

Case Report

Primary intracranial Hodgkin's lymphoma after a blunt trauma: A case report

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Abstract

We report a case of 30-year-old immunocompetent man, with a previous history of cranial-facial trauma, who presented with progressive left exophthalmos due to an intracranial left frontal-ethmoidal-orbital mass. Histology of the resected tumor revealed a classical Hodgkin's Lymphoma (HL). Epstein-Barr virus encoded RNA/EBER was detected in typical Hodgkin and Reed-Sternberg cells. After postoperative radiotherapy and chemotherapy administration, the patient remains free of systemic disease or recurrence on 4 years of follow-up.

Intracranial involvement by HL has rarely been described, mostly as a late localization or as a recurrence of a disseminated disease, in a setting of immunosuppression. Primary HL of the central nervous system occurring as an isolated disease is even more uncommon, with only 16 reported cases documented to date. The prognosis of these rare cases appears comforting with appropriate treatment. Tumor resection and, in appropriate cases, treatment with radiation and/or chemotherapy seem to warrant a durable response. For this reason a systemic disease should be excluded in all cases intracranial HL by a comprehensive work-up.

To the best of our knowledge, this case represents the first report that documents the association of intracranial HL and local trauma with subsequent intracranial infection.

Introduction

Primary central nervous system lymphomas (PCNSL) account for 2.7% of the malignant disease of the central nervous system (CNS) [1]. Most of cases are intracerebral aggressive diffuse large B cell lymphoma, or indolent marginal zone with a meningeal dural localization. Intracranial involvement by Hodgkin's lymphoma (HL) is rarely encountered, more frequently in the setting of immunosuppression. It occurs in 0.2% - 0.5% of patient with HL [2] and the majority and these cases had typical systemic manifestation of Hodgkin's disease (HD) prior to the development of cerebral and intracranial localizations.

Herein we describe a new case of primary intracranial HL that occurred after a serious blunt facial trauma, with no evidence of systemic disease. To our knowledge this is the first report that documents this association. A review the pertaining literature to HL and CNS is provided.

Case report

A 30-year-old immunocompetent male presented to Hospital with a progressive left esophthalm. He had a serious cranial-facial trauma six years before, which was treated with surgical intervention twice, firstly, after two years, for reconstruction of his skull base and another year after, for treatment of a local intracranial infection. Magnetic resonance imaging (MRI) scans showed an intracranial left frontal-ethmoidal-orbital mass, with contrast enhancement on T1 weighted images (Figure 1). Two months later he underwent craniotomy and the lesion was totally resected.

The specimen was routinely processed for histology. Sections were stained with Haematoxylin and Eosin (&E). Immunohistochemical and in situ hybridization (ISH) studies were respectively performed with pre-diluted commercially available antibodies and EBV-encoded mRNA/EBER probe, all from Novocastra, using Leica Bond Max automated autostainer. The reaction product was detected with diaminobenzidine chromogen.

More Information

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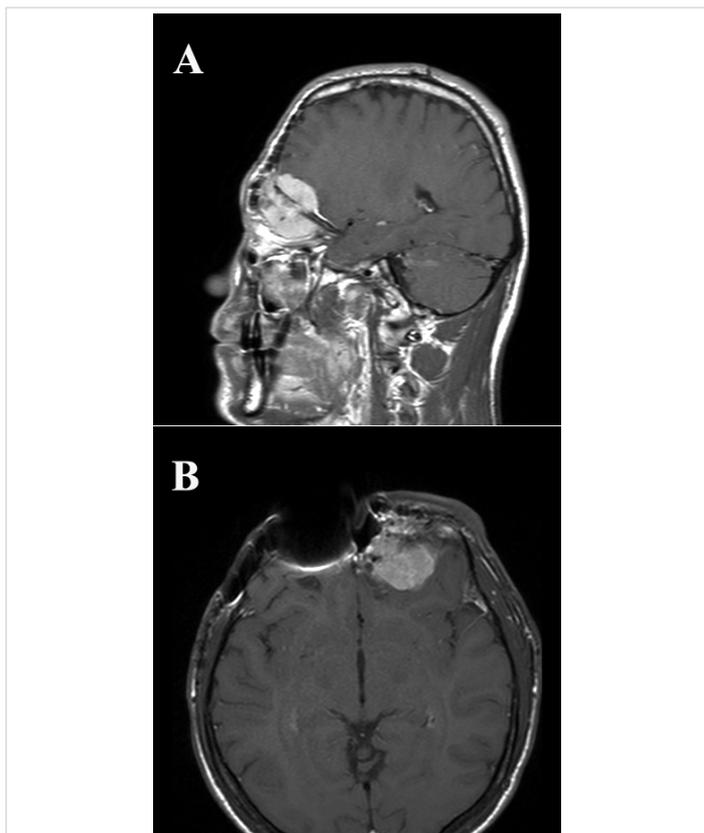


Figure 1: Sagittal (A) and transverse (B) T1 MRI images post-gadolinium injection demonstrate a left-sided enhancing lesion infiltrating the ethmoidal-orbital region and the cerebral frontal lobe. Artifacts due to protestic material are present.

