Acute Disseminated Encephalomyelitis After Mixed Malaria Infection (*Plasmodium falciparum* and *Plasmodium vivax*) With MRI Closely Simulating Multiple Sclerosis

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Introduction: Acute disseminated encephalomyelitis (ADEM) is a monophasic, inflammatory, immune-mediated disorder of the central nervous system. It is particularly difficult to distinguish between ADEM and an initial attack of multiple sclerosis (MS) clinically and based on magnetic resonance imaging (MRI) or cerebrospinal fluid. ADEM is quite rare after malaria infection. Our patient, although diagnosed provisionally of ADEM after mixed malaria infection, had neuroimaging closely simulating MS.

Case Report: We report a case of a woman with an adult type 2 diabetes presenting with fever and diagnosed by antigen assay to be suffering from mixed malaria infection (*Plasmodium falciparum, Plasmodium vivax*). While recovering with artesunate and doxycycline therapy, she developed acute onset bladder retention followed by paraparesis. On examination she had evidence of Upper Motor Neuron (UMN) signs in all the 4 limbs along with truncal sensory loss.

Discussion: Her MRI of spine showed T2 hyperintensities suggestive of resolving myelitis. MRI of the brain showed multifocal and confluent areas of demyelination mostly involving the corpus callosum and periventricular region. Lesions, particularly the callosal ones, closely simulated MS. In accordance with the McDonald Criteria and Barkhof's MRI Criteria, this patient did not fit into the diagnosis of MS. Our provisional diagnosis was ADEM.

Key Words: malaria, (ADEM), MRI, multiple sclerosis

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Acute disseminated encephalomyelitis (ADEM) is a monophasic, inflammatory, immune-mediated disorder of the central nervous system (CNS) after a viral infection but it may appear after vaccination, bacterial, or parasitic infection, or even appear spontaneously. Hess[1] provided criteria to facilitate diagnosis, including (1) a history of recent infection, although it may have been clinically silent; (2) a monophasic disease course; (3) disseminated CNS disease with neurological findings; and (4) the absence of metabolic or infectious disorders.

It is particularly difficult to distinguish between ADEM and an initial attack of multiple sclerosis (MS) clinically and based on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF), although this distinction becomes important from a therapeutic and prognostic point of view. ADEM is quite rare after malaria infection; only a few reports have been published.

Our patient, although diagnosed provisionally with ADEM after mixed malaria infection, had neuroimaging closely simulating MS.

CASE REPORT

A 32-year-old woman had been diagnosed with type 2 diabetes mellitus 1 year ago when she had complained of tingling and burning sensations in distal limbs. She was doing well on oral hypoglycemics until she started having high-grade fever 15 days before admission, which was quotidian in nature and associated with chills and rigors. After 1 week of fever she developed acholuric jaundice without itching or steatorrhoea. She had no anorexia, but had occasional episodes of nausea. Abdominal pain, cough, expectoration, dyspnoea, headache, visual disturbance, and dysuria were absent. On examination she was febrile at 102°F, and had severe pallor and jaundice. The pulse was 114/min, respiratory rate was 30/min, and blood pressure equaled 110/70 mm Hg. There was mild hepatomegaly and splenomegaly. Otherwise the systemic examination was within normal limits. Her investigations were:

- Hb%, 4.9gm/dL; total white blood cell count, 14900 (N-69, L-24, M-5, E-2); platelet count, 1.6 lac/mm^3; packed cell volume,15; mean corpuscular volume, 86.7 fL; mean corpuscular haemoglobin, 28.3 pg/cell; mean corpuscular haemoglobin concentration, 32.7 g/dL; red cell distribution width- cell volume, 15.6; eruthrocyte sedimentation rate, 90 mm at end of first hour; reticulocyte count, 3.9% red cells.
- Bilirubin, 23 mg/dL; (ID, 18.8; D, 4.2); albumin, 2.3 gm/dL; globulin, 2.7 gm/dL; serum glutamic oxaloacetic transaminase, 147 IU/L; serum glutamic pyruvic transaminase, 38 IU/L; ALP, 201 IU/L.
- C-peptide (fasting), 1.39 ng/mL (N: 0.4 to 2.1 ng/mL)
- Na^+/K^+, 136/3.98 mmol/L
- Fasting blood sugar, 136 mg/dL
- Urea, 26 mg/dL
- Creatinine, 0.7 ng/mL
- Malarial antigen test showed positive result for both *Plasmodium falciparum* and *Plasmodium vivax*.
- G-6-PD level was normal. Hepatitis B surface antigen, anti-Hepatitis C virus, anti-Hepatitis A virus, anti-Hepatitis E virus were all nonreactive.
- Human immunodeficiency virus serology, negative

Patient was treated with intravenous artesunate (2.4 mg/kg/dose) and oral doxycycline (100 mg BD twice daily). She became afebrile within 2 days of therapy. Two units of concentrated red blood cells were transfused. On the second day of therapy she developed sudden retention of urine for which she had to be catheterized. Over the next 3 days she developed paraparesis, which progressed proximal to distal. Ultimately, she was unable to turn in bed. No sensory symptoms or cranial nerve involvement were present. Her Glasgow Coma Score was 15/15 and her minimental status score was 29/30. Speech was normal

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in content and quality. Opthalmoscopy was normal. Meningeal signs were absent. There was bilateral flaccid paralysis of the lower limbs with bilateral extensor plantar responses, grade 2/5 power, and hyperactive knee and ankle reflexes. In the upper limbs, tone was normal with grade 4/5 power and hyperactive biceps, triceps, and supinator reflexes. Abdominal reflexes were absent bilaterally. All modalities of sensation were grossly but equally diminished in both lower limbs below a T-10 level. Sensation in upper limbs were also diminished but to a lesser extent. Coordination and gait could not be properly tested due to weakness. Cerebellar dysfunction was absent.

