CASE REPORT

Small cell lung carcinoma presenting with acute disseminated encephalomyelitis

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ABSTRACT. Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease characterised by subcortical high-signal white matter lesions on T_2 weighted MRI. It most commonly occurs in children following an acute viral illness. We present a case study in which ADEM was the presenting condition in an adult female with small cell lung carcinoma. We discuss the evidence in the literature suggesting that ADEM may be viewed as a paraneoplastic syndrome.

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Acute disseminated encephalomyelitis (ADEM) is an acute monophasic demyelinating disease. It most commonly follows a viral infection or vaccination. The diagnosis is made from an appropriate history, the presence of cerebrospinal fluid (CSF) oligoclonal bands and the imaging findings. The most common MRI finding is subcortical high-signal white matter lesions on T_2 weighted images. There are a number of case reports in the literature in which ADEM has been the initial presentation in patients who are subsequently shown to have a malignancy. Some authors have suggested that ADEM can present as a paraneoplastic syndrome — a non-neoplastic disorder accompanying a malignant tumour. We present the case of a patient who presented with ADEM and was later diagnosed with advanced small cell lung carcinoma.

Case history

A 75-year-old woman was admitted with a history of increasing confusion, reduced mobility and falls. She had a medical history of atrial fibrillation, hypertension and previous removal of a basal cell carcinoma. She took antihypertensives and a thiazide diuretic. She had a history of smoking (20 pack-years), but had given up in 1980. Her family could not recall any recent bacterial or viral infections.

On examination, she exhibited frontal symptoms but had no lateralising signs. She proceeded to CT, which showed areas of low attenuation in both frontal lobes and the right temporal lobe (Figure 1). She then underwent an MRI brain scan. This showed abnormal high signal on fluid-attenuated inversion-recovery (FLAIR) and T_2 weighted images in the subcortical white matter of both frontal lobes, the right temporoparietal region and the left cerebellar hemisphere. The frontal changes

crossed the midline via the corpus callosum (Figure 2). There was no enhancement with gadolinium. A repeat MRI four weeks later showed similar features.

A lumbar puncture was performed. CSF glucose and protein were normal but polymerase chain reaction (PCR) proved positive for oligoclonal bands. Serum oligoclonal bands were not present. An electroencephalogram (EEG) was non-diagnostic, and an autoimmune screen was negative.

A chest radiograph 6 weeks later revealed a left-sided pleural effusion, and so CT of the chest, abdomen and pelvis was carried out. This showed a 4-cm soft tissue mass in the aortopulmonary window, with ipsilateral and contralateral mediastinal lymphadenopathy (Figure 3). There was a further small nodule in the right upper lobe. There were multiple liver metastases and bilateral adrenal nodules. Cytology of the pleural effusion found cells consistent with a small cell carcinoma of the lung. The patient received palliative care and sadly died.

Discussion

ADEM most commonly follows a viral infection or vaccination. The most common causative viruses are measles, rubella, varicella-zoster and mumps or upper respiratory tract infections. With the increased use of vaccines for childhood infections, most cases follow an upper respiratory tract infection.

ADEM is thought to be an autoimmune reaction to myelin triggered by the virus or vaccine. Animal models suggest that the pathogenesis of ADEM could be accounted for by one of two possible mechanisms. The first is that direct central nervous system (CNS) infection by a pathogen leads to tissue damage and the subsequent leak of auto-antigens into the systemic circulation via a disrupted blood–brain barrier. The auto-antigens are processed by lymphatic organs and lead to a self-reactive attack on the CNS by an activated T-cell response. The second theory of “molecular mimicry” proposes that

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Figure 1. Unenhanced CT image of the brain showing areas of low attenuation in both frontal lobes and the right temporal lobe.

structural homology between the proteins of the pathogen and the host's myelin can induce T-cell activation. Activated T cells and, secondarily, activated B cells reactivate when they encounter antigen-presenting cells in the CNS and cause an inflammatory immune response [1].

Pathologically, ADEM is characterised by "sleeves" of demyelination surrounding venules. Lesions are usually bilateral, occurring in the white matter and brain stem. It occasionally affects the cerebellum and spinal cord. Small veins and venules in affected white matter are surrounded by an inflammatory infiltrate of lymphocytes, macrophages

Figure 2. T_2 weighted axial MR image demonstrating white matter changes involving both frontal lobes and the right temporal lobe.

Figure 3. Axial contrast-enhanced CT image of the chest showing a soft-tissue aortopulmonary window mass (white arrow), with associated paratracheal lymphadenopathy (white arrowhead), and a left-sided pleural effusion.

and, occasionally, plasma cells. The adjacent white matter is oedematous and demyelinated. Arteries and arterioles are relatively free of inflammation. Inflammatory cells may be present in the CSF [2].

