Case 23

U.W. is a 32-year-old woman who presented to the emergency room complaining of unsteady gait and dizziness. Her review of systems was notable for an episode of blurry vision in her right eye associated with a dull ache behind the eye, which resolved over 2-4 weeks. Three years ago she presented to the emergency room complaining of numbness on the entire left side of her body as well as the face and was told she was anxious and was sent home on Motrin. This numbness improved after one week but she says it never completely resolved. Last year she noticed that she was forgetting things at work that she attributed to working long hours and not sleeping enough. She was otherwise healthy until three weeks ago when she developed a cold with sore throat, nasal congestion, and a mild cough. This resolved after 5 days. Three days ago, she felt mildly unsteady when she was going up the stairs in her house and felt very tired. On the morning of presentation to the emergency room she woke up with severe dizziness and difficulty walking.

Neurologic exam revealed an ataxic (wide, unsteady) gait and nystagmus (abnormal eye movements seen in a variety of neurological diseases, particularly involving the cerebellum). Routine chemistries and CBC, ECG, and CXR were all normal. She had a lumbar puncture; her cerebrospinal fluid was clear with 22 WBC/mm$^3$, all of which were lymphocytes. Levels of total CSF protein and glucose were normal. Further evaluation demonstrated an oligoclonal banding pattern in her CSF that was absent in the serum and an elevated IgG in the CSF. An MRI of the head showed multiple areas of inflammation scattered throughout the white matter (Fig. 1) and electrical studies showed slowing of conduction in central white matter pathways. A serological test for Lyme disease was negative. She was diagnosed with multiple sclerosis and was started on IV corticosteroids.

![Fig. 1. Serial T2-weighted MRI images of the brain of U.W. were taken at three month intervals. Note changing appearance of predominant right hemisphere lesion. Gray area surrounding lesion in middle image probably reflects edema. Intravenous administration of gadolinium, which leaks from blood vessels in recently inflamed tissue, can often enhance acute/active lesions.](image-url)
She gradually improved and was begun on weekly intramuscular injections of IFN-β.

**Questions for Case 23**

(1) What are oligoclonal bands? What do they tell us about the immunobiology of this patient’s illness?

(2) Many healthy individuals that are DR2-positive have T-cells in their peripheral blood that can respond to myelin basic protein peptide 81-103. Why are these T-cells not negatively selected in the thymus? Why are these individuals not sick if they have potentially autoreactive T-cells in their blood? How might a viral infection precipitate MS in a susceptible individual?

(3) Some of the lymphocytes in this patient’s CSF were shown to be CD4+ T-cells that responded to peptide 81-103 of myelin basic protein. How might the analysis of TCR usage and lymphokines secreted by these CNS MBP-reactive CD4+ T-cells differ from MBP-reactive CD4+ T cells derived from the peripheral blood?

(4) What is epitope spreading and how does it help explain the clinical course of MS?

(5) Two disease-modifying agents have been approved for the treatment of relapsing-remitting MS: IFN-β and Glatiramer acetate (formerly called Copolymer 1; trade name: Cop 1 or Copaxone). This compound, which is a random amino acid copolymer of tyrosine, glutamic acid, alanine and lysine, binds to HLA-DR2 (Class II) molecules and is thought to mimic the major antigenic peptide in MBP. *In vitro* studies have demonstrated that Copaxone induces the following:

   a- inhibition of MBP-induced proliferation of MBP-restricted T-cell clones
   b- induction of IL-4 secretion from CD4+ T-cells
   c- induction of TGF-β secretion from CD4+ T-cells

Explain how each of the above might be beneficial in MS.