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Case Report

B-Cell Lymphoma of the Brainstem with Central Neurogenic Hyperventilation

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Abstract

Non-Hodgkin's lymphoma of the brainstem is a rare entity. Central Neurogenic Hyperventilation (CNH), an associated manifestation of this disease, is an even rarer event. We report a case of an immunocompetent individual who presented to us with tachypnea and facial nerve palsy. Neuroimaging showed a Cerebellopontine angle tumour which on histopathology showed feature consistent with a Non-Hodgkin's B-Cell Lymphoma. The patient went on to develop severe respiratory alkalosis with findings consistent with CNH. Chemotherapy with Methotrexate was started and high dose Dexamethasone was added to the regimen a month later. Radiologically, the tumour size decreased by 50% but the patient's clinical condition deteriorated. He eventually expired due to cardiopulmonary arrest. Some common clinical presentations of this disease and various diagnostic modalities and treatment options available to such patients are discussed.

Keywords: Brainstem, Central Neurogenic Hyperventilation, Lymphoma.

Introduction

Primary CNS lymphoma (PCNSL) is a rare form of extra-nodal non-Hodgkin's lymphoma, accounting for 4% of all primary brain tumours. It affects the brain, leptomeninges, spinal cord and the eyes. It remains confined to CNS in majority of the cases.[1] Localization primarily in the brainstem occurs in 3% of PCNSL and most are T-Cell in origin.[2] The only established risk factor is congenital or acquired immunodeficiency. Only 1.9-6% of patients afflicted with AIDS develop PCNSL.[2] In the past few years, there has been a threefold increase in the incidence of PCNSL in immunocompetent individuals. Tumour induced CNH in an awake patient is a rare manifestation of this disease.[3] To date, only a few cases have been reported. We report a case of Primary Brainstem B-cell Lymphoma in an immunocompetent individual who eventually developed CNH.

Case Report

A 47 year old man, known case of Chronic Obstructive Pulmonary Disease and Hypertension was presented to the ER, with a history of shortness of breath, fever and headache for 3 days. He also developed recurrent left-sided facial weakness which had started 2 months earlier. There was no other significant past history be it medical, surgical, drug or family. On general physical examination he was tachypnoeic with a respiratory rate of 47 breaths/minute. He was otherwise vitally stable. Cardiovascular, genitourinary, gastrointestinal and immunologic reviews were all negative. On chest examination diffuse bilateral crackles were present. On facial nerve examination there was left sided facial drooping with flattening of naso-labial fold, weak gag and inability to close the left eye. Motor examination showed left-sided motor paresis grade 4/5 in both upper and lower limbs. Rest of the neurological examination was unremarkable. His Karnofsky performance score was 50.

A CT scan brain was done one month prior to admission which showed a hypodense irregular lesion in left cerebellum measuring 2.5x1.8cm. It was suspected to be an intrinsic cerebellar or cerebello-pontine (CP) angle tumour. Further treatment and investigations were deferred by the patient and his family. The patient was admitted with the provisional diagnosis of pneumonia with left sided CP tumour and empirically started on Anti-Tuberculous therapy, antibiotics and hydrocortisone.

Initial Complete Blood Count (CBC) and Serum Electrolytes results revealed no abnormality. TSH, Creatinine and Liver function tests were normal. HIV, Hepatitis B and Hepatitis C serology were all nonreactive. Initial CSF analysis did not reveal any abnormalities.

A contrast enhanced Magnetic Resonance Imaging (MRI) scan of the brain showed a mass lesion measuring 3.2x2.5x2.5cm in left cerebellar peduncle extending into the medulla and midbrain. It showed homogenous enhancement with gadolinium and diffuse meningeal enhancement. There were no signs of hydrocephalus, areas of recent infarction or intracranial haemorrhage.

A sub-occipital craniotomy was performed to obtain a sample for biopsy. Histopathology showed a neoplastic lesion

with cells predominantly arranged around blood vessels exhibiting cellular atypia, nuclear pleomorphism, hyperchromasia and increased mitotic activity. The GFAP, LCA, PAN-B and Ki-67 tumour markers were positive. These findings were suggestive of a High Grade Non-Hodgkin's B-cell lymphoma of large cell type. Smears for Fungi and Acid Fast Bacilli were negative. Bone Marrow Aspirate and Trephine showed no evidence of lymphomatous infiltration of the bone marrow. CT Chest, Abdomen and Pelvis were performed to check for organ metastasis and lymphadenopathy, all of which revealed no disease.

The ATT was discontinued and combination chemotherapy was begun. The patient received ATT only for a period of 10 days, which is too short a time to assess its efficacy. The patient however showed no clinical improvement with it. Chemotherapy with Methotrexate 2.5g/m^2 alternating with Vincristine was begun. A month later high dose Dexamethasone was added to the regimen. During his hospital stay the patient had multiple progressively worsening episodes of hyperventilation which persisted during sleep. He developed respiratory alkalosis with ABGs showing pH, 7.54; pCO2 30.2mmHg and pO2 147.6mmHg. No metabolic cause for his tachypnoea could be discerned and his Chest Radiography, ECG and Echocardiography were normal. His tachypnoea persisted with repeat ABGs showing pH of 7.51, pCO2, 25.6mmHg and pO2 92mmHg. The findings suggested the diagnosis of Central Neurogenic Hyperventilation (CNH) due to brainstem infiltration. Midazolam resulted in immediate reduction of respiratory rate but it's effect was transient and repeated administration was necessary. He subsequently developed generalized tonic-clonic seizures and septic shock despite being on multiple antibiotics and antiepileptic medication. He had to be shifted to the intensive care unit where he was mechanically ventilated. A repeat MRI showed a 50% reduction in size of lymphoma after receiving 4 cycles of chemotherapy. However, the patient's clinical condition progressively deteriorated. Despite intensive investigations we could not discern a plausible cause for this disparity between a good radiological response but worsening clinical condition. His status was discussed with his family and he was declared Do Not Resuscitate (DNR). The decision not to institute any form of radiotherapy was based on the patients weakened state and his personal as well as his family's wishes. No benefit of an alternative therapy could be foreseen since the tumour had significantly decreased in size and seemed to be vigorously chemo-sensitive. He went into cardiopulmonary arrest after 2 months of receiving intensive in-patient care and expired.

