Ocular Findings in a Patient With Castleman's Disease Before and After Treatment With Immunosuppression and Plasmapheresis

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ABSTRACT
A 12-year-old girl with a 3-month history of epistaxis and Castleman’s disease presented with blurred vision in both eyes for 2 weeks. Indirect ophthalmoscopy revealed a blurred optic disc margin, venous engorgement and tortuosity, intraretinal hemorrhages and cotton wool spots, and serous detachment of the neurosensory retina in the posterior pole of each eye. Fluorescein angiography and laboratory tests revealed abnormalities consistent with the clinical examination. Six months following institution of immunosuppressive treatment, cryoglobulin levels decreased and visual acuity and funduscopic abnormalities were markedly improved. However, a few microaneurysms, retinal hemorrhages, and venous engorgement and tortuosity persisted. One month after the cessation of immuno suppressive treatment, symptoms related to the hyperviscosity syndrome recurred and the patient was treated with one session of plasmapheresis. One month after the plasmapheresis, the patient’s symptoms resolved, laboratory values were normal, visual acuity was 20/15 in both eyes, and the funduscopic examination of each eye was unremarkable. [Ophthalmic Surg Lasers Imaging 2010;41:e1-e4.]

INTRODUCTION
Castleman’s disease, also called angiofollicular lymph node hyperplasia, is a rare atypical lymphoproliferative disorder characterized by massive growth of lymphoid tissue. It has two clinical forms: the localized form and the multicentric form. The diagnosis is based on clinical findings supported by pathological features and the disease may be associated with several autoimmune features, including cryoglobulinemia, positive antinuclear antibodies, and hypergammaglobulinemia.

Cryoglobulinemias are characterized by elevated concentrations of cryoglobulins in the serum and may lead to hyperviscosity syndrome. Cryoglobulins are immunoglobulins or immunoglobulin-containing complexes that precipitate spontaneously and form a gel at low temperatures. They become soluble again when the temperature rises. There are three major types of cryoglobulins. Type I is a single monoclonal immunoglobulin with only one class or subclass of heavy or light chain that is related to lymphoproliferative diseases and could cause hyperviscosity syndrome. Type...
II comprises mixed cryoglobulins with a monoclonal component that acts as an antibody against polyclonal IgG. Type III includes mixed polyclonal cryoglobulins, composed of one or more classes of polyclonal immunoglobulins. Types II and III are observed most frequently in patients with hepatitis B or C virus or autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis).

Many ophthalmologic findings have been described in patients with hyperviscosity syndrome and cryoglobulinemia, including dilated and tortuous retinal and/or conjunctival vessels, microaneurysms, cotton wool spots, intraretinal hemorrhages (dot-blot or flame-shaped), serous detachment of the neurosensory retina, pars plana cysts, and optic disc swelling. Besides hyperviscosity, the ocular findings in Castleman’s disease may also be related to lymphoproliferative tissue development in the leptomeninges, orbit, optic disc, and choroid, and consequently may lead to ocular signs and symptoms such as papilledema, transient

Figure. Color fundus photographs before treatment (A and B) showing marked venous tortuosity, dot-blot hemorrhages, and whitening of the retina in the posterior pole secondary to serous retinal detachment. After immunosuppressive treatment and plasmapheresis, complete resolution of funduscopic abnormalities was observed (C and D).
visual loss, hemianopia, and nystagmus and may be a rare cause of pseudotumor cerebri.\(^7\)

The purpose of the current report is to describe the funduscopic findings before and after treatment with immunosuppression and plasmapheresis in a patient with Castleman’s disease.

**CASE REPORT**

A 12-year-old girl with a 3-month history of episcleritis and Castleman’s disease presented with blurred vision in both eyes for 2 weeks. Best-corrected visual acuity was 20/25 in each eye and there was no relative afferent pupillary defect. Slit-lamp examination was unremarkable. Intraocular pressure was 17 mm Hg in each eye. Indirect ophthalmoscopy revealed a blurred optic disc margin, venous engorgement and tortuosity, intraretinal dot-blots hemorrhages and cotton wool spots in the posterior pole, and serous detachment of the neurosensory retina in the macula of each eye (Figure). Fluorescein angiography revealed no vessel leakage, but a few microaneurysms were observed. Laboratory tests at that time confirmed abnormally high levels of cryoglobulins (IgG = 12 mg/mL), positive antinuclear antibodies, speckled pattern, and a serum viscosity of 3.8 (normal, 1.5 to 2.0 centipoise) (Table).

The patient also had an enlarged thymus demonstrated by magnetic resonance imaging and the diagnosis of thymoma was made. Histological analysis of the patient’s thymus showed monoclonal plasma cell infiltration (10% to 20% plasma cells), with polyclonal expression of lambda light chains by immunohistochemical staining, consistent with Castleman’s disease, plasma cell variant, unicentric form.

The following immunosuppressive treatment was instituted for 6 months: chloroquine (125 mg/d), methylprednisolone (125 mg/d), acetylsalicylic acid (100 mg/d), and a monthly pulse of cyclophosphamide (500 mg/m\(^2\) of body surface area). Six months following institution of immunosuppressive treatment, cryoglobulin levels decreased (Table), funduscopic abnormalities were markedly improved, and visual acuity was 20/15 in each eye. However, a few microaneurysms and retinal hemorrhages, as well as mild venous engorgement and tortuosity, persisted.

One month after the cessation of immunosuppressive treatment, symptoms related to the hyperviscosity syndrome such as weakness, dyspnea, and vertigo recurred and the patient was treated with one session of plasmapheresis. One month after plasmapheresis, the patient’s symptoms resolved and laboratory values were found to be normal (Table). Ophthalmoscopic evaluation at this time showed a visual acuity of 20/15.

<table>
<thead>
<tr>
<th>Laboratory Test*</th>
<th>Before Treatment</th>
<th>After Immunosuppressive Treatment (6 Mo)</th>
<th>After Plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g%)</td>
<td>13.60</td>
<td>9.20</td>
<td>7.3</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3</td>
<td>3.60</td>
<td>4.2</td>
</tr>
<tr>
<td>Gammaglobulin</td>
<td>10.1</td>
<td>5.40</td>
<td>1.6</td>
</tr>
<tr>
<td>Immunoglobulins (serum) (g%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IgA</td>
<td>0.80</td>
<td>0.44</td>
<td>0.13</td>
</tr>
<tr>
<td>IgM</td>
<td>0.60</td>
<td>0.32</td>
<td>0.22</td>
</tr>
<tr>
<td>IgG</td>
<td>8.90</td>
<td>3.89</td>
<td>1.1</td>
</tr>
<tr>
<td>Cryoglobulins (serum) (mg%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>26</td>
<td>&lt; 5.8</td>
<td>&lt; 5.8</td>
</tr>
<tr>
<td>IgM</td>
<td>28</td>
<td>7.4</td>
<td>&lt; 5.8</td>
</tr>
<tr>
<td>IgG</td>
<td>673</td>
<td>284.0</td>
<td>39</td>
</tr>
<tr>
<td>Serum viscosity (centipoