CASE REPORT

An extended chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids phenotype

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SUMMARY

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described central nervous system inflammatory condition. In this case report we describe a patient initially with features consistent with this syndrome, who represented with seizures (not previously reported in this syndrome) and corresponding prominent cortical involvement on imaging (also not previously noted). Owing to diagnostic uncertainty, cerebral biopsy was performed revealing histology consistent with CLIPPERS, excluding other differentials. Following a further brainstem relapse, this patient was treated with high-dose steroids, subsequently switched to a tapering oral regime and now, azathioprine, a steroid-sparing agent. She remains well on this.

BACKGROUND

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) syndrome is a rare, relapsing–remitting predominantly brainstem central nervous system (CNS) inflammatory condition which has recently been described.^{1 2} Debate continues over whether CLIPPERS syndrome is a unique disease entity or whether it may represent differing underlying pathologies.³ It continues to remain a diagnosis of exclusion, with key differentials including other neuroinflammatory conditions such as neuro-Behcets, neurosarcoid, cerebral vasculitis and CNS lymphoma.

This case report describes an extended CLIPPERS syndrome phenotype, including seizures and more prominent cortical involvement, with compatible histology on biopsy. This case highlights the importance of biopsy in cases of diagnostic uncertainty and provides further insight into the clinical and radiological features that might be seen in this syndrome.

CASE PRESENTATION

A 62-year-old woman with no medical history initially developed a crawling sensation over the vertex in November 2010 but did not seek medical attention. Three months later she developed a sudden onset right-sided facial weakness. She also had a sensation of coldness affecting her left leg. She was given oral steroids for a presumptive diagnosis of Bell's palsy by her general practitioner. The weakness resolved over 3 months but the sensory symptoms persisted. She was systemically

well although she did report dry eyes. She had no joint symptoms, rashes or ulcers.

A year after her original symptoms developed the patient was reviewed by a neurologist. A contrast-enhanced MRI brain scan revealed scattered high signal foci on T2-weighted and fluid attenuation inversion recovery with some postcontrast enhancement in the pons, middle cerebellar peduncles, right-posterior temporal cortex and left parietal cortex. None of the lesions exhibited restricted diffusion. She was admitted for investigations including cerebrospinal fluid (CSF) analysis; the only positive finding was faint unmatched oligoclonal bands (OCB), with an atypical pattern for CNS inflammation. Extensive serological screening was negative/normal (antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigens, rheumatoid factor, paraneoplastic antibodies, HIV, human T-lymphotropic virus, venereal disease research laboratory (VDRL), toxoplasmosis, borrelia, cytomegalovirus, varicella-zoster virus). In view of the patient's dry eyes a Schirmer test was performed. This was positive but subsequent labial gland biopsy was normal. An ophthalmology review revealed no evidence of retinopathy or vasculopathy. She was given a brief course of steroid treatment but her sensory symptoms persisted. She was given the presumptive diagnosis of CLIPPERS and was discharged, off immunosuppression.

She was well until May 2012 when she had a tonic-clonic seizure in Australia. She had no other new neurological symptoms at that time. She returned to the UK and presented to our service. Repeat MRI showed evolution of white matter changes including a prominent lesion in the left occipital lobe showing peripheral enhancement and extensive vasogenic oedema, not previously reported in CLIPPERS (figure 1A, B). EEG revealed a left occipital epileptogenic focus. She was treated with carbamazepine and remained seizure free.

Owing to diagnostic uncertainty the occipital lesion was biopsied in July 2012. The histology was consistent with a diagnosis of CLIPPERS.

In October 2012 she developed ataxia, dysarthria and diplopia, and was admitted for further investigations.