Classically, ADEM occurs 5–20 days after the infective insult or vaccination [3]. Clinical presentation is variable and ranges from headache, fever and lethargy to coma and seizures. Focal neurology may occur.

The mortality rate is up to 25% following measles, but is lower after other causes. If fatal, death usually occurs within two weeks [4]. The duration of untreated disease is approximately three weeks. Ongoing focal weakness or mental retardation can occur following measles but is much less common after other causes [4]. A proportion of patients relapse and follow a clinical course similar to multiple sclerosis (MS) [5].

A diagnosis is often made in the absence of an identifiable cause [5]. CSF analysis may reveal lymphocytosis, increased oligoclonal bands or the presence of immunoglobulin (Ig) G.

CT may be normal or show patchy low attenuation in the white matter. Focal or more diffuse cortical enhancement can occur. Lesions on CT do not tend to correlate with the extent or pattern of disease [6].

MRI shows a high sensitivity and correlates with the extent of disease [6]. The typical findings are multiple, asymmetrical, poorly marginated areas on T_2 weighted and FLAIR images. Unenhanced T_1 weighted images are usually unremarkable unless the lesions are large, in which case subtle hypointensity is seen. Contrast enhancement is variable [7]. Lesions are predominantly seen in the subcortical white matter and thalami and basal ganglia but may also involve the grey matter or the brain stem.

Lesions tend to be larger and more irregular than in MS and can dramatically regress with steroids, immunoglobulin therapy or plasmapheresis [8]. Haemorrhage is

rare. ADEM is typically a monophasic illness; however, on MRI, new lesions are seen frequently within the first month after the initial attack. There may also be a delay of 1 month between the onset of symptoms and the appearance of lesions on MRI [9].

Some cases of ADEM are associated with neoplasms and AIDS [4]. There are a number of case reports in the literature in which focal demyelination has been seen in the brains of patients presenting with biopsy-proven malignancies. These include haematological malignancies, such as lymphoma and myeloma [10–14], and solid tumours, such as seminoma [14–16].

In 2004, Sumelahti et al [17] produced an epidemiological report that found a higher incidence of haematological and brain malignancies in patients with MS. Some authors speculate that ADEM can be considered a paraneoplastic syndrome rather than a chance association [14, 15].

Paraneoplastic syndromes are a rare heterogeneous group of disorders that are caused by underlying neoplasms but are non-metastatic. A biochemical or immunological substance can occasionally be identified as the causative agent, but often the link is unknown. These syndromes can be triggered by an altered immune response to a neoplasm. They affect less than 1% of patients with cancer, but can target the nervous system, as well as the endocrine, haematological and musculoskeletal systems [18].

Tumours commonly involved in paraneoplastic syndromes of the CNS, including small cell lung carcinoma, express neuroendocrine proteins. Paraneoplastic syndromes occur in 3–5% of patients with small cell lung carcinoma [19], of which the most common is the Lambert–Eaton myasthenic syndrome. Others include syndrome of inappropriate antidiuretic hormone secretion (SIADH) and paraneoplastic cerebellar degeneration.

17% of patients with small cell lung carcinoma have an antibody known as anti-Hu, which can be detected in the serum and CSF by immunobiochemistry. Patients with anti-Hu antibodies develop an immune response to a family of RNA-binding proteins highly homologous to a *Drosophila* protein (Elav) critical for nervous system development in the fly, although the exact function of Hu proteins in humans is unknown. Anti-Hu antibodies are associated with an asymmetric sensory neuropathy resembling mononeuritis multiplex [20]. The anti-Hu antibody is also associated with limbic encephalitis, which is a syndrome affecting the limbic structures in the medial temporal lobes. It presents with short-term memory loss, seizures, hypothalamic dysfunction or psychiatric symptoms. CSF analysis may reveal lymphocytes and oligoclonal bands. ECG can show epileptic activity in the temporal lobes. MRI typically shows T_2 weighted or FLAIR hyperintensities in one or both medial temporal lobes [21]. Limbic encephalitis can remain isolated or evolve to a more widespread paraneoplastic encephalomyelitis [20].

In our patient, no involvement of the limbic structures was seen on either of the MRI scans, and it was thought that the imaging features were typical of ADEM rather than limbic encephalitis.

Conclusions

In summary, we report a case of a patient who presented with typical features of ADEM who was

subsequently found to have disseminated small cell carcinoma of the lung. In patients with ADEM who have no obvious precipitating cause, a search for underlying malignancy should be considered.

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