Discussion

In immunocompetent patients PCNSL typically occurs during the 6th and the 7th decade of life and presents with focal findings. The data of 378 PCNSL patients was collected by The International Extranodal Lymphoma study group. It revealed that the frontal lobe was involved in 44%, parietal lobe in 13%, temporal lobe in 14%, occipital lobe in 6%, basal ganglia in 28%, brainstem in 6%, cerebellum in 6%.[4] Approximately 90% of PCNSLs are Diffuse large B-Cell Lymphomas; the remaining 10% are poorly characterized by low-grade lymphomas, Burkitt's lymphomas and T-Cell lymphomas.[5] However, the brainstem shows a penchant for T-Cell lymphomas.[3] The median age at diagnosis is 53-57 years with a male-to-female ratio of 1.2 to 1.7:1.[5]

In a study that focused on the clinical presentations of 248 immunocompetent patients with PCNSL. The authors reported that 70% had focal neurological deficits, 43% had neuropsychiatric symptoms, 33% had raised intracranial pressure, 14% had seizures and 4% had ocular symptoms.[6] Our patient had the most common clinical presentation of focal neurological deficit in the form of facial nerve palsy.

Lumbar puncture with CSF sampling should be performed at the time of initial assessment in patients with suspected PCNSL. In a study of 96 patients with newly diagnosed PCNSL, the initial CSF cytological studies were positive in only 15%.[7] However, in another study two-thirds of PCNSL patients who developed positive CSF cytological findings had negative results on an initial examination, suggesting that the serial CSF samples would result in increased diagnostic sensitivity.[7] CSF sampling in our patient was deferred due to prior radiological evidence of a space-occupying lesion in the posterior fossa.

Contrast enhanced MRI is the optimal imaging modality for assessing these patients. The lesions are isointense or slightly hypointense in T1-weighted images and slightly hyperintense in T2-weighted images. About 75% of immunocompetent patients show an intense homogeneous enhancement after contrast administration. On CT scan PCNSL are isodense or slightly hyperdense with a mild mass effect, showing homogeneous enhancement after contrast administration.[8] Consistent findings were present in our patient.

Five year survival approaches 4% of patients with primary malignant lymphomas.[2] If untreated, the median survival is only 4.6 months.[9] A unique feature of PCNSL compared with other brain tumours is its unique sensitivity to steroids. The steroids have a direct cytotoxic effect but purely steroid-induced remission is short-lived in most patients. However 40% of the patient's tumour shrinks or disappears with an administered combination of steroids and whole brain radiation therapy (WBRT).[9] Radiation and steroid treatment lead to a median survival of 12-18 months. In the last decade

several phase II studies have shown that the 5-year actuarial probability of survival with certain chemotherapy regimens followed by WBRT is approximately 28%-40%. This is superior to the reported 2-year survival of 28% with WBRT alone. The primary Chemo therapy (CHT) regimen in PCNSL should include Intravenous High Dose methotrexate, the most effective drug against these malignancies in lieu of its ability to cross the Blood Brain Barrier.[1] In a recent study, addition of cytarabine produced a statistically significant improvement in survival.[10] Stereotactic radiosurgery as a treatment option for PCNSL has only been recently explored and reported in the literature.[9]

Our patient had the unique feature of Central Neurogenic Hyperventilation (CNH) associated with his tumour. Diagnostic criteria for CNH are hyperventilation that persists during sleep, low arterial PaCO2, high arterial PaO2 and high arterial pH in the absence of drugs or metabolic causes.[3] CNH results from the uninhibited stimulation of both inspiratory and expiratory centers in the medulla by the lateral pontine reticular formation and by laterally located descending neural pathways. Of the 21 cases of CNH reported in the literature, all were associated with either an infiltrative brainstem lesion or diffuse cerebral involvement. Out of the 18 reported cases that specified tumour histopathologic features, there were 9 with lymphoma, 6 with slow-growing astrocytoma, 1 with metastatic tumour, 1 with medulloblastoma and 1 with aggressive astrocytoma.[3]

Despite the highly responsive nature of PCNSL to initial treatments, local control remains the largest obstacle in the treatment of this disease. Recurrence occurs in more than 90% of patients, most commonly in the brain.[7] In conclusion, PCNSL is a rare malignancy; however, the extraordinary frequency of primary cerebral lymphoma among the few patients with tumour induced CNH suggests that lymphoma must be high in differential diagnosis and should guide therapy.[3] If there is a suspicion of a lymphoma, steroid therapy should be avoided as it can cause radiological and clinical improvement in the patient, but making the histopathological confirmation undesirable. Thus delaying diagnosis. The variable clinical presentation and poor prognosis associated with PCNSL warrant a prompt and critical evaluation of these patients followed by aggressive and multidisciplinary treatment approach.

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