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TWO CASES OF INTRACRANIAL TUMOR WITH POSITIVE PARANEOPLASTIC NEUROLOGICAL SYNDROME ANTIBODY

Neurology

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KEYWORDS

SUMMARY
Paraneoplastic neurological syndromes (PNS) are a heterogeneous group of immune-mediated neurological syndromes related to malignant neoplasm, but intracranial neoplasms are rarely described. PNS antibody screening is important for the diagnosis of PNS.

We describe two unique patients with positive PNS antibodies. The first patient with weakly positive anti-amphiphysin antibody presented with seizure. One focal mass lesion was found in his right prefrontal lobe. He underwent surgery for lesion excision and the lesion was diagnosed as low -grade astrocytoma. The second patient with positive anti-CV2 antibody presented with numbness and weakness in his right upper limb. Cranial MRI scans revealed multiple nodular abnormal lesions with enhancement in his left frontal, temporal and parietal lobes, which progressed rapidly in less than two months and diagnosed as primary gliomatosis cerebri.

This case illustrates that PNS is due to the remote effect of non-neurological neoplasm, but intracranial tumors might also coexist with positive PNS antibodies.

BACKGROUND
Paraneoplastic neurological syndromes (PNS) are a heterogeneous group of immune-mediated neurological syndromes, which are attributed to a remote effect of a malignant neoplasm. [1-5] The most common tumor is small-cell lung cancer (SCLC). Ovarian cancer, breast cancer and testicular germ cell tumor are also found.[1, 2, 4] Well characterized onconeural antibodies such as anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2 and anti-amphiphysin in the cerebrospinal fluid (CSF) or sera can be used as diagnostic biomarkers. As classical PNS, limbic encephalitis (LE) is a neurological disorder characterized by memory loss, seizures and psychiatric symptoms. [5] In most of paraneoplastic LE, mesial-temporal lobes are frequently involved, but no direct neoplastic space-occupying lesion (SOL) in the brain is found.[6-8] Here, we report two unique patients with well characterized onconeural antibodies who were diagnosed with intracranial tumors.

CASE PRESENTATION
Case 1 A 39-year-old man presented with one generalized tonic-clonic seizure since three months. Then he felt throbbing headache in the bilateral temporal regions. His first brain MRI revealed one focal mass lesion in the right prefrontal lobe. Nineteen days later, his second MRI revealed the same focal mass lesion with perilesional edema (Fig. 1A). Therefore, he was admitted to our department.

Case 2 A 55-year-old man presented with repeated paroxysmal (lasting 10 seconds) numbness and weakness in the right upper limb two months ago. His first brain MRI showed multiple nodular abnormal lesion with enhancement in the left frontal, temporal and parietal lobes. One month later, his second MRI showed similar small round hyperintensity signal areas with enhancement (Fig. 2A-C). Another month later, he presented with slurred speech and was admitted to our department.

INVESTIGATIONS
Case 1 Lumbar puncture was performed in the patient. His intracranial pressure (ICP) was 210 mm H2O. The PNS antibody screening of his serum revealed the weakly positive anti-amphiphysin antibody. The protein in CSF was 0.49 g/L (0.15-0.45 g/L). The white blood cell (WBC) in CSF was normal. He performed a whole-body CT scan and breast ultrasound. Only possible old pulmonary tuberculosis was found. Subsequently, he underwent a whole-body positron emission tomography-computed tomography (PET/CT). It showed that the node in the lung was possible tuberculosis; the decreased density of right prefrontal parenchyma and its low FDP metabolism indicated infectious lesion.

Case 2 Lumbar puncture was performed in the patient. His ICP was 190 mm H2O. The PNS antibody screening of his serum revealed positive anti-CV2 antibody. The protein in CSF was 0.8 g/L. The WBC in CSF was normal. Therefore, he performed a whole-body CT, but no abnormality was found. Subsequently, he underwent a whole-body PET/CT. The high FDP metabolism in intracranial lesions indicated possible multiple primary intracranial malignant tumors. Fifty-one days later, his third MRI revealed larger abnormal lesions with perilesional edema, necrosis, and enhancement. MR spectroscopy showed elevation of choline and reduction in N-acetylaspartate in lesions. Diffusion tensor imaging showed broken fibers in lesions.

DIFFERENTIAL DIAGNOSIS
Case 1 The initial differential diagnosis encompassed those diseases resulting in seisure and abnormal signals in the brain. The diagnoses thus considered included encephalitis (infectious or autoimmune) and intracranial tumor. When the screening of onconeural antibodies showed positive anti-amphiphysin antibody and PET/CT indicated infectious lesion in the brain, PNS was considered. Dexamethasone and mannitol were used. Ten days after the treatment, his third MRI revealed no remarkable change of the lesion. There was no contrast enhancement after gadolinium administration (Fig. 1B-D).

Considering no effect of dexamethasone, he underwent surgery for the excision of SOL. Mass lesion histopathology revealed that small round nucleus oncocytes with a few processes were distributed diffusely, with pia mater infiltration. Ki67 immunohistochemistry showed proliferation index of 3%. Immunohistochemistry also showed glial fibrillary acidic protein, Olig2, ATRX, IDH1, Nestin positivity. This was suggestive of low -grade astrocytoma (WHO II).

Case 2 The initial differential diagnosis encompassed those diseases resulting in multiple confluent and extensive lesions in the brain. The diagnoses thus considered included multiple sclerosis, viral encephalitis, adrenoleukodystrophy, subacute sclerosing panencephalitis, acute disseminated encephalomyelitis and intracranial tumor. Although positive anti-CV2 antibody was found in his serum, high FDP metabolism revealed by PET/CT and rapidly progressive lesions showed by MRI indicated the diagnosis of primary gliomatosis cerebri (GC) (Fig. 2D-F).

TREATMENT
Case 1 The patient underwent resection of astrocytoma.

Case 2 The patient refused the surgery and chose palliative treatment.

OUTCOME AND FOLLOW-UP

Case 1 In the next one and a half years after the resection, the patient had no seizure and recurrence of neoplasm.

Case 2 Three months after the last MRI, the patient presented with aphasia and paraplegia of right limbs. He died another 2 months later.

DISCUSSION

In this case series, we describe two unique patients with well characterized onconeural antibodies. They presented with neurological symptoms such as seizure, aphasia and paraplegia, which might be considered PNS if only based on typical positive antibodies. However, intracranial tumors were finally confirmed with histopathological, immunohistochemical methods and repeated MRI scans.

In case 1, the patient with weakly positive anti-amphiphysin antibody was diagnosed with low-grade astrocytoma. Syndromes associated with anti-amphiphysin are mostly stiff-person syndrome and encephalomyelitis and the associated cancer are SCLC and breast cancer.[3, 9] However, astrocytoma is not listed as a possible tumor associated with anti-amphiphysin. Deshmukh reported a similar case in which the patient exhibited memory loss and gait disturbance with intracranial SOLs. The brain MRI showed two well-defined focal mass lesions in the right posteromedial temporal lobe and occipital lobe. Finally, he was diagnosed as paraneoplastic encephalitis. The histopathological examination showed high-grade astrocytoma.[6] It was the first time that paraneoplastic encephalitis was found associated with intracranial tumor, but PNS antibodies were not screened. Likewise, Seki reported of two patients with malignant spinal cord astrocytoma with possible paraneoplastic encephalitis. However, no pathological evidence confirmed the diagnosis.[7] Furthermore, poorly differentiated tumors are associated with high titers of PNS antibodies. The low-grade astrocytoma in the patient in case 1 was well differentiated, which might explain the low titer of anti- amphiphysin. [1]