INVESTIGATIONS

Repeat contrast MRI revealed progression of the punctate hyperintensities within the pons, with perivascular enhancement. Numerous small foci of enhancement were seen in the basal ganglia in a

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Figure 1 Axial (A) FLAIR and (B) gadolinium-enhanced T1-weighted images at presentation postseizure demonstrating a prominent left occipital lesion with surrounding vasogenic oedema and heterogeneous peripheral enhancement. Axial (C, D) gadolinium-enhanced T1-weighted images at the time of subsequent presentation with a new brainstem syndrome demonstrating extensive punctate/linear areas of enhancement within the pons, characteristic of CLIPPERS and extension of the occipital lesion with scattered areas of enhancement surrounding it (C), and 7 days after treatment with intravenous steroids demonstrating dramatic improvement (D). CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; FLAIR, fluid attenuation inversion recovery.

perivascular distribution, plus new scattered foci of enhancement within cerebral hemispheres and progression of the left occipital lesion (figure 1C). This subsequently improved with steroid treatment (figure 1D).

CSF findings remained compatible with CLIPPERS including a mildly elevated protein (0.5) and weakly unmatched OCB. CSF cytology revealed a small number of reactive T cells.

Serological tests revealed no evidence of an autoimmune or infective cause (erythrocyte sedimentation rate, C reactive protein, ACE, autoantibody screen (including paraneoplastic antibodies), low-density lipoprotein, protein electrophoresis (and urine Bence-Jones protein), lupus anticoagulant, anticardiolipin

antibody, tumour markers, HIV, borrelia and VDRL serology were all normal or negative).

A CT positron emission tomography (head, thorax, abdomen and pelvis) showed no evidence of an 18F-fluorodeoxyglucose-avid lymphomatous process, or neoplasm.

Mammogram revealed no malignancy.

DIFFERENTIAL DIAGNOSIS

The diagnosis of CLIPPERS syndrome remains very much a diagnosis of exclusion. The imaging findings reported in classic CLIPPERS cases, including pontine perivascular enhancement on contrast enhanced MRI, are seen in other CNS inflammatory

Figure 2 Representative images from the biopsy are illustrated in the panel (A–D). An intraoperative smear preparation stained with Toluidine blue shows an inflammatory infiltrate comprising small lymphocytes and plump histiocytes (A). Paraffin sections stained with H&E show a diffusely infiltrative growth pattern (B) as well as highlighting prominent perivascular cuffing (C). Immunostaining for glial fibrillary acidic protein further confirms the diffusely infiltrative pattern and frequent entrapped residual astroglial cells are noted among the infiltrate. The plump histiocytes are strongly immunoreactive for CD68 (D). The small lymphocytic component is overwhelmingly immunoreactive for CD4. Scale bar: A=50 μ m; B–D=100 μ m.

conditions, including neuro-Behcet's, Sjogren's disease, lymphocytic vasculitis and neurosarcoidosis. In addition, CNS lymphoma, which in the early stages is exquisitely steroid-sensitive, can produce a similar picture. As summarised above, a host of investigations were repeatedly negative for systemic inflammatory, infective and neoplastic processes. Owing to diagnostic uncertainty the occipital lesion was biopsied, revealing a densely packed lymphohistiocytic infiltrate, showing prominent perivascular arrangement as well as diffuse parenchymal infiltration (figure 2A–D). True vasculitis was absent. The histiocytic component (CD68/CD11c/S100–/CD1a–) was intimately admixed and nearly equal in proportion to the predominantly CD3/CD4 T-cell component. Small numbers of CD20/EBER– B cells and few plasma cells were present. Eosinophils or neutrophils were absent, well-formed granulomas were not seen and special stains did not reveal any microorganisms. There was no selective myelin loss. PCR analysis did not reveal clonal T-cell expansion. These histological findings are consistent with those described in the two case series of CLIPPERS.^{1 2}

TREATMENT

On representation in October 2012, following repeat investigations, the patient was treated with a 5-day course of pulsed intravenous methylprednisolone (500 mg/day), which was then converted to a tapering oral prednisolone regime (starting at 60 mg/day).

OUTCOME AND FOLLOW-UP

Her symptoms dramatically improved within a week, which correlated with a dramatic improvement on her MRI (figure 1D), supporting an exquisitely sensitive steroid responsive process. The patient remained well 5 months later and was started on a steroid-sparing agent (azathioprine). She has had no further relapses after 6 months on this treatment. She remains under neurology outpatient follow-up.

