months

(*Contd...*)

Table 1: (*Continued*).

Case	Author	Year	Age/ sex	Immunocom promised	Location of the lesion	Type	EBV	Adjuvant treatment	Outcome
17.	Kresak *et al.*[24]	2013	70/M	Known COPD . H/o sq cell ca, HIV-ve	Lt cerebellum	Classical HL NOS	Not investigated	RT	NED 10 years
18.	Kresak *et al.*[24]	2013	72/F	No	Cerebellum	Classical HL NOS	Positive	RT	NED 6 months
19.	Henkenberens *et al.*[25]	2014	47/M	Known MS 20 years on azothioprine	Cerebellum	HL mixed cellularity type	Positive	RT 20 Gy+CT (BEACOPP)	NED 9 months
20.	Mercadal *et al.*[26]	2015	59/M	Known ulcerative colitis on azathioprine	Rt thalamus, midbrain	Classical HL NOS	Positive	CT (methotrexate+ cytosine arabinoside)	NED 65 months
21.	Szelernej *et al.*[27]	2016	47/F	Known dermatomyositis on methotrexate	Lt parietal lobe	Classical HL NOS	Not investigated	RT 30 Gy+6 Gy boost	NED 110 months
22.	Cecyn *et al.*[7]	2017	46/M	No	Rt frontal lobe	Classical HL NOS	Negative	RT 30 Gy+CT (ABVD)	NED 87 months died due to unrelated cause
23.	Godbe *et al.*[8]	2019	82/F	Rheumatoid arthritis, unknown skin cancer, chroic kidney disease	Lt parietooccipital region	HL mixed cellularity type	Positive	RT	Not known
24.	Fu *et al.*[28]	2021	60/M	No	Cerebellum	HL mixed cellularity type	Positive	CT (Methotrexate, cytosine arabinoside, and sintilimab)	NED 58 months
25.	Alfaseh *et al.* [29]	2019	38/M	No	Cerebellum	HL mixed cellularity type	Not investigated	RT 40 Gy+10 Gy boost+CT (ABVD)	NED 7 years
26.	Wallizada *et al.*[30]	2024	33/F	No	Dural based left sphenoid wing lesion	Classical HL NOS	Not investigated	CT (Multiple drug combinations)	NED 4 months
27.	Present case	2024	76/M	No	Left frontal lobe	Classical HL NOS	Not investigated	CT	NED 2 months

Table adopted from: Godbe KN, Guilliams EL, Benko MJ, Grider DJ, Stump MS. primary central nervous system Hodgkin lymphoma versus lymphoproliferative disorder in an asymptomatic immunocompromised patient – a case report and review of the current literature. 2019 J. Blood Lymph 9: 250. And updated. NED: No evidence of disease, NOS: Not otherwise specified, HIV: Human immunodeficiency virus, CNS: Central nervous system, HL: Hodgkin's lymphoma, CT: Computed tomography, Lt: Left, Rt: Right, RT: Radiotherapy, MS: multiple sclerosis, COPD: Chronic obstructive pulmonary disease, BEACOPP: Bleomycin sulfate, etoposide phosphate, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, and prednisolone, ABVD: Adriamycin, bleomycin sulfate, vinblastine sulfate, dacarbazine.

CONCLUSION

Primary CNS-HL should be kept in the differential diagnosis of intracranial malignant tumours, especially in old men, with immunocompromised state. EBV-DNA testing and PD-L staining should be performed in all cases of suspected HL to establish the diagnosis and this will also help in planning adjuvant chemotherapy.

Ethical approval: The Institutional Review Board approval is not required.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consents.
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Thrinadh B, Karthikeyan KV, Raghavan V, Sathyaseelan M, Ramesh VG. Primary central nervous system Hodgkin's lymphoma – A case report and review of literature. J Neurosci Rural Pract. 2025;16:109-14. doi: 10.25259/JNRP_402_2024