Histologically the tumor consisted of fragments of lymphoid tissue infiltrating the brain parenchyma at the periphery and focally covered by mucosa of ethmoidal sinuses. It was characterized by the presence of numerous large sized mononuclear Hodgkin's cells, with vesicular nuclei and prominent eosinophilic nucleoli. There were also rare bi-nucleated Reed-Sternberg cells and tumor cells that exhibited a "lacunar" morphology with perinuclear halo. Tumor cells were scattered, either within a lymphocyte depleted fibrillar background, admixed with fibroblasts, small lymphocytes, plasma cells and numerous eosinophils, either within a lymphocytic-rich inflammatory areas close to the cerebral tissue (Figure 2). Immunohistochemistry demonstrated that tumor cells with Hodgkin's morphology were diffusely positive for CD30, IRF4/MUM-1 and HLA-DR, focally immunoreactive for CD15 (paranuclear, dot-like positivity). They showed a faint nuclear positivity for PAX-5 and were negative for CD45-LCA, ALK protein, CD20, CD5, CD2, CD8, CD56, CD57, Granzyme-B, GFAP and cytokeratin AE1/AE3. The small reactive lymphocytes showed a prevalent T phenotype, without any expression of cytotoxic markers. There was no expression of CD21, S100 and CD1a. The Hodgkin's cells resulted diffusely positive for Epstein Barr virus (EBV)-encoded latent membrane protein-1 (LMP-1); ISH for EBV (EBER) resulted positive (Figure 3). The overall results were consistent with a classical HL, with features of the lymphocyte depleted subtype.

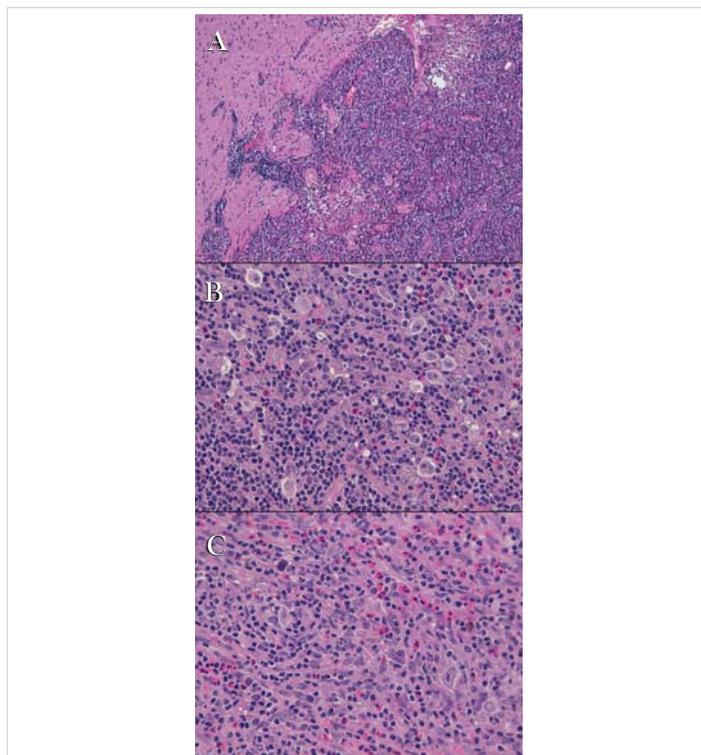


Figure 2: Tumor resected from the brain: A) the image display the jagged boundary between the brain parenchyma and lymphomatous infiltrate (H&E; original magnification 2.5x); B) numerous Hodgkin's and lacunar cells are readily seen admixed with small lymphocytes and eosinophils (H&E; original magnification 40x); C) lymphocyte's depleted areas with Hodgkin's and binucleated Reed Sternberg cells (H&E; original magnification 40x).