In case 2, anti-CV2 antibody was found in the patient. Because repeated brain MRI scans revealed that the lesions involving three lobes progressed rapidly in two months, primary GC was considered. The neurological symptoms of patients with anti-CV2 antibody (expressed in brain-stem, cerebellum and spinal cord) exhibit different types, such as chronic inflammatory demyelinating polyneuropathy-like, cerebellar ataxia, myelopathy, chorea and myasthenic syndrome. [1, 10] The associated cancers are SCLC, thymoma etc, but GC was never reported in patients with anti-CV2 [1, 10]. Gliomatosis cerebri is a rare, diffuse glial tumor, which infiltrates the brain extensively and spread to more than two lobes.[8] Previously Nagata and Deramecourt reported that GC mimicked limbic encephalitis which manifested amnesia, disorientation and behavior changes, but PNS antibodies were not screened.[8, 11] The limitation of case 2 is the lack of brain pathology.

Patients who presented with seizure, amnesia, psychosis and abnormal signals in the brain are often associated to PNS.[5] It is a routine for clinicians to detect PNS antibodies and search for tumors outside the brain in these patients. Conversely, if the space-occupying lesion in the brain is likely a tumor, it is not a routine to screen PNS antibodies. Koszewicz et al. tried to look for the evidence of PNS in primary brain tumors. They included 33 patients with primary brain tumors and screened onconeuronal antibodies (anti-Hu, anti-Yo, anti-Ri, antiy-CV2, antiy-Ma/Ta, anti-amphiphysin) and antineuronal antibodies (anti-GAD,anti-MAG, anti-neuroendothelium, anti-peripheral myelin,anti-GFAP),but no onconeuronal antibodies were found.[12] In our cases positive PNS antibodies were found in patients with intracranial tumors. It is possible that there is some relationship between the production of PNS antibodies and the pathogenesis of intracranial tumors.

In summary, our cases emphasize that paraneoplastic neurological syndrome is a group of rare disorders due to the remote effect of non-neurological neoplasm, but intracranial tumors might also coexist with positive PNS antibodies.

LEARNING POINTS/TAKE HOME MESSAGES

- Paraneoplastic neurological syndromes are a heterogeneous group of immune-mediated neurological syndromes, which are attributed to a remote effect of a malignant non-neurological neoplasm.
- Intracranial tumors such as astrocytoma and GC might mimick limbic encephalitis which manifested seizure, amnesia, disorientation and behavior changes.
- Intracranial tumors might coexist with positive PNS antibodies. There might be some relationship between the production of PNS antibodies and the pathogenesis of intracranial tumors.
- Pathology is very important for the accurate diagnosis of patients with intracranial occupying lesion and positive PNS antibodies.

FIGURE/VIDEO CAPTIONS

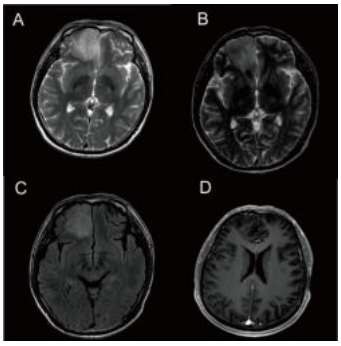

Figure 1 Cranial MRI images of the patient in case 1

(A) Axial T2-weighted image showing a hyperintensity signal area in the right prefrontal lobe. (B-D) Axial T2-weighted and FLAIR images showing a hyperintensity signal area in the right prefrontal lobe. Gadolinium-enhanced axial T1-weighted image showing no enhancement.

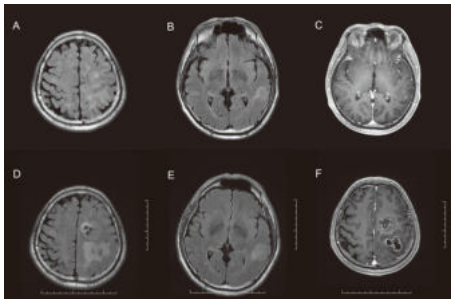

Figure 2 Cranial MRI images of the patient in case 2

(A-C) Axial MRI images showing small round hyperintensity areas with enhancement in the left frontal, temporal and parietal lobes. (D-F) Axial MRI images showing larger round hyperintensity areas with edema, necrosis and enhancement in the left frontal, temporal and parietal lobes.

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