CASE REPORT

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in limited cutaneous sclerosis: a rare disease combination

Sucharita Anand, Animesh Das, Surjyaprakash Shivnarayan Choudhury

Department of Neurology,
Sanjay Gandhi Post Graduate
Institute of Medical Sciences,
Lucknow, Uttar Pradesh, India

Correspondence to

Dr Animesh Das,
animeshdas05@gmail.com

Accepted 7 December 2018

SUMMARY

A 26-year-old patient of limited cutaneous sclerosis presented to us with insidious-onset posterior fossa symptoms of headache, vomiting, vertigo and gait imbalance, progressing over a period of 3 weeks. A diagnosis of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids was made by combining the clinical features with radiological evidence showing punctate infiltration of the pons, brainstem and cerebellum. Relevant differentials in the form of neurosarcoid, infections, central nervous system (CNS) lymphoma and Neuro-Behcet's disease were ruled out by history and investigations. The patient responded dramatically to steroid therapy, and had no neurological deficits after 18 months of follow-up. This case highlights the rare association of a not-so-common immunological disease with a rare neurological disease.

BACKGROUND

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was first described by Pittock *et al* as a treatable cause of subacute brainstem syndrome, showing good initial response in both symptomatology and radiology to steroids. The disease is characterised by predominant involvement of the pons, midbrain and cerebellum with punctuate infiltrates showing curvilinear contrast enhancement without any mass effect.¹ Herein, we describe a case of CLIPPERS in a patient of limited cutaneous sclerosis. To the best of our knowledge, an association of this immunological condition with CLIPPERS has not been described in literature.

CASE PRESENTATION

A 26-year-old woman was being followed up in our Immunology department as a case of limited cutaneous systemic sclerosis. She had a history of polyarthralgia, raynaud's phenomenon and recurrent digital ulcerations since the age of 7 years. She had chronic cough with clubbing and reduced oxygen saturation on pulse oximetry. Her investigations at the initial visit showed high antinuclear antibody titres (1:160). Extractable nuclear antigen screen was also positive for ribonuclear protein. She was diagnosed as a case of limited cutaneous sclerosis with interstitial lung disease.

She was referred to the outpatient wing of Neurology department with new symptoms of insidious-onset headache, vomiting, vertigo and gait unsteadiness that progressed gradually over a 3-week period. The headache was holocranial without any autonomic symptoms. Her vertigo and vomiting were not relieved by over-the-counter medications that she had been taking before presenting to us. There was no history of fever or any prodrome prior to the onset of symptoms. There was no history of altered sensorium, visual blurring, diplopia, seizures, focal deficit or sensory loss. Her vitals and systemic examination were unremarkable. Cranial nerves were normal on examination. The only positive findings were gait ataxia, bilateral gaze-evoked horizontal nystagmus (more towards the left side), positive finger-nose and heel-shin tests.

INVESTIGATIONS

Investigations showed normal haematology and clinical chemistry reports except for an erythrocyte sedimentation rate of 120 mm/hour. Cerebrospinal fluid examination (CSF) showed raised protein of 133 mg/dL with normal cytology (5 lymphocytes/mm³) and glucose levels (58 mg/dL against blood glucose of 70 mg/dL). MRI brain showed non-specific T2 weighted /fluid attenuation inversion recovery hyper-intense lesions involving the pons, bilateral middle cerebellar peduncles and cerebellar hemispheres with punctate areas of enhancement in the pons (figures 1, 2, 3, 4 and 5). Diffusion-weighted images showed no diffusion restriction, and magnetic resonance spectroscopy images showed a normal choline/n-acetyl aspartate ratio.

Chest X-ray was normal. CSF was negative for malignant cells, cryptococcal antigen and tubercular bacilli. Biopsy from the central nervous system (CNS) lesions was not done due to technical issues. Human leukocyte antigen-B51, aquaporin-4 antibody and venereal disease research laboratory (VDRL) test from the blood were negative. CSF examination for oligoclonal bands was also negative. Visual evoked potentials from both eyes were normal in amplitude and latency.

© BMJ Publishing Group Limited 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Anand S, Das A, Choudhury SS. *BMJ Case Rep* 2019;**12**:e226259. doi:10.1136/bcr-2018-226259

Figure 1 Axial T1 contrast image showing middle cerebellar peduncle and cerebellar infiltration.

DIFFERENTIAL DIAGNOSIS

Keeping in mind important differentials such as CNS vasculitis, CNS lymphoma, neurosarcoidosis, neuro-Behcet's disease, neuromyelitis optica (NMO), infective process (like tuberculosis, parasitic infections, neurosyphilis) and Whipple's disease, relevant investigations were done. There was no history of weight

Figure 2 Coronal T1 contrast image showing punctate pontine contrast enhancement.