Spine MRI detected faint intramedullary signal changes from the lower thoracic region to the conus thought to possibly be resolving myelitis. Mild degenerative changes were present in the cervical spine. Brain MRI showed multifocal and confluent areas of demyelination mostly involving the corpus callosum and periventricular region. The patient refused contrast injection. Lesions were suggestive of MS considering their periventricular location and vertically oriented lesions involving the undersurface of the corpus callosum, simulating "Dawson fingers."

The CSF showed:

- Cells—3; all lymphocytes
- Protein—47 mg/dL
- Glucose—91 mg/dL
- Gram stain and acid-fast stain—negative
- ADA—2.3 IU/L
- Culture—no growth

No oligoclonal bands were in the CSF or serum.

ADEM was our final diagnosis considering the incongruency with McDonald and Barkhof Criteria for MS.

The patient received methyl-prednisolone intravenously (1 gm × 3 d) followed by oral prednisolone 60 mg per day gradually tapered over 2 weeks. The patient improved and presently has grade 3/5 power in the right leg and grade 2/5 power in left leg. Her behavioral and cognitive abnormalities improved. Follow-up peripheral blood smears were negative for malaria parasites and the patient remained afebrile (Figs. 1–4).

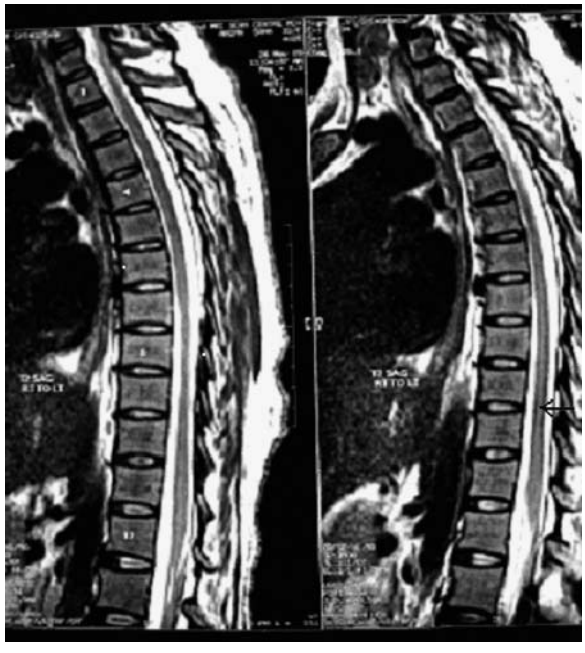

FIGURE 1. Sagittal T2-weighted magnetic resonance image showing faint intramedullary signal changes (arrow) from the thoracic level to the conus, suggesting a resolving myelitis.

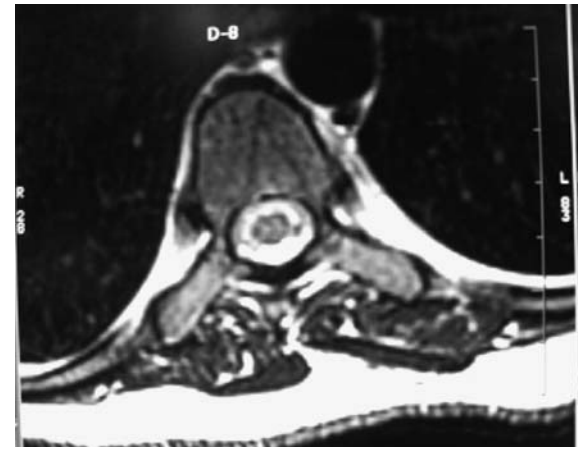

FIGURE 2. Axial T2-weighted magnetic resonance image showing faint intramedullary signal changes.

