CASE REPORT OF A CLASSICAL HODGKIN’S LYMPHOMA PRESENTING WITH BRAIN METASTASIS

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ABSTRACT
Background: The involvement of the CNS in Hodgkin’s lymphoma is uncommon and has been reported to be occurring in 0.2 -0.02% of the cases. Less than thirty cases have been reported in literature for Hodgkin’s lymphoma with brain involvement. We describe here a patient with systemic classical HL who presented with relapse of disease with brain secondaries.
Case presentation: We report the case of a young boy previously treated for classic HL and tuberculosis presented with headache and diplopia four months after the completion of chemotherapy. MRI brain revealed multiple intracranial lesions for which he underwent stereotactic biopsy and was confirmed on histopathological examination to be metastatic classical HL to the brain. He has also been diagnosed with relapsed pulmonary tuberculosis. He is currently undergoing further treatment with anti tubercular drugs and is due for Autologous stem cell transplant.
Conclusion: Intracranial presentation of classical Hodgkin’s Lymphoma is a rare entity but still has to be taken into account, especially when dealing with advanced stage disease.

Keywords: Hodgkin’s Lymphoma, CNS

INTRODUCTION
Hodgkin’s lymphoma is a rare monoclonal lymphoid neoplasm with high cure rates. This disease entity is divided into two distinct categories: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL). Classical Hodgkin lymphoma accounts for about 95% of all HL, and is further subdivided into four subtypes: nodular sclerosis (NSHL), lymphocyte-rich (LRHL), mixed cellularity (MCHL) and lymphocyte-depleted (LDHL). CHL is characterized by the presence of mononuclear Hodgkin’s and multinucleated Reed-Sternberg cells. Hodgkin’s and Reed-Sternberg cells are usually in the minority, residing in a reactive infiltrate of a variable mixture of non-neoplastic lymphocytes, eosinophils, neutrophils, plasma cells, fibroblasts, and collagen fibres. The median age of diagnosis in Indian population is 38 years. The gender ratio is 2:1 (male: female). B symptoms are present in about 50% patients. The commonest subtype is mixed cellularity in 60% followed by nodular sclerosis in 26%, lymphocyte rich in 9%, and lymphocyte depleted in 2% (Bhurani et al., 2022).

Treatment of Hodgkin’s lymphoma typically includes chemotherapy and or radiotherapy. It has very good prognosis with approximately 80% cure rate (Metzger and Mauz-Körholz, 2019). Classic Hodgkin lymphoma (HL) primarily affects the lymphatic system. As compared with non-Hodgkin lymphoma (NHL), central nervous system (CNS) involvement in HL is very rare and has been reported to
be occurring in 0.2 -0.02% of the cases. Less than thirty cases have been reported in literature for Classical Hodgkin’s lymphoma with CNS involvement.

We hereby report the case of a young boy previously treated for classic HL presenting with relapse in the brain.

**CASE**

A 19 year old male, non smoker, non diabetic or hypertensive, hailing from Chittoor district, in Andhra Pradesh located in southern part of India, who helps his father in sericulture industry, presented with complaints of headache since 3 days and vomiting since 2 days. He was previously diagnosed and treated for Hodgkin’s lymphoma in the year 2021.

He was apparently well 3 days back when he suddenly started having headache and blurring of vision. Headache was insidious in onset, dull aching and gradually progressive in nature. Headache was associated with blurring of vision and double vision but no aura or floaters .It was also associated with fever which was high grade with no h/o chills or rigors.

Headaches and Fever was associated with 3episodes of vomiting projectile in nature, containing food particles non foul smelling and non-blood tinged. It was non-bile stained and not associated with pain abdomen and bowel and bladder changes.

His sleep was disturbed and appetite greatly reduced from past 3 days. No history of loss of consciousness, abnormal behavior, disorientation, memory loss or any speech abnormality .No history of cough, chest pain, breathlessness or palpitation.

No history of allergies.

He was born by normal vaginal delivery, at term and cried immediately after birth with no perinatal complications. His immunization status is up to date.

He suffered from recurrent skin infections during his childhood. In the year 2020, at 18 years of age he underwent hernioplasty, for a right sided inguinal hernia. One month following which he complained of pain and swelling in the right iliac fossa region which was diagnosed to be psoas abscess and the abscess was drained .He also gives history of recurrent abscess in the upper back and chest wall, which were drained and was diagnosed of tuberculosis. He was also diagnosed with pulmonary tuberculosis (TB) in February 2022 and was started on empirical anti-tubercular therapy which he discontinued after a month against the medical advice.

He had completed the six cycles of chemotherapy with ABVD, for Hodgkin’s Lymphoma (stage IIIB), by January 2022 .Follow up PET/CT scan done in march 2022, showed near complete response to chemotherapy, before presenting with the above complaints on 3rd may 2022.

MRI brain done and was suggestive of multiple lesions in the temporal and parietal region with cerebral edema. He was started on intra venous antiepileptics, mannitol and antipyretics. His symptoms improved next day following which a stereotactic brain biopsy was done which confirmed metastatic classical HL in the brain.

His HIV status was negative.

He was also negative for HbsAg and anti HCV antibody.

**Physical Examination:**

On presentation patient was conscious, alert, cooperative and well oriented to person, place and time.

Thin built with poor nutritional status.