Figure 3 Coronal T1 contrast image showing punctate enhancement in the cerebellum.

loss, high-risk sexual exposure, chronic cough, diarrhoea and recurrent oral or genital ulcers. There was no history to suggest systemic vasculitis. The other differentials were ruled out by the investigations.

TREATMENT

She was given injectable methylprednisolone 1 gram per day for 5 days (total of 5g). She had remarkable improvement on

Figure 4 Sagittal T1 contrast image showing punctate pontine and cerebellar enhancement.

Figure 5 Axial T2 weighted image showing hyper intensity in middle cerebellar peduncle and cerebellum with minimal surrounding oedema.

the second day of treatment, and her cerebellar signs resolved completely within a week. Thereafter, steroids were tapered and stopped over a period of 6 months.

OUTCOME AND FOLLOW-UP

She was followed-up for the next one year, during which she had no relapse of symptoms. A repeat MRI brain at 3 months of follow-up period was absolutely normal (figure 6).

DISCUSSION

CLIPPERS has a varied clinical presentation. The core features of CLIPPERS include clinical, radiological, glucocorticoid response and histopathological criteria.² The clinical features consist of brainstem, cerebellar and multiple cranial nerve involvement, in isolation or in variable combination.¹ Other symptoms may be present, including features of spinal cord involvement, pseudobulbar effect, headache or fatigue.^{2,3} Our patient had symptoms of posterior fossa involvement in the form of headache, vertigo, vomiting and ataxia. CSF showed

Figure 6 Axial T1 contrast and T2 weighted images at the level of pons and middle cerebral peduncle showing resolution of the previous lesions.

Table 1 Cases of CLIPPERS with unusual associations

Authors	Unusual associations of CLIPPERS
Crowell <i>et al</i> ¹⁰	Bilateral anterior uveitis with human leukocyte antigen-B27 positivity.
Ohta <i>et al</i> ¹¹	Limbic encephalitis with bilateral hippocampal lesions.
Ma <i>et al</i> ¹²	Intracranial Epstein-Barr virus infection (elevated Epstein-Barr virus-DNA in cerebrospinal fluid examination).
Mashima <i>et al</i> ¹³	CLIPPERS developing after treatment of stage 2 Hodgkin's lymphoma.
Wang <i>et al</i> ¹⁴	CLIPPERS following herpes zoster and subsequent trigeminal neuralgia.
Taieb <i>et al</i> ¹⁵	Primary central nervous system lymphoma, primary central nervous system lymphomatoid granulomatosis developing after a variable period of treatment of CLIPPERS.
Kleinschmidt-DeMasters and West ¹⁶	Small vessel vasculitis with left frontal lobe lesion.
Bendahan and Boulanger ¹⁷	Associated with multiple myeloma.
Ortega <i>et al</i> ⁸	CLIPPERS developing after withdrawal of natalizumab in a patient of multiple sclerosis.

CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids.

raised protein with normal cells and glucose consistent with the CSF findings in CLIPPERS.^{1,2,4} MRI brain showed punctate lesions predominantly in the pons, bilateral cerebellar peduncles and midbrain, giving a salt-and-pepper appearance and curvilinear enhancement on contrast. There was no mass effect, and spinal cord imaging was normal. These imaging findings favoured CLIPPERS.^{1,5} Our patient started recovering on day 2 of intravenous steroids and had complete resolution of symptoms after 1 week of steroid administration, which also favours the diagnosis of CLIPPERS.

The pattern of contrast enhancement seen in our case is not routinely seen in primary demyelinating diseases like multiple sclerosis (MS) or NMO, laboratory and serological markers did not support the above diseases, either.⁶ Recently, Ferreira *et al* has described CLIPPERS like MRI findings in a case of already proven MS while Ortega *et al* has described CLIPPERS developing in a case of MS after stopping natalizumab.^{7,8} But in our case, complete resolution of the lesions in MR imaging on follow-up were against a diagnosis of MS. Bickerstaff brainstem encephalitis (BBE) may be a close differential diagnosis of CLIPPERS, but, as there was no altered sensorium or ophthalmoplegia in our case, BBE seemed unlikely.⁹ Other differentials like Miller-Fischer syndrome or pontine glioma were also less likely in our case.