DISCUSSION

This patient demonstrates an extension of the previously reported CLIPPERS phenotype.^{1 2 4 5} She presented with a brainstem syndrome—initially scalp paraesthesia and right-sided facial nerve palsy, and subsequently a gait ataxia with dysarthria and diplopia. She also developed tonic-clonic seizures as a result of a prominent occipital lesion. Seizures have not been reported as part of the CLIPPERS syndrome phenotype.

The brainstem and subcortical findings on MRI in our patient are similar to those seen in the previous case series,^{1 2} with multiple punctate lesions within the pons and, to a lesser degree, the basal ganglia with curvilinear gadolinium enhancement. Additionally, cortical white matter lesions were also present, although of a lower density, with a particularly prominent left occipital lesion. In the original CLIPPERS case series, remote cortical white matter lesions were not reported.¹ In the second CLIPPERS case series,² white matter abnormalities were seen in the cortical white matter, with decreasing density with increasing distance from the hindbrain, as seen in our patient. The prominence of the occipital lesion is unusual as such tumefactive lesions in cases of CLIPPERS are not reported elsewhere.^{1 2 4 5} Interestingly, in one case series,² significant cortical atrophy was noted in three of the five patients on follow-up scanning, suggesting significant cortical involvement, even if not identified on routine imaging. Both case series^{1 2} comment on the paucity of vasogenic oedema associated with lesions. Significant vasogenic oedema seen surrounding our patient's occipital lesion may, in fact, have been related to recent seizure activity, as this was less prominent on subsequent scans, pretreatment with steroids. Diffusion weighted imaging has been reported to be unremarkable in the case series to date^{1 2}; this is consistent with the case reported here, apart from the occipital lesion, which did reveal peripheral restriction of diffusion with central non-diffusion. This pattern can be seen in other causes of tumefactive lesions, such as inflammatory demyelinating lesions, but as discussed the biopsy was not consistent with this.

As seen in other cases of CLIPPERS, our patient was exquisitely sensitive to parenteral steroids, showing dramatic clinical and radiological improvement within a week.

There has been some discussion in the literature about whether biopsy is necessary if the clinical and radiological picture is typical in CLIPPERS,^{1–4} particularly given the relatively high risk of brainstem biopsy. Clearly, given the atypical nature of our case, biopsy was important and the accessibility of the occipital lesion made this viable. The findings on biopsy are similar to those seen in both case series.^{1–2} A battery of immunostains and PCR combined with careful morphological assessment was necessary to exclude a wide range of pathologies including sarcoid, Langerhan's cell histiocytosis, lymphocytic variant of primary CNS angiitis, inflammatory demyelination, CNS lymphoma and lymphomatoid granulomatosis, as all of these entities may variably overlap with CLIPPERS pathology.

CLIPPERS syndrome is thought to be caused by an autoimmune process.^{1–4} Previous authors have suggested a

peri-vascular antigen,¹ given the predominant perivascular inflammatory infiltrate. Other have suggested a particular local immunological target within pontine and peripontine areas.⁴ The findings in our patient would suggest a more widespread antigenic target, which would be supported by the previous finding of widespread cortical atrophy, on long-term follow-up.²

In this case report we have demonstrated an extended phenotype of CLIPPERS syndrome, perhaps a 'CLIPPERS plus' syndrome, where the clinical presentation has been influenced by a prominent cortical lesion. Presumably, dependent on where the cortical lesions are, the clinical phenotype might extend further, determined by local cortical dysfunction.

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Contributors CA drafted the paper, performed the literature search and collated the radiology images. RP edited the paper and provided the histology images. RH was the key consultant in the care of the patient, had the idea for the article, performed the literature search and edited the paper. RH is the guarantor.

Competing interests None.

Patient consent Obtained.

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Learning points

- ▶ CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) syndrome is a rare, predominantly brainstem, relapsing–remitting central nervous system inflammatory condition which remains a diagnosis of exclusion.
- ▶ Cerebral biopsy, although invasive, remains an important investigation in cases of diagnostic uncertainty. This case demonstrates an extended CLIPPERS imaging and clinical phenotype with prominent, cortical involvement on imaging, clinically resulting in seizures.
- ▶ Steroid-sparing agents can be effective in the long-term management of CLIPPERS.

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