Primary Central Nervous System Anaplastic Large Cell Lymphoma is an Unusual Brain Tumour

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Abstract

We present a case of a 64-year-old man who was diagnosed with a primary anaplastic large cell lymphoma of the central nervous system (PCNSAL). He had received radical chemotherapy and radiotherapy for a non-small cell lung cancer (NSCLC) in the past. There is no known association between NSCLC and PCNSAL. We describe the diagnostic and therapeutic challenges associated with these rare intracranial lymphomas and highlight the potential role of newer biological agents in patients with anaplastic lymphoma kinase (ALK-1) positive PCNSAL.

Keywords

Primary CNS lymphoma, ALCL, ALK+ cancers, intracranial space occupying lesion, chemotherapy

Disclosure: Dionysus Papadatos-Pastos, James Hall, Ruth Pettengell, Leslie R Bridges, Barry Newell and Jens Samol declare no conflict of interest. No funding was received in the publication of this article.

Received: 16 April 2014 **Accepted**: 6 May 2014 **Citation**: *European Oncology & Haematology*, 2014;10(1):48–50 *DOI: 10.17925/EOH.2014.10.1.48*

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Case Presentation

A 64-year-old male presented with a 1-month history of progressively worsening headaches. He had no other central neurological symptoms, including ocular symptoms, and examination of the central and peripheral nervous system was normal. Physical examination did not reveal lymphadenopathy or organomegaly and was normal for all systems examined. No constitutional symptoms such as fever, weight loss or night sweats were present. Four years prior to this, he was diagnosed with a lung cancer through cytomorphology, with no immunocytochemistry being available due to the paucity of cells following a computed tomography (CT)-guided procedure. The radiological findings of a spiculated mass in the left upper lobe were typical for lung cancer. The lung multi-disciplinary team (MDT) made a final diagnosis of a stage IIIa non-small cell lung cancer (NSCLC). Due to his underlying medical conditions, the patient was not a surgical candidate. He was treated with six cycles of cisplatin and vinorelbin chemotherapy, followed by radical radiotherapy (36 Gy in 12 fractions), achieving a complete response as per Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Other medical history included severe peripheral vascular disease requiring abdominal aortic aneurysm repair with an aortobiiliac graft, and mild to moderate chronic renal failure (baseline creatinine clearance of 45 ml/minute).

At presentation he had an elevated lactate dehydrogenase (LDH). An unenhanced CT of the brain revealed a mass lesion within the right parietal lobe with significant associated vasogenic oedema, causing both local and general mass effect with effacement of adjacent sulci and complete effacement of the right lateral ventricle. The subsequent magnetic resonance imaging (MRI) confirmed the presence of a solitary mass lesion with significant mass effect (see *Figure 1*). A staging CT of the neck, chest, abdomen and pelvis was performed and no evidence of lung cancer recurrence or distant metastatic disease was found. The patient was referred by the lung cancer multi-disciplinary meeting to the neurosurgeons for resection of the intracranial space occupying lesion (ICSOL). Complete resection of the ICSOL was performed and the patient made a full recovery post-surgery. The surgical specimen was reviewed by three independent histopathologists. Immunostaining was negative for CK7 and CK20 and positive for CD3, CD30 (see *Figure 2*) and aberrant CD20, raising the possibility of anaplastic lymphoma. The morphology was those of anaplastic large cell lymphomas (ALCLs). ALK1 staining was negative. The final diagnosis was primary central nervous system, ALK1-negative, ALCL with aberrant CD-20 expression. The patient underwent further staging investigations for the primary ALCL of the central nervous system (PCNSAL). A bone marrow (BM) trephine and a lumbar puncture showed no evidence of malignant infiltration in the BM and the cerebrospinal fluid (CSF), respectively. A slit lamp examination was negative. The patient received two renal dose-adjusted 21-day cycles of intravenously administered methotrexate (MTX), 3.6 g on day 1 followed by cytarabine, 2,450 mg twice daily on days 2 and 3. Chemotherapy was discontinued because of an infection in the aortobiiliac graft and the patient received whole brain radiotherapy (WBRT), a total of 36 Gy in 20 sessions. A post-treatment MRI (see *Figure 3*) demonstrated satisfactory post-treatment appearances.

The patient died from bronchopneumonia 3 months after the completion of treatment for the PCNSAL. This was perceived to be unrelated to his PCNSAL treatment. A post mortem was declined by the patient's relatives.