There are no published cases of CLIPPERS with limited cutaneous sclerosis as in our patient. table 1 summarises the unusual associations of CLIPPERS. The basic pathophysiology of CLIPPERS is unknown and a possibility of autoimmune trigger has been proposed. So the association of both diseases in the same patient may plausibly be attributed to autoimmunity. Since limited cutaneous sclerosis never manifests with central nervous system features, these findings are likely attributable to CLIPPERS. Resolution of the symptoms within 2 days after injectable steroids again favoured CLIPPERS. Remarkably, none of the patients in one published series of CLIPPERS cases had full recovery, and almost all suffered from late onset cerebellar symptoms that were also confirmed on MRI by marked cerebellar atrophy. Perhaps, the early introduction of steroids in our

case may have contributed to the complete recovery seen in our patient.

The limitation in our case was the non-availability of a brain biopsy. However, Pittock *et al* have shown that a brain biopsy is not required if a patient fulfils other clinical criteria of CLIPPERS.¹

Patient's perspective

I have read about the rarity of the disease chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids in limited cutaneous sclerosis and I am signing consent for publication of my case as a teaching material.

Learning points

- Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids is a rare disease and a diagnosis of exclusion. It should be differentiated from other acute or subacute causes of brainstem and cerebellar symptoms, as it responds to steroids quite dramatically and the diagnosis may be difficult once treatment is started.
- It may present in isolation or may be associated with other autoimmune diseases. Early diagnosis and treatment may have a beneficial effect on long-term prognosis.

Contributors SA collected the data. AD designed the report. SSC supervised the followup.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Pittock SJ, Debruyne J, Krecke KN, *et al*. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain* 2010;133:2626–34.
- 2 Simon NG, Parratt JD, Barnett MH, *et al*. Expanding the clinical, radiological and neuropathological phenotype of Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS). *J Neurol Neurosurg Psychiatry* 2012;83:15–22.
- 3 Safdieh JE. CLIPPERS: is it for real? *Neurology Alert* 2012;30:45.
- 4 Taieb G, Duflos C, Renard D, *et al*. Long-term outcomes of CLIPPERS (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids) in a consecutive series of 12 patients. *Arch Neurol* 2012;69:847–55.
- 5 Kastrup O, van de Nes J, Gasser T, *et al*. Three cases of CLIPPERS: a serial clinical, laboratory and MRI follow-up study. *J Neurol* 2011;258:2140–6.
- 6 Masdeu JC, Quinto C, Olivera C, *et al*. Open-ring imaging sign: highly specific for atypical brain demyelination. *Neurology* 2000;54:1427–33.
- 7 Ferreira RM, Machado G, Souza AS, *et al*. CLIPPERS-like MRI findings in a patient with multiple sclerosis. *J Neurol Sci* 2013;327(1–2):61–2.
- 8 Ortega MR, Usmani N, Parra-Herran C, *et al*. CLIPPERS complicating multiple sclerosis causing concerns of CNS lymphoma. *Neurology* 2012;79:715–6.
- 9 Koga M. [A nationwide survey of patients with Bickerstaff brainstem encephalitis: diversity of underlying mechanism]. *Rinsho Shinkeigaku* 2013;53:1322–4.
- 10 Crowell EL, Pfeiffer ML, Kamdar AA, *et al*. Idiopathic central nervous system inflammatory disease in the setting of HLA-B27 uveitis. *Ocul Immunol Inflamm* 2018;16:1–6.
- 11 Ohta Y, Nomura E, Tsunoda K, *et al*. Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) with limbic encephalitis. *Intern Med* 2017;56:2513–8.
- 12 Ma Y, Sun X, Li W, *et al*. Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) with intracranial epstein-barr virus infection: a case report. *Medicine* 2016;95:e5377.
- 13 Mashima K, Suzuki S, Mori T, *et al*. Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) after treatment for Hodgkin's lymphoma. *Int J Hematol* 2015;102:709–12.
- 14 Wang L, Holthaus EA, Jimenez XF, *et al*. MRI evolution of CLIPPERS syndrome following herpes zoster infection. *J Neurol Sci* 2015;348(1–2):277–8.
- 15 Taieb G, Labauge P. CLIPPERS features before, during and after lymphoma. *J Neurol Sci* 2016;366:251–2.
- 16 Kleinschmidt-DeMasters BK, West M. CLIPPERS with chronic small vessel damage: more overlap with small vessel vasculitis? *J Neuropathol Exp Neurol* 2014;73:262–7.
- 17 Nathaniel Bendahan, Jean-Martin Boulanger. A case of clippers syndrome with atypical distribution associated with multiple myeloma,neurology. 2016;86.P6.111.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow