CLIPPERS: INDUCTION AND MAINTENANCE OF REMISSION USING HYDROXYCHLOROQUINE

Chronic lymphocytic inflammation and pontine perivascular enhancement responsive to steroids (CLIPPERS) is a condition that was first described by Pittock et al. in 2010 and is characterized by brainstem symptoms, gait ataxia, and diplopia. Brain MRIs of patients demonstrate punctate or nodular gadolinium-enhancing lesions in the pons. CLIPPERS is a diagnosis of exclusion through laboratory, radiologic, or histologic tests. Most patients to date have been treated with steroids, with some eventually switching to other immunosuppressants with variable and significant side effect profiles. We describe a patient with CLIPPERS in whom treatment with hydroxychloroquine was successful in inducing and maintaining the remission of symptoms confirmed by radiologic resolution.

Classification of evidence. This article provides Class IV evidence. It is a single observational study without controls.

Case presentation. A 54-year-old man presented in 2009 with a 12-month history of intermittent bilateral motor and sensory symptoms eventually progressing to blurred vision. Examination revealed square wave jerks and saccadic intrusion of pursuit movements, gait ataxia, and bilateral trigeminal sensory involvement. Serial postcontrast T1-weighted MRI sequences revealed multiple progressive punctiform white matter lesions involving the pons and cerebellar peduncles bilaterally (figure). Laboratory tests including full blood count, liver function, renal function, autoimmune screens, paraneoplastic antibodies, vitamin levels, and inflammatory markers were normal. CSF showed a mildly elevated protein of 0.44 g/L (normal range 0.1–0.4 g/L), unremarkable cell count (4 red cells/μL, 3 lymphocytes/μL), and an elevation in unmatched oligoclonal bands. Treatment with glatiramer acetate was started in April 2010 for a presumptive diagnosis of multiple sclerosis. After further neuroradiologic review, multiple sclerosis was considered unlikely and the possibility of neurosarcoidosis was considered, although serum angiotensin-converting enzyme and chest x-ray were normal. Glatiramer acetate was stopped within 6 weeks of initiation, and treatment with hydroxychloroquine 200 mg twice daily was started in May 2010. This was followed by significant and prompt resolution of symptoms and improved imaging. With the lack of peripheral and laboratory features of sarcoidosis and eventual recognition that the MRI brain findings were similar to those recently reported in the literature, the diagnosis was changed to CLIPPERS in 2011. He was diagnosed with Dukes’ C colon cancer and underwent a hemicolectomy and 12 cycles of chemotherapy at the end of 2012. His hydroxychloroquine was put on hold for a month while he received the chemotherapy but was resumed after completion of the cancer treatment. At follow-up 4 years later, there is no evidence of residual malignancy. There has been no recurrence of neurologic symptoms and complete resolution of the MRI changes (figure) on maintenance hydroxychloroquine.

Discussion. CLIPPERS is a relapsing-remitting condition and long-term sequelae are dependent on the severity of relapses. The pathogenesis of CLIPPERS eludes the scientific community, and our understanding of this condition is still in its infancy. Reports have suggested that it could be part of a subset of multiple sclerosis or could overlap with systemic lupus erythematosus. The current proposal that CLIPPERS is an immune-mediated condition is based on T-cell–predominant infiltrates in affected lesions and resolution of these lesions radiographically with immunosuppression.

Hydroxychloroquine was initially used as an antimalarial drug and subsequently as an immunomodulator in the treatment of rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus. Fox et al. proposed its action as an immunomodulator in 1996, suggesting that it may have an effect on macrophages. However, the mechanism of action of hydroxychloroquine has not been replicated and validated since this proposal and remains uncertain. Hydroxychloroquine was used in a patient with CLIPPERS described by Pittock et al., but it was withdrawn due to radiologic progression despite maintenance of clinical remission. Since then, hydroxychloroquine has not been used in subsequent
cases. Although hydroxychloroquine was originally initiated to treat presumed sarcoidosis, induction of remission was achieved within 2 weeks of commencement of treatment in this patient with CLIPPERS. The lesions on imaging resolved concurrently with his clinical improvement and he remains symptom-free to date. The initial brief exposure to glatiramer acetate would not account for the sustained remission seen. The clinical and radiologic recovery more than 2 years prior to recognition and successful treatment of his malignancy is inconsistent with his presentation being due to paraneoplastic syndrome. To the best of our knowledge, this is the first case of CLIPPERS successfully treated and maintained with hydroxychloroquine. Hydroxychloroquine is a relatively inexpensive option that is generally well-tolerated with a favorable side effect profile compared to other immunosuppressive therapies. We believe it should be considered as an alternative in the treatment of CLIPPERS.

Figure Postcontrast axial and coronal brain MRI in a patient with CLIPPERS treated with hydroxychloroquine

T1-weighted spin echo post IV gadolinium contrast media axial (A) and coronal (B) sequences show the temporal evolution of changes in this patient. The August 2009 scan demonstrates punctate and curvilinear enhancement predominantly in the pons and right middle cerebellar peduncle (indicated by arrows), which is characteristic of CLIPPERS. These changes progressed over 8 months, as evidenced on the April 2010 scan. The patient commenced hydroxychloroquine in May 2010, and the scan performed in August 2010, after 2 months of treatment, shows complete resolution of the pontine and right cerebellar peduncle enhancement. The patient remained on hydroxychloroquine and there is no evidence of recurrence on the scan from November 2013.

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Correspondence to Dr. Tan: bltan1982@hotmail.com

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Boon Loong Tan, Marc Agzarian and David W. Schultz
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