DISCUSSION

ADEM is a monophasic, inflammatory disorder of the CNS with a favorable long-term prognosis. A T-cell mediated autoimmune response to myelin basic protein, triggered by an infection or vaccination, possibly underlies its pathogenesis.[2] Unlike viral encephalitis, microorganisms do not invade the CNS. Instead, ADEM is a postinfectious disease mediated by autoreactive cells or molecules. Clinical characteristics of ADEM are consistent with disseminated involvement of the CNS, including encephalopathy and pyramidal, cerebellar, and brainstem signs. Bilateral optic neuritis and transverse myelitis are particularly suggestive of demyelinating diseases such as ADEM.[3] The differentiation of ADEM from a first attack of MS has prognostic and therapeutic implications, although it is often difficult. Most patients with ADEM improve with methylprednisolone, as did our case. If corticosteroid therapy fails, intravenous immunoglobulin therapy, plasmapheresis, or cytotoxic drugs can be tried. Recent literature suggests that a significant proportion of patients with ADEM will later develop MS.[4]

Malaria, particularly *P. falciparum*, has been known to cause a multitude of neurological abnormalities including

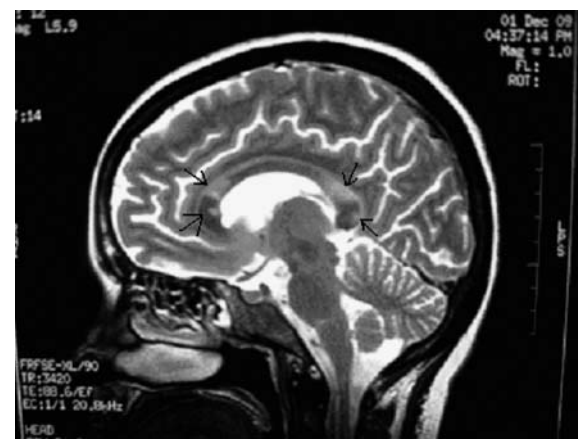

FIGURE 3. Sagittal T2-weighted magnetic resonance image showing multiple hyperintense lesions (arrows) in the corpus callosum simulating "Dawson fingers."

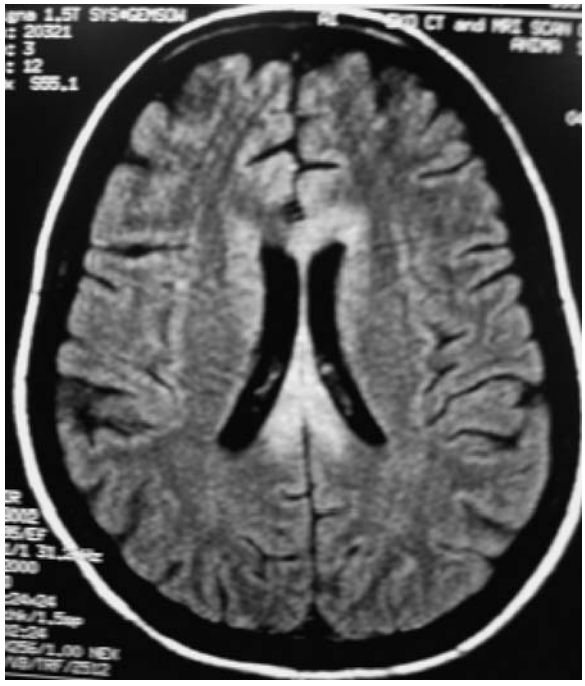

FIGURE 4. Axial T2-weighted magnetic resonance image showing multiple hyperintense confluent lesions in the periventricular white matter, classic for multiple sclerosis.

ADEM[5–7] cerebellar ataxia, psychosis, extrapyramidal rigidity, cranial nerve deficits and hemiplegia,[8,9] central pontine myelinosis,[10] and postmalaria neurological syndrome. ADEM has also been reported following *P. vivax*.

MRI findings are difficult to distinguish between MS and ADEM. T2-weighted images in ADEM show lesions that are more pronounced with poorly defined margins in deep white matter and periventricular sparing and less commonly involve the corpus callosum.[11] In contrast, lesions in MS characteristically involve the periventricular white matter, internal capsule, corpus callosum, and pons, although plaques can be found anywhere in the white matter. On MR imaging, the prevalence of lesions in the corpus callosum has been reported to be up to 93%.[12] The lesions of the corpus callosum can be focal or confluent nodular lesions and tend to affect the callosal—septal interface, which is the central inferior aspect of the corpus callosum.[13] In our case, the periventricular region and the corpus callosum were distinctly involved and the lesions closely simulated MS.

Analysis of CSF is another important diagnostic tool in differentiating MS and ADEM. In regard to ADEM, the CSF can be normal or, more likely, show nonspecific changes including an elevated protein and pleocytosis with lymphocytic predominance, a normal glucose, and negative cultures. The CSF profile was inconclusive in our case.

Whether malaria and MS have any causal relationship is unknown but is relevant here considering the close mimicry of MRI lesions with MS in our case. Some studies have shown that *P. falciparum*-induced proliferation, cytokine production, and parasite killing are significantly augmented in Sardinian MS patients as compared with controls ($P < 0.01$). In addition, a correlation is found with genes associated with Sardinian MS, namely the tumour necrosis factor—376A promoter polymorphism and the class II HLA-DRB1 0405 allele.[14]

Presently, as per the McDonald Criteria and Barkhof Criteria, our case cannot be diagnosed as MS. We need to follow our patient for any recurrence of similar episodes, which may lead to revision of our diagnosis.

CONCLUSIONS

We report this case as ADEM after malaria infection as a rare presentation and the MRI simulated MS leading to a diagnostic dilemma. This is a rare presentation of ADEM after mixed malaria indection where the MRI imaging was closely simulating Multiple sclerosis.

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