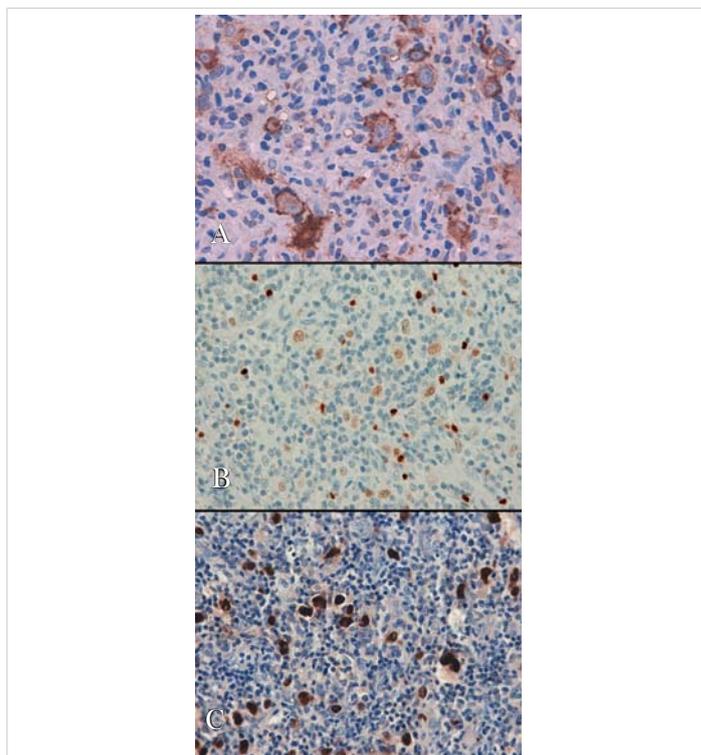


Figure 3: Immunohistochemical stains: A) Hodgkin's cells are highlighted by CD30 antibody; B) Hodgkin's cells show a faint nuclear positivity with Pax-5 antibody, compared with the intense immunoreactivity of the scattered small B lymphocytes. C) ISH: neoplastic cells show an intense positivity for EBV (EBER).

The post-surgical recovery was uneventful. The computed tomography (CT) assisted and pathologic staging with bone marrow examination, performed after the HL diagnosis, gave all negative results. The patient was subsequently treated with four cycles of chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), followed by 30.6 Gy radiotherapy to the left orbital region. The patient is alive and disease free at 11 years of follow-up, with no systemic manifestations of HL, neither local recurrences of the disease.

Discussion

A case of primary intracranial HL has been described in an immunocompetent male with a past history of facial trauma and subsequent local infection. The patient had no signs of recurrence or systemic disease on follow-up for four years. Because of the consequences of the trauma to the skull base and the intracranial extension of the tumor at time of its discovering from the ethmoidal-orbital regions to the left frontal lobe, the site of origin cannot be restricted to one of these three different, but contiguous, anatomic locations.

Rare cases of intraorbital HL, with skull base and dural infiltration, and of nasopharyngeal HL with intracranial extension, have been described in patient with systemic Hodgkin's disease [3-5].

Primary intracranial HL at presentation is an exceedingly rare occurrence. Since the first case report of Ashby, et al. in 1988 [6], convincingly supported by a limited immunohistochemical assay, additional 30 cases of initial presentation of intracranial HL have been reported to date, as isolated case reports and more recently in two case series [2,5,7-21]. Among these cases, only 16 were an isolated intracranial finding, with no evidence of a systemic disease [2,5-11,17-21], neither at staging, nor at follow-up (Table 1).

Additional 16 cases of secondary involvement of the brain or spine by HL have been described, mainly in patients with a history of autoimmune disease or immunosuppression, which may be related to HIV infection [5,22-27]. Two of these cases were an intracranial recurrence of HL in HIV-positive male patients, with evidence of EBV infected tumor cells [23,24]. Another more recent case was a 65-year-old man who developed isolated intracerebral EBV-positive HL, almost 8 years after the diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma. Authors advocated a potential role to reactivate a latent EBV infection to the immunosuppression-related effects of fludarabine-based combination therapies for CLL [15]. In immunosuppressed patients PCNSL, virtually always arises from EBV-infected lymphocytes. Conversely the pathogenesis in immunocompetent patients is not so well-documented. We can speculate that the trauma was a predisposing factor for the development of the lymphoma in the case described here. Traumas may be responsible of prolonged or repeated inflammation of the tissue, or create a locus of minoris resistentiae, favoring viral infections, such as Epstein-Barr virus, or may attract peripheral blood lymphoid cells that are stimulated to proliferate locally and/or to undergo clonal selection and thus progress to a monoclonal neoplastic state. To our knowledge, five previous case reports have described the development of malignant lymphoma at site of a previous trauma in the head and neck and ocular region [28], but none of these cases was a HL. The clinical history of the patient led clinicians and pathologist to consider the differential diagnosis mainly with an inflammatory pseudotumor arising from the orbital-ethmoidal region or with a space occupying lesion due to an infectious etiology. The presence of numerous mononuclear Hodgkin's cell with the proper immunophenotype, allowed the differential diagnosis with a pseudotumor and other histotypes of PCNS.

Table 1: Cases of primary intracranial HL with no evidence of systemic disease at staging and follow-up.

Case	Year, author	age/sex	Disease site	Type HL	Treatment	Outcome at last FU
1	1988, Ashby	62/M	Fronto-parietal/meningeal R	NS	RT 4000 cGy; IT CT	NED (14 m)
2	1990, Sickler	84/F	Parieto-occipital/ intraparenchymal R	NOS	RT 3500 cGy;	NED 8 m
3	1992, Clark	53/F	Cerebellar R	NS	RT 4500 cGy	NED 6 m
4	1999, Klein	54/M	Occipital/subcortical R	NS	RT 3600 cGy WB boost 1400 cGy +CT	NED 16 m
5	2000, Johnson	55/F	Cerebellar tentorium	NS	RT operative site 14 Gy; WBRT 36 Gy	NED 8 m
6	2000, Biagi	52/M	Temporo-parietal L	NS	RT 300 cGy WB boost 500 cGy	NED 21 m
7	2000, Herrlinger	66/F	Fronto-parietal/cortical L	MC	45 Gy WBRT, 2 x PCV CT	CR 18 m
8	2008, Gerstner	58/F	NA	NOS	WBRT (35 Gy)	CR 90.3 m
9	" "	60/F	NA	NS	WBRT	NED 1 m
10	2011, Foo	58/M	Temporal L	NOS	WBRT (30 Gy)	RD, 14 m
11	2012, Gessi	77/M	Cerebellar L	MC	RT (38 Gy)	NED 8 m
12	" "	59/M	Brainstem L	MC	NA	NA
13	2013, Kresak J	70/M	Cerebellar L	NS	RT	NED 10 y
14	" "	72/F	Cerebellar dural based	NS	RT	NED 6 m
15	2014, Sharaf	77/M	Cerebellar L	MC	RT	NED 7 m
16	2019, Alfaseh	38/M	Intra-axial IV ventricle	MC	WBRT + CT (ABVD)	NED 7 y
17	present case	30/M	Frontal - orbital - ethmoidal L	LD	ABVD CT, 4 cycles; RT 30.6 Gy left orbital region	NED 30 m

L: Left; R: Right; F: Female; M: Male; NA; Not Available; NS: Nodular Sclerosis; MC: Mixed Cellularity; LD: Lymphocyte Depleted; NOS: Not Otherwise Specified; CT: Chemotherapy; IT: Intrathecal; RT: Radiotherapy; WBRT: Whole Brain Radiotherapy; NED: No Evidence of Disease; CR: Complete Remission; RD: Recurrent Disease (Intracranial); M: Months; Y: Years.



Nodular sclerosis and mixed cellularity are the more frequently reported variants of CNS-HL [29]. However a recent larger series did find no association with a particular HL histology. Moreover is difficult to sub classify this disease in limited diagnostic biopsy, where the WHO sub classification criteria are not clearly reproducible.

Intracranial HL involves the brain either as a mass or as a diffuse infiltrate of the meninges. Intraparenchymal lesions are more frequent, probably due to not contiguous hematogenic spread of the disease. Dural involvement mimics radiologically meningioma as well as an inflammatory mass and seems to be much more common than parenchymal lesions in advanced stages of HD [9,13-15,22,25]. So when a dura-based lesion with imaging consistent with meningioma is discovered in a patient affected by HL, the possibility of an intracranial localization of the disease should be always considered.

There is no a standard therapeutic approach to CNS-HL, which usually varied with stage and presentation of the disease. Cases diagnosed concomitantly or at relapse of a widespread HL, usually received a combination of radiation and chemotherapy. At difference, patients with isolated primary intracranial HD more frequently underwent surgical tumor resection and received partial or whole brain radiotherapy alone.

Patients with IC-HL cerebral disease discovered at presentation seem to fare well, more than patients with cerebral disease at relapse [29]. The majority of cases of primary CNS-HL and systemic HD with primary CNS involvement, achieved complete remission of the disease and only 2 out of the 30 cases reported in literature died of systemic or cerebral progressive disease [2,5,7-18]. Conversely in AIDS and immunosuppressed patients with CNS-HL localizations the prognosis is still dismal, with shorter response to treatment, frequent relapses and dead of disease.

In conclusion, even if no long term follow-up data are available, isolated intracranial presentations of HL seem to have a favorable prognosis after surgical removal and adjuvant radiotherapy and chemotherapy administration.

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