Mild pallor was present, no icterus, clubbing or cyanosis.

No palpable lymphadenopathy and no venous engorgement.

He was having a Blood pressure of 110/60, pulse rate of 110/ min, temperature of 101 degree fahrenheit.

Chest on auscultation had bilateral normal vesicular breath sounds and with no adventitious sounds.

Heart sounds S1, S2 auscultated with no murmur.

Abdomen was soft with no guarding, rigidity or tenderness.

No testicular swelling observed.

Diplopia present suggesting 3rd,4th or 6th cranial nerve involvement.

No nystagmus.
No cerebellar signs.  
Power, tone and movement of all the four limbs were normal.  
Reflexes were normally elicited.  
Normal gait.  

**Investigations on presentation:**  
Hb- 14.5, total WBC count –9,200, platelet-1,20,000 .  
Urea -20, Creatinine- 0.65, LFT –normal, LDH- 291.  
BIOPSY at initial diagnosis- Hodgkin lymphoma- LD  
Current MRI brain - MRI brain done and was suggestive of multiple lesions in the temporal and parietal region with cerebral edema.  
Stereotactic brain biopsy –features of metastatic classical HL in the brain.  
A diagnosis of metastatic classical HL was established with the help of a stereotactic biopsy and the patient symptomatically improved with the supportive care.  
His sputum was also positive for mycobacterium tuberculosis. He is currently on antitubercular drugs and later planned for Autologous stem cell transplant for relapsed lymphoma.

**DISCUSSION**

Intracranial metastasis in classical HL is very rare but well characterized (Sapozink and Kaplan, 1983). Majority of the cases of HL with central nervous system involvement are in patients with advanced and refractory disease. Although even more rarely, CNS involvement or intracranial disease may occasionally be present at diagnosis of HL (Vera et al., 1985; Young, 1999; Hirniz et al., 2004) in literature review of patients with intracranial HL, the sites of involvement were brain parenchyma in 64%, dura or leptomeninges in 19%, corpus callosum in 3%, pituitary in 3%, and unknown/not stated in 12% (Shet et al., 2004). The presenting signs and symptoms depend upon the location of metastases and include cranial nerve palsies (55%), headaches (36%), weakness (33%), papilledema (19%), nausea and vomiting (17%), memory problems (17%), seizures (14%), gait disturbance (5%), and other (3%). The treatment for intracranial metastatic HL is not well established because of its rarity, but fractionated radiotherapy or chemotherapy is mostly employed.  
CNS involvement in HL occurs more frequently in relapsing disease. Possible risk factors include a family history of HL, immune compromised status, EBV infection and male sex (Vera et al., 1985; Shet et al., 2004; Klein et al., 1999). Commonly attributed histological subtypes are mixed cellularity and nodular sclerosing types.  
The mechanism, how lymphoma cells form brain metastases has recently been unraveled by Scientists at the German Cancer Research Center (DKFZ)and have now discovered the molecular mechanism that leads to lymphomas forming metastases in the central nervous system (Tracy et al., 2019). Using a mouse model, the researchers proved that chronic inflammatory processes in the brain lead to lymphoma cells that have entered the brain tissue being retained instead of being released back into the blood. They have also identified key molecules of this mechanism in tissue samples from patients with lymphomas of the central nervous system.  
Classical HL of the central nervous system (CNS) is rare and very aggressive. Patients with secondary CNS HL in particular have a poorer prognosis. Up to now, it was largely unclear how lymphoma cells enter the brain and become lodged there.  
In a healthy brain without inflammation, a messenger substance ensures that both white blood cells and lymphoma cells leave the brain tissue and go back into the blood vessels. The DKFZ scientists have identified an important antagonist of this messenger substance in their experiments: the signaling molecule CCL19, the production of which is stimulated by NF-kappaB. In the event of inflammation with increased NF-kappaB activity, there is also more CCL19, which means it gains the upper hand and keeps the lymphoma cells in the brain. There, they multiply and develop into tumors.  
The German researchers found a similar situation in human brains. In people affected by primary or secondary brain lymphomas, the NF-kappa B signaling pathway is also activated, so there is more CCL19. As in the mice, the messenger substance is released by special brain cells known as astrocytes.
The DKFZ researchers have thus not only provided the first explanation of how secondary CNS lymphomas arise. In their experiment, lymphoma cells in older animals that were not genetically modified behaved exactly like those in young genetically modified animals with chronic inflammation (Shet et al., 2004).

Our patient presented with the history of tuberculosis and classical HL and this coexistence is well documented. His TB was diagnosed few months prior to HL. Tuberculosis and HL can both involve the CNS although there is no literature evidence of an increased risk of CNS TB in HL or vice versa.

Whole brain radiotherapy, with or without chemotherapy, was the most common treatment employed in literature. In our patient, we chose myeloablative chemotherapy with autologous stem cell transplant. In the literature, median overall survival of patients diagnosed with brain metastases from HL is around 18 months.

CONCLUSION
Intracranial presentation of classical Hodgkin’s Lymphoma is a rare entity but still has to be taken into account, especially when dealing with advanced stage or recurrent disease. The treatment decision should be based on a multidisciplinary approach as there is lack of consensus on the best treatment approach - surgery, radiotherapy, chemotherapy or a combination of modalities, which should be individualised.

REFERENCES


