CASE REPORT

Lymphomatosis cerebri: diagnostic challenges and review of the literature

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SUMMARY

Lymphomatosis cerebri (LC) is a rare variant of a primary central nervous system non-Hodgkin's lymphoma (PCNSL) characterised by diffuse infiltration of tumour cells throughout the brain parenchyma. We present a 68-year-old immunocompetent woman with headaches, dizziness, blurred vision, localised right leg weakness and rapidly progressive dementia. A brain MRI demonstrated diffuse T2 hyperintense white matter lesions that did not enhance with contrast. The clinical differential diagnosis of these lesions included metastatic disease, infectious or inflammatory process such as sarcoidosis, lymphoma, demyelinating disease and less likely vascular aetiology, such as vasculitis or ischaemic stroke. A right frontal stereotactic brain biopsy was non-diagnostic. The patient eventually died from aspiration pneumonia following a pneumonectomy for a primary lung adenocarcinoma. The diagnosis of LC was established on postmortem examination of the brain.

BACKGROUND

Primary central nervous system lymphomas (PCNSLs) have an incidence between 0.8% and 6.6% of primary intracranial neoplasms and usually present as solitary or multifocal lesions.¹ A PCNSL that diffusely infiltrates brain parenchyma rather than presenting as a discrete lesion is referred to as lymphomatosis cerebri (LC) and is an unusual and uncommon presentation of PCNSL.^{2–4} Approximately 40 case reports of LC have been reported.^{5–7} Owing to its rarity, clinicians are less likely to include LC in the differential, which may lead to delay in diagnosis and treatment. We present a case in which the clinical presentation with history of retinal sarcoid and imaging findings were initially puzzling and further complicated by a diagnosis of a primary lung adenocarcinoma.

CASE PRESENTATION

We describe a case of a 66-year-old right-handed immunocompetent woman with history of presumptively treated retinal sarcoid who presented to the neurology clinic with 6 months history of worsening loss of balance, dizziness and intermittent vertigo, blurred vision, word finding difficulties, right leg weakness and headaches. Her dizziness contributed to multiple falls that has been increasing in frequency. The severe headaches were associated with photophobia and relieved by ibuprofen. Neurological examination revealed mild right leg weakness and minimal ataxia. The patient's cognitive function continued to decline over the course of several months after original presentation with

difficulties in executive function as well as memory. Concurrent with her neurological symptoms, a 1.0 cm right lung nodule was discovered on a CT scan. A primary lung adenocarcinoma was diagnosed for which the patient underwent a right upper lobectomy followed by a completion pneumonectomy. Over the course of a year, her ataxia and right-sided hemiparesis worsened.

INVESTIGATIONS

A brain MRI on initial presentation revealed a non-enhancing T2/FLAIR hyperintense lesion in the left parietal white matter extending anteriorly and along the base of the left precentral gyrus (figure 1A, B). MRI of the cervical and thoracic spine with contrast did not reveal an acute demyelinating process (figure 2A, B). Infectious workup with PCR: HSV1, 2 and John Cunningham Virus (JCV), Lyme antibodies, Venereal Disease Research Laboratory (VDRL) and tuberculous antibodies in the Cerebrospinal fluid (CSF) were all negative. An autoimmune workup was performed and was negative. Inflammatory workup showed elevated erythrocyte sedimentation rate (ESR) up to 85, normal C-reactive protein (CRP) 5.2. ANA, ANCA and myeloperoxidase antibodies were negative. Serum protein electrophoresis was negative. CSF cytology without flow cytometry, from two consecutive samples, was negative for malignant cells.

In view of the patient's deteriorating cognitive function after a couple of months of original presentation, a repeat brain MRI showed multiple T2 hyperintense lesions of the brain parenchyma, the largest one in left centrum semiovale/perirolandic region extending to the basal ganglia, thalamic-capsular region, ipsilateral cerebral peduncle and anterior aspect of the pons, with irregular contrast enhancement significantly increased compared to previous MRI (figure 3A–E). A stereotactic biopsy of the right frontal lobe lesion revealed only reactive gliosis. No neoplastic cells, inflammatory infiltrates, granulomas or vasculitis were observed.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the brain lesions included inflammatory process such as sarcoid due to previous history of retinal sarcoid, infection, lymphoma, demyelinating disease and less likely vascular aetiology. An atypical presentation of metastatic carcinoma or a paraneoplastic syndrome was considered after the diagnosis of adenocarcinoma of the lung was made.

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Figure 1 (A and B) MRI of the brain shows a non-enhancing T2/FLAIR hyperintense lesion in the left parietal white matter extending anteriorly and along the base of the left precentral gyrus.

TREATMENT

On first presentation, the patient received 3 days of high-dose intravenous methylprednisolone empirically with mild improvement of her symptoms. A follow-up MRI showed more conspicuous lesions, and the patient was started on a second trial of high-dose intravenous methylprednisolone, which was complicated by a steroid-induced psychosis. The patient was switched to a high-dose oral steroid (prednisone). She tolerated the oral steroid well and was maintained empirically for the rest of her clinical course without major clinical or imaging improvement.

OUTCOME AND FOLLOW-UP

The patient was eventually discharged to a rehabilitation facility, but returned to the hospital 1 month after discharge with aspiration pneumonia and altered mental status. The patient was transferred to the intensive care unit due to increasing respiratory requirement resulting in intubation and died 1 week later.

The autopsy revealed a fibrotic postsurgical lung with aspiration pneumonia. No residual adenocarcinoma was identified in the lung. Gross examination of the brain revealed slight enlargement of the left thalamus but otherwise normal-appearing brain parenchyma. Except for an organising haematoma at the site of the previous biopsy, no other discrete masses were identified in the brain. Microscopic examination showed atypical neoplastic lymphoid cells aggregated around blood vessels and diffusely

infiltrating the adjacent brain parenchyma (figure 4A, B). The neoplastic cells were present bilaterally in the cerebral white matter, basal ganglia, thalamus, hippocampus, midbrain, pons and cerebellum. The neoplastic cells were immunopositive for CD45, CD20 and BCL-2, and negative for CD10, CD5, pan-cytokeratin and BCL6 (figure 4C). Ki-67 immunostain demonstrated a high proliferative index, ~50–60% (figure 4D). Reactive astrocytes were positive for glial fibrillary acidic protein (GFAP), but the neoplastic lymphoid cells were negative. These findings were consistent with the diagnosis of LC. The immunohistochemical stains established the B cell identity of the neoplastic cells, although it was not possible to further classify the lymphoma. The lymphomatous cells were limited to the cerebrum, cerebellum and brainstem, but did not involve spinal cord. No lymphoma was present elsewhere in the body. The brain did not show any metastases from the lung adenocarcinoma.

DISCUSSION

This is the first report, to the best of our knowledge, of LC coexisting with a lung adenocarcinoma. The clinical manifestations of LC have been typically described as ataxia, personality changes, weight loss and rapidly progressive dementia.⁸ However, LC cases can present with variable clinical symptoms. The non-specific clinical presentation and variable imaging findings often result in the delay of diagnosis of LC.⁹ Our patient

Figure 2 MRI of (A) cervical and (B) thoracic spine shows no spinal cord hyperintensities.

Figure 3 (A–E) Repeat brain MRI showed multiple T2 hyperintense lesions of the brain parenchyma, the largest one in left centrum semiovale/periolcund region extending to the basal ganglia, thalamic-capsular region, ipsilateral cerebral peduncle and anterior aspect of the pons, with irregular contrast enhancement significantly increased compared to previous MRI.

demonstrated the focal finding of right hemiparesis along with the cognitive decline. PCNSL often occurs in the setting of immunosuppression, such as organ transplantation or HIV/AIDS, the latter associated with Epstein-Barr virus infection.¹⁰ However, most reported cases of LC have occurred in immunocompetent individuals.^{11 12}

Patient's previous diagnosis of retinal sarcoid may have played a role in this presentation, although the significance is unknown. The possibility of an association between

sarcoidosis and the development of malignant disease has been proposed by some authors, with an incidence 11 times greater in patient with respiratory sarcoid. The increased mitotic activity and dysregulation of lymphocytes seen in sarcoidosis in conjunction with immunosuppressant therapy may favour the possibility of the development of lymphoma.^{13 14}

Owing to the patient's diagnosis of a primary lung adenocarcinoma, a paraneoplastic neurological syndrome (PNS) was

Figure 4 (A) H&E photomicrograph of a diffuse infiltration of atypical lymphoid cells with concomitant reactive gliosis (200×). (B) Significant perivascular infiltration is identified (400×). (C) CD20 immunostaining demonstrating B-cell lineage. (D) Ki67 shows a high proliferation index (~50–60%).

considered in the differential diagnosis. Although a diagnosis of primary lung adenocarcinoma was made, the neurological symptoms for the patient did not demonstrate the classical symptoms of PNS.¹⁵

The radiological findings of LC have been described as diffuse, poorly circumscribed T2 hyperintense non-contrast enhancing lesions that most often involve the white matter of the cerebral hemispheres.¹⁶ However, other reports have demonstrated that more than 50% of 42 patients had lymphomatosis identified in the basal ganglia with concurrent supratentorial and infratentorial lesions as well as bilateral hemispheric lesions.⁷ They are not associated with a mass effect. Biopsy is recommended if empirical treatment with corticosteroids and antiviral agents has not yielded clinically apparent improvement.¹⁷ However, brain biopsy may result in a non-diagnostic specimen, especially if a discrete mass or target is not evident on imaging, as in this case.

The diagnosis of LC confers a poor prognosis. The 5-year survival after combined chemotherapy and radiation therapy for PCNSL was reported in one report to be 32%.¹⁸ However, in a recent series of LC cases, 47.2% of patients did not survive past 3 months after the onset of symptoms.⁷ They found that a high Karnofsky score ≥ 70 and treatment with methotrexate was associated with improved survival and that T-cell LC is an independent poor prognostic factor. While an aggressive treatment of high-dose steroid and/or methotrexate-based chemotherapy has been used to treat LC, the additional use of radiotherapy has demonstrated some efficacy in select patients.^{5 19–21} Owing to the rarity of LC and no consensus on treatment regimen, the current recommendation for LC is to treat like PCNSL with high-dose methotrexate-based chemotherapy followed by whole brain radiation.¹⁸

Learning points

- ▶ The clinical presentation and differential diagnosis of lymphomatosis cerebri (LC) can be challenging especially when complicated by the presence of a secondary neoplasm such as a primary lung adenocarcinoma as well as a previous history of retinal sarcoid.
- ▶ An atypical clinical presentation of LC in conjunction with relatively, non-specific radiological and laboratory findings may fail to yield a definitive diagnosis of LC until a histological examination can be made.
- ▶ A definitive diagnosis of LC can be established by brain biopsy, however because of the diffuse and non-focal nature of the lesions, a small biopsy sample may be non-diagnostic. Since patients with LC may show benefit from appropriate therapy, consideration should be given to biopsy of another lesion, if clinically warranted.

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