Cerebellar Hemorrhage Secondary to CLIPPERS: a Case Report

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Abstract

Cerebral hemorrhage is an extremely rare complication of CLIPPERS. We report a patient who developed CLIPPERS in his 50s and was responding to glucocorticoid therapy developed cerebellar space-occupying hemorrhage with high glucose metabolism in bilateral cerebellar hemispheres during hospitalization.

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Abstract

Cerebral hemorrhage is an extremely rare complication of CLIPPERS. We report a patient who developed CLIPPERS in his 50s and was responding to glucocorticoid therapy developed cerebellar space-occupying hemorrhage with high glucose metabolism in bilateral cerebellar hemispheres during hospitalization.

Key Clinical Message

Neurological deterioration in CLIPPERS alerted doctors to the possibility of intracranial hemorrhage. Knowledge of CLIPPERs disease should complement the possibility of this complication.

Key words

CLIPPERS, Perivascular infiltrate, Peppercorns, Intracranial hemorrhage, case report

1. Background

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare central nervous system (CNS) inflammatory disease. It was first described by Pittock et al in 2010(Pittock, et al.,2010). CLIPPERS are rarely reported in China, Yang B et al(Yang, et al.,2021) first summarized the clinical manifestations of CLIPPERS in China. All of the patients developed a neurological syndrome dominated by gait ataxia and dysarthria, none of them with intracranial hemorrhage(Yang, et al.,2021). Our literature search revealed only three reported cases of intraparenchymal hemorrhage secondary to CLIPPERS(Buttmann, et al.,2013; Blaabjerg, et al.,2016; Sudhakar, et al.,2021). Buttmann et al have reported a case of subacute bleeding in the right cerebellar(Buttmann, et al.,2013). For reasons unknown, there have been fewer reported cases of cerebral hemorrhage secondary to CLIPPERS. Our case is unique in that we present a case of a 54-year-old man who developed a cerebellar hemorrhage following CLIPPERS. To our knowledge, this is the first case reporting cerebellar hemorrhage secondary to CLIPPERS in China and the second report of pathologic lesions showing ring-enhancing hypermetabolism on PET/CT(Sudhakar, et al.,2021).

2. Case presentation

In November 2020, a 54-year-old man presented with manifestations of unsteady gait and dysarthria, with mild dizziness and cognitive decline. The patient's past history was unremarkable. Neurological examination revealed free movement of both eyes, slurred speech, broad footbed, unstable posture, leaning to the right when walking, hyperreflexia in the limbs, no focal sensory disturbances, and no focal muscle atrophy. Magnetic Resonance Imaging(MRI) examination showed multiple abnormal signal shadows in bilateral fronto-parietal cortex, hind limb of internal capsule, midbrain, and right cerebellum, which suggested poisoning or metabolic encephalopathy (Fig.1(A-D)). Magnetic Resonance Angiography(MRA) reported normal blood vessels. Routine blood, liver function tests, renal function tests and serum electrolytes were normal. Serum antinuclear antibody (ANA) and cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) levels were normal. β2_microglobulin (β2_MG): 2.321 mg/L. Cerebrospinal fluid (CSF) examination revealed 2 cells, increased protein levels of 616 mg/dL (normal range: 150-450 mg/dL), and normal glucose levels of 3.07 mmol/L (normal range: 2.5-4.4 mmol/L). CSF fungal and Gram stain tests were negative, and no oligoclonal bands were detected. Serology was negative for typhoid fever, leptospirosis, dengue, Japanese encephalitis and toxoplasmosis. Chest tomography (CT) showed diffuse inflammation in both lungs, predominantly interstitial pneumonia.

He received 20 mg of dexamethasone intravenously for 7 days, gradually transitioning to oral prednisone. During corticosteroid treatment, the patient's neurological symptoms improved significantly. One month later, the lesions detected by head MRI were less than before. Oral corticosteroids were discontinued after 3 months.

However, in April 2021, the patient experienced gait instability and dysarthria again. Physical examination revealed a positive Barthel sign. The enhanced scan of MRI showed multiple patchy enhancement signals in the cerebellum and pons, Contrast-enhanced MRI scans show multiple patchy enhanced signals in the cerebellum and pons, resembling peppercorns Fig.1(E). DWI showed cerebellar softening foci (Fig.1(F)). We restarted dexamethasone 20 mg intravenous infusion for 7 days. During the treatment, the patient developed intractable hiccups, and with the reduction of hormone dose and the application of baclofen, the patient's hiccups gradually eased. The patient's dysarthria improved, but gait instability remained.

Considering the complexity of the lesions, we further refined PET/CT to reveal abnormal glucose metabolism in bilateral cerebellar hemispheres (Fig.1(G)). However, during hospitalization, the patient suddenly devel-

oped a right cerebellar hemorrhage and fell into a coma (Fig.1(H)). Surgery was performed in the emergency department. Pathological examination revealed infiltration of perivascular lymphocytes and neutrophils. Immunohistochemistry showed perivascular infiltrate primarily composed of CD3+ T cells, scattered CD20+ B cells, and no signs of malignancy, consistent with perivascular inflammation (Fig.2). After the operation, the patient woke up quickly and gradually carried out rehabilitation training, and the symptoms of the nervous system remained stable. Therefore, we never initiated immunosuppressive therapy.

3. Discussion and conclusions

We describe a case of acute cerebellar hemorrhage secondary to CLIPPERS, with PET/CT suggesting increased metabolism in both cerebellar. In a recent review of the published cases, Buttmann et al(Buttmann, et al.,2013) have reported a case of subacute bleeding in the right cerebellar. Blaabjerg et al(Blaabjerg, et al.,2016) presented a patient that responded to steroid treatment but then had a fatal brainstem hemorrhage. Additionally, In the case report presented by Vivek Sudhakar, susceptibility-weighted angiography (SWAN) imaging demonstrated a hemorrhagic component of the right occipital lobe lesion in the patient(Sudhakar, et al.,2021). Since cerebrovascular events in CLIPPERS patients are rare, the mechanism by which CLIPPERS leads to cerebrovascular manifestations has not been established yet.

There are usually a large number of lymphocytes or lymphoid tissue infiltration around the blood vessels of CLIPPERS lesions, and the affected lymphocytes are mainly $CD3^+$ and $CD4^+$(Axelerad, et al.,2021). Different from previous case reports showing CD4+T cell infiltration around CLIPPERS related intracerebral hemorrhage lesions, our patient's cerebellar biopsy showed diffuse CD3+T cell infiltration around blood vessels, which indicated significant inflammation around blood vessels(Buttmann, et al.,2013; Blaabjerg, et al.,2016; Sudhakar, et al.,2021). Similar to most CLIPPERS, there is perivascular infiltration of inflammatory cells pathologically in our case, but no characteristic histological features of vasculitis such as fibrinoid necrosis(Axelerad, et al.,2021). However, transmural lymphocytic infiltrates and inflammatory vessel occlusion have been shown to be present in biopsy samples in patients with CLIPPERS(Taieb, et al.,2016; Axelerad, et al.,2021), suggesting the direct destruction of immune cells around the blood vessel wall may be the main cause of bleeding. Interestingly, most CLIPPERS secondary to cerebral hemorrhage are characterized by a long course or recurrent disease. The patients reported in our report had cerebral hemorrhage during hormone therapy due to multiple relapses of the disease. We can speculate that the long course of disease and repeated intensive treatment may easily cause cerebral hemorrhage.

It is worth mentioning that Primary central nervous system lymphomas (PCNSL) is easily confused with CLIPPERS clinically. In addition to similar clinical symptoms, PCNSL can also show CLIPPERS like image appearance, and lesions can show high metabolism on PET/CT(Lin, et al.,2014). The pathology of PCNSL is not specific and therefore cannot be completely distinguished from CLIPPERS(Axelerad, et al.,2021). However, PCNSL is not sensitive to hormone therapy, and the condition cannot be effectively improved(Schaff and Grommes,2021). Recently, one case reported that patients with intracerebral hemorrhage secondary to CLIPPERS showed hypermetabolism at the focal site on PET/CT(Sudhakar, et al.,2021), and our patient also showed hypermetabolism at the focal site, which was confined to the brain. In addition, our patient was responding to glucocorticoid therapy and were more radiologically and pathologically prone to CLIPPERS. Although there is no more evidence, this led us to wonder if hypermetabolic lesions were associated with bleeding.

Intracranial hemorrhage is an unfamiliar complication of CLIPPERS, and physicians should be reminded to pay attention to the possibility of intracranial hemorrhage, especially in patients with acute neurological deterioration. In addition, intracranial hemorrhage may be associated with a long course of disease and repeated treatment. To our knowledge, this is the first report of cerebellar hemorrhage and PET shows hypermetabolism in a Chinese CLIPPERS patient. The possibility of this complication should also be considered when finding hypermetabolic lesions in CLIPPERS patients.

List of abbreviations

CLIPPERS(chronic lymphocytic inflammation with pontine perivascular enhancement responsive to

steroids), CNS(central nervous system), ANA (antinuclear antibody), MRI (Magnetic Resonance Imaging), CT (Computed Tomography), DWI (Diffusion Weighted Imaging), MRA (Magnetic Resonance Angiography), susceptibility-weighted angiography (SWAN), PCNSL (Primary central nervous system lymphomas),

Disclosure statement

No potential conflict of interest was reported by the author(s).

Declarations of interest

The authors report no conflict of interest.

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Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

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