Discussion

PCNSALs are very rare, with just a few cases reported in the published literature. They represent a small percentage of all primary central nervous system lymphomas that themselves only account for approximately 5 % of all primary brain tumours.[1] In the largest case series of nine PCNSAL cases, a bimodal distribution was suggested, with six patients being less than 22 years of age and three patients being over 46 years of age.[2] The most common presenting symptoms are focal neurological deficits, neuropsychiatric disorders, signs of raised intracranial pressure and seizures.[3] B symptoms are uncommon.[3] Radiological differential diagnoses include other malignant ICSOLs, such as glioblastomamultiforme, metastatic brain lesions and benign lesions, such as demyelinating diseases, infectious or parasitic conditions.[4]

Intracranial lymphoma is often an unexpected diagnosis following a brain tumour resection or biopsy. MRI is the imaging modality of choice when PCNSL is suspected. Lesions appear iso-intense to hypo-intense on T2-weighted MRI, often with surrounding oedema.[5] CT-guided biopsy is recommended to confirm the diagnosis of PCNSL. It is recommended that steroids are interrupted for at least 7 to 10 days before the biopsy as they can interfere with the histopathological diagnosis.[6] Complete tumour resection is rarely necessary as it has not been associated with improved survival benefit.[7]

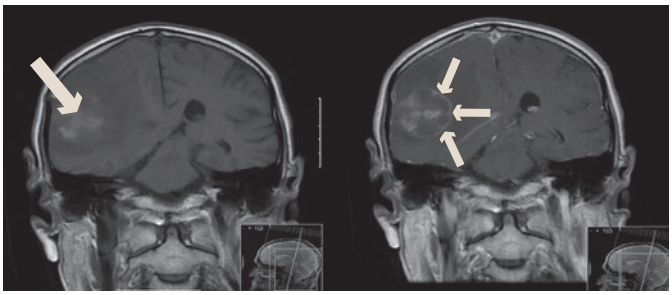
ALCLs are composed of large, pleomorphic cells that express the CD30 antigen. Their morphological diversity can present a challenge in diagnosis since their cellular pleomorphism and their tendency to fill the sinuses of the lymph nodes can be suggestive of Hodgkin's lymphoma, metastatic carcinoma or melanoma.[2] Most ALCL express T cell antigens and the less common 'null cell' variants often have genetic evidence of T cell origin.[8] The majority of ALCL (70–75 %) have detectable anaplastic lymphoma kinase (ALK-1) protein expression resulting from a genetic alteration in the ALK locus on chromosome 2.[9] More specifically, there is a distinct 2:5 translocation that fuses the *ALK* gene on chromosome 2 and the nucleophosmin gene (*NPM*) of chromosome 5.[9] Although the pathogenesis of PCNSAL is not yet clear, it could be suggested that in the ALK-1 positive anaplastic lymphomas, translocation of the *ALK* gene is partly responsible for the neoplastic transformation.[10] There is no evidence suggesting a familial inheritance of PCNSAL.[2]

Pre-treatment staging includes brain and extracranial imaging to assess the extent of the lymphoma in the CNS and to exclude the presence of extra-neural disease. CSF-protein, BMA/T, blood tests including HIV testing, USS of testes and slit lamp examination are to be performed as work-up for all PCNSLs. Positron emission tomography (PET) scanning for patients with no evidence of extracranial disease in CT scan remains investigational, although a retrospective study reports that a small percentage of patients will be diagnosed with systemic lymphoma.[11]

The rarity of PCNSAL makes the identification of reliable prognostic factors a challenge for oncologists.[2] A better outcome is associated with young age, unifocal tumour, lack of necrosis and ALK positivity. The 5-year survival rates for systemic ALCL are 70–80 % for patients with good prognosis features, in contrast to rates of 30–40 % in patients with poor prognosis tumours.[12] However, PCNSAL has a more aggressive clinical behaviour compared with its extracranial counterpart.[2] Our literature search has yielded no evidence of an association of NSCLC and PCNSAL.

