Exacerbation of Susac Syndrome Retinopathy by Interferon Beta-1a

Susac syndrome features the triad of multiple branch retinal artery occlusions, hearing loss due to microinfarctions of the cochlea, and encephalopathy due to brain microangiopathy. Initial misdiagnosis as multiple sclerosis (MS) is not uncommon. Magnetic resonance imaging evidence of microinfarctions of the corpus callosum and multiple yellow retinal arterial wall plaques on fundus examination are helpful in differentiating this condition from demyelinating diseases.

We describe a patient initially diagnosed as having MS who, after treatment with interferon beta-1a, was found to have multiple branch retinal artery occlusions. After interferon beta-1a cessation, rapid improvement of his visual fields and fluorescein angiographic appearance suggested that the interferon beta-1a may have exacerbated the retinal findings of Susac syndrome.

Report of a Case. A 23-year-old white man experienced extremity numbness and paresthesia as well as headache. Magnetic resonance imaging showed periventricular lar white matter changes in the corpus callosum, which were attributed to demyelinating disease. One month later, he experienced a confusional episode. Three months later, he noted peripheral visual field loss in the left eye. Owing to concern for optic neuritis related to MS, he was treated with a short course of oral prednisone and began subcutaneous interferon beta-1a treatment. His visual symptoms improved, but 3 months later he developed peripheral vision loss in the right eye, resolving completely after a 1-week course of prednisone. Ten months after the initial visit, he experienced bilateral sequential hearing loss. Repeated magnetic resonance imaging findings of the brain were unchanged.

He had neuro-ophthalmic and retinal evaluations 15 months after beginning interferon beta-1a treatment, noting little improvement in his symptoms. Visual acuity was 20/20 OU. Funduscopic examination revealed punctate retinal hemorrhages along the superotemporal arcade, subtle sclerotic-appearing retinal arterioles, and yellow retinal arterial wall plaques (Figure 1A). Humphrey visual field showed bilateral nasal defects with a mean deviation of −7.87 dB OD and −12.0 dB OS. Fluorescein angiography showed peripheral retinal artery occlusions and retinal arterial wall hyperfluorescence (Figure 1C and D). Review of the prior magnetic resonance imaging findings showed small round microinfarctions in the corpus callosum (Figure 2). Formal audiology evaluation showed borderline mild sensorineural hearing loss in the right ear with excellent speech discrimination and moderate sensorineural hearing loss in the left ear with good speech discrimination. Impedance testing suggested normal pressure and good compliance in both ears. These findings were highly suggestive of Susac syndrome, and interferon beta-1a treatment was discontinued.

Two weeks after interferon beta-1a cessation, repeated fluorescein angiography showed remarkable improvement in the retinal arterial wall hyperfluorescence (Figure 1G and H). Continued improvement in the areas of peripheral retinal ischemia was observed at the 3-month follow-up, and functional improvement by static perimetry was also observed with mean deviations of −1.67 dB OD and −6.60 dB OS.

Table. Summary of the Endogenous Salmonella Endophthalmitis Cases in the Literature

<table>
<thead>
<tr>
<th>Source</th>
<th>Reported Risk Factors</th>
<th>Salmonella Species</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corman et al, 1979</td>
<td>Aged 7 wk, pneumonia</td>
<td>S enteritidis</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Weinstein et al, 1982</td>
<td>Aged 48 y, chronic lymphocytic leukemia</td>
<td>S typhimurium</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Shohet et al, 1983</td>
<td>Aged 1 y</td>
<td>S typhimurium</td>
<td>Not reported</td>
</tr>
<tr>
<td>Appel et al, 1986</td>
<td>Aged 1 y</td>
<td>S typhimurium</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kestelyn et al, 1986</td>
<td>Aged 11 mo, malaria</td>
<td>S typhimurium</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Carvalho et al, 1990</td>
<td>Aged 55 y, rheumatoid arthritis, receiving immunosuppressive agents and corticosteroids</td>
<td>S arizonae</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Senth et al, 1993</td>
<td>Aged 4 mo, prematurity, presumed retinopathy of prematurity</td>
<td>Salmonella serotype B</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Suvarnamani et al, 1995</td>
<td>Aged 2 mo</td>
<td>S typhimurium</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Yu et al, 2002</td>
<td>Aged 3 mo</td>
<td>S enteritidis</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yodprom et al, 2007</td>
<td>Aged 54 y, HIV positive</td>
<td>S choleraesuis</td>
<td>NLP</td>
</tr>
<tr>
<td>Arora et al, 2008</td>
<td>Aged 32 y, no risk factors</td>
<td>S typhi</td>
<td>NLP</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NLP, no light perception.

11. Kestelyn et al, 1986 Aged 11 mo, malaria
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20. Corman et al, 1979 Aged 7 wk, pneumonia
21. Shohet I, Davidson S, Boichis H, Rubinstein E. Endogenous endophthalmitis due to brain microangiopathy.1 Initial misdiagnosis as multiple sclerosis (MS) is not uncommon. Magnetic resonance imaging evidence of microinfarctions of the corpus callosum and multiple yellow retinal arterial wall plaques on fundus examination are helpful in differentiating this condition from demyelinating diseases.
22. We describe a patient initially diagnosed as having MS who, after treatment with interferon beta-1a, was found to have multiple branch retinal artery occlusions. After interferon beta-1a cessation, rapid improvement of his visual fields and fluorescein angiographic appearance suggested that the interferon beta-1a may have exacerbated the retinal findings of Susac syndrome.
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25. Two weeks after interferon beta-1a cessation, repeated fluorescein angiography showed remarkable improvement in the retinal arterial wall hyperfluorescence (Figure 1G and H). Continued improvement in the areas of peripheral retinal ischemia was observed at the 3-month follow-up, and functional improvement by static perimetry was also observed with mean deviations of −1.67 dB OD and −6.60 dB OS.
Our patient was initially misdiagnosed as having MS and treated with interferon beta-1a. Once his diagnosis of Susac syndrome was established and the interferon beta-1a treatment was stopped, he experienced rapid and dramatic improvement of the retinopathy, suggesting that the interferon beta-1a may have worsened the ocular manifestations of Susac syndrome. Interferon retinopathy is a well-known condition, usually manifesting with cotton-wool spots and retinal hemorrhages that resolve with medication cessation. Retinopathy developing specifically following subcutaneous interferon beta-1a treatment has been rarely reported. The multiple peripheral branch retinal artery occlusions and areas of retinal arteriolar wall hyperfluorescence in our patient are classic findings in Susac syndrome but would be very atypical manifestations of interferon retinopathy alone.

It is arguable that the angiographic findings and their resolution in our patient are consistent with the natural history of Susac syndrome, especially considering that the patient’s visual symptoms began prior to his beginning treatment with interferon beta-1a. However, the temporal association of interferon beta-1a treatment cessation with the rapid resolution of the peripheral retinal ischemic process and improved visual fields suggests a causal and reversible association. Concurrent interferon beta-1a treatment for presumed MS may cause retinal vascular changes that may exacerbate or mimic Susac syndrome.

**Comment**. Our patient was initially misdiagnosed as having MS and treated with interferon beta-1a. Once his diagnosis of Susac syndrome was established and the interferon beta-1a treatment was stopped, he experienced rapid and dramatic improvement of the retinopathy, suggesting that the interferon beta-1a may have worsened the ocular manifestations of Susac syndrome. Interferon retinopathy is a well-known condition, usually manifesting with cotton-wool spots and retinal hemorrhages that resolve with medication cessation. Retinopathy developing specifically following subcutaneous interferon beta-1a treatment has been rarely reported. The multiple peripheral branch retinal artery occlusions and areas of retinal arteriolar wall hyperfluorescence in our patient are classic findings in Susac syndrome but would be very atypical manifestations of interferon retinopathy alone.

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**Figure 1.** Color fundus photographs and fluorescein angiograms. A, Color fundus photograph of the left eye shows yellow retinal arterial wall plaques. B, Higher magnification of the fundus photograph of the left eye shows yellow retinal arterial wall plaques (arrows). C, Fluorescein angiogram of the posterior pole of the left eye shows multiple areas of retinal arterial wall hyperfluorescence. D, Fluorescein angiogram of the nasal periphery shows areas of pruned retinal arterioles involving the nasal retinal periphery. E, Repeated color fundus photograph of the left eye 15 days after cessation of interferon beta-1a treatment shows resolution of the yellow retinal arterial wall plaques. F, Higher magnification of the color fundus photograph of the left eye shows resolution of the yellow retinal arterial wall plaques. Repeated fluorescein angiograms of the left eye 15 days after cessation of interferon beta-1a treatment show complete resolution of all areas of retinal arterial wall hyperfluorescence (G) and reestablishment of arteriolar perfusion in the nasal retinal periphery (H).

**Figure 2.** Sagittal T1-weighted magnetic resonance imaging scan shows small round microinfarctions of the corpus callosum (arrows), consistent with the diagnosis of Susac syndrome.

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COMMENTS AND OPINIONS

Systemic and Ocular Risks Associated With Therapies for Macular Degeneration: Clarification vs Confusion

Understanding the possible safety issues related to anti-vascular endothelial growth factor agents as used in ophthalmology is important, and Curtis et al. attempted to clarify these issues. Independent of the risks inherent in intravitreous injections themselves (endophthalmitis, cataract) or concerns about just how a batch of bevacizumab-filled syringes was compounded, systemic safety questions still linger. Apparent higher incidences of cerebrovascular accident and myocardial infarction (MI) were intermittently signaled during the ANCHOR and SAILOR clinical trials of ranibizumab. Although the overall significance was difficult to interpret, 2 subsequent independent meta-analyses of these and other studies continue to raise questions of the potential stroke risks of intravitreous ranibizumab, particularly in patients who had already had such an event. Even if such risks are small, there is physiological plausibility for having such concerns, especially when using a pan-vascular endothelial growth factor inhibitor (bevacizumab and ranibizumab).

Curtis et al. attempted to understand the systemic adverse effects of different age-related macular degeneration (AMD) therapies. They conducted a retrospective cohort study of patients with AMD treated between 2005 and 2007. They made a rather sweeping conclusion that ranibizumab and bevacizumab were not associated with increased risks in mortality, MI, bleeding, and stroke compared with photodynamic therapy (PDT) and pegaptanib use. Some have interpreted their findings as meaning that all of these drugs are equivalent with respect to risk, independent of any other plausible explanations.

Their observational study retrospectively compared the apparent safety issues found after pegaptanib, ranibizumab, and bevacizumab treatment and compared them with those occurring in a group receiving PDT. They used Medicare procedure and medicine reimbursement codes to categorize the particular therapy that was given to each subject. They also censored data from patients who had received more than 1 therapy within a given index period, although switching from one therapy to another is commonly done in the management of wet AMD. Indeed, they indicated that 32.6% of the subjects receiving PDT and the majority of subjects in the pegaptanib group (55.3%) were switched to a different therapy during their follow-up period. As if this is not confounding enough, the follow-up interval after the first treatment was rendered was apparently quite variable, with the mean follow-up of the switched subjects being less than 1 year (146 days). When subjects were switched to another drug, the authors indicated that the data were censored, but it is not clear how the censored data were handled. From the tables, it appears that they were not excluded but were simply assigned to the original treatment group as if that was all they had ever received. Furthermore, the authors apparently did not control for the number of injections given, but more extensive exposure to a drug should influence the hazard ratios. How the authors handled these numerous potential statistical challenges is not at all clear as their Methods section is devoid of much needed detail.

In addition to these issues, potential exaggeration or minimization of the Medicare coding algorithm creates statistical challenges. The authors noted the lack of significant differences when comparing mortality, MI, bleeding, and stroke rates among the treatment groups until they made adjustments with coding algorithms for comorbid conditions. Several key variables were not considered. The standardization of treatment groups in terms of severity of comorbid conditions was never reported. For example, under the Medicare coding algorithm used, a patient with AMD who recently had a “new” MI is compared with a patient with AMD with a history of recurrent MI who then has a “new” MI within the index dates. This comparison could attenuate the true risk within a treatment group.

Also, we must assume in their study that proper International Classification of Diseases, Ninth Revision coding was used. Errors may occur not only in the given comorbidity diagnoses but also in whether the proper code was assigned by the medical examiner and especially the temporal sequence of such coding. Of further concern in this study is selection bias. Looking at the figure, one can see that most of the PDT sessions and pegaptanib treatments were administered before January 1, 2006, but bevacizumab and ranibizumab were generally given much later. According to Chen et al., substantial declines in hospitalization rates were reported in Medicare patients during that same period. From 2002 to 2007, the acute MI hospitalization rate declined 23.4%. After adjustment for age, sex, and race, the average decline per year was 5.8%. Without making similar adjustments, the implicit conclusions stated by Curtis and colleagues may be biased and invalid.

Finally, the authors mentioned the question of socioeconomic disparity among the treatment groups. The concern that people with higher standards of living receive better treatment, are more compliant, and are better suited to pay for expensive therapies such as ranibizumab complicates interpretation of their study. The authors address these issues partially by censoring the patient data to patients who received either ranibizumab or bevacizumab at “a medical practice that used a single drug exclusively.” They did not, however, address this potential bias regarding pegaptanib or PDT use.