Since patient populations are small, evidence for the treatment of PCNSAL is derived from studies that include, in their majority, patients with B-cell derived primary CNS lymphomas. As PCNSAL is a chemo-sensitive tumour, chemotherapy is the backbone of treatment. Chemotherapeutics that have the ability to cross the blood brain barrier (BBB) and achieve adequate concentrations in the CNS are preferred to drugs that have poor BBB penetration. Therefore, the role of CHOP-chemotherapy is limited in PCNSALs.[6] A recent phase II study confirmed the efficacy of the combination of the antimetabolite MTX and cytarabine as first-line treatment. At our institution this is currently the chemotherapeutic approach for newly diagnosed PCNSL. Other high-dose-containing regimens are also effective care for first-line treatment of PCNSL. The role of additional rituximab to first-line chemotherapy regimens in PCNSL is still unclear. This is largely due to the retrospective

Figure 1: Pre-treatment Magnetic Resonance Imaging of Brain



The unenhanced T1-weighted study (left image) revealed diffuse high signal within the lesion, suggesting probable tumour haemorrhage (arrow). The post-gadolinium T1-weighted study (right image) showed peripheral post-contrast enhancement (arrowheads).

Figure 2: CD30 Immunohistochemistry

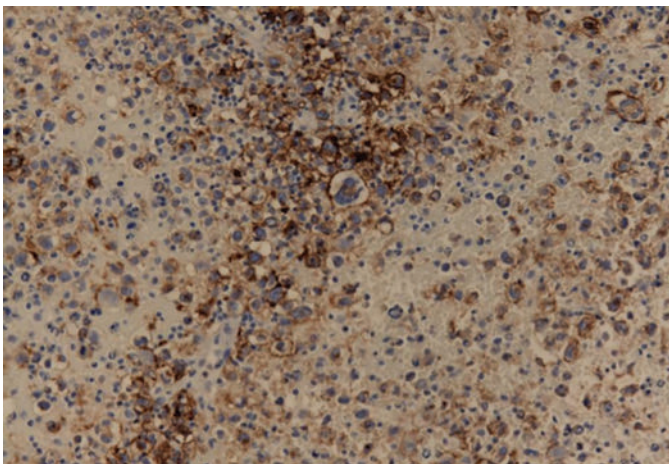
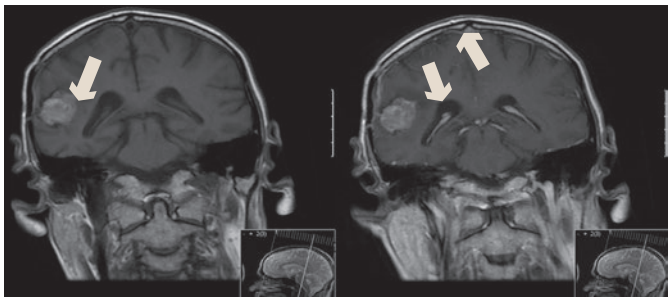


Figure 3: Post-treatment Magnetic Resonance Imaging of Brain



Unenhanced T1-weighted images (left image) showed a haemorrhagic post-resection cavity (arrow). The post-contrast study (right image) revealed no significant enhancement. There was minimal associated oedema, with no mass effect, and the previously effaced right lateral ventricle had a normal appearance (arrowheads).

nature of the published studies.[13,14] Ongoing large prospective trials, such as the NCT01011920 and NTR2427, should help to establish the role of additional rituximab for PCNSL treatment.[15] Unfortunately, although patients initially respond to treatment, relapse is not uncommon. Salvage therapies, such as temozolomide or etoposide, can be used, and we also encourage the enrolment of these patients in clinical trials, wherever possible. Of increasing interest is the potential role of crizotinib, which has recently been licensed by the Food and Drug Administration (FDA) for the treatment of ALK-1 positive NSCLCs. Crizotinib was shown to have activity in peripheral ALK-1 positive anaplastic lymphomas,[16] appeared to achieve adequate CSF concentration[17] and could be a future treatment option for patients with ALK-1 positive PCNSAL.[18]

Radiotherapy has been a treatment option for intracranial lymphomas for many years. Its use as consolidation treatment is advised in patients with residual disease after chemotherapy. However, for patients that achieve a complete response, there appears to be no additional benefit, particularly given the significant short- and long-term toxicities of WBRT.[19] Results from a recent phase II study published in abstract form suggest that consolidation WBRT can be deferred until relapse.[20]

In this case report, PCNSAL is a second primary in a patient who has completed curative treatment for a solid tumour 2 years previously. This case highlights the importance of tissue diagnosis and should alert oncology MDTs to consider wider differential diagnoses (DDs) in patients presenting with ICSOLs, especially where there is no evidence of extracranial disease. We also strongly advocate entering patients into clinical trials wherever possible. In patients where the PCNSAL expresses ALK-1, crizotinib may be a candidate for targeted treatment in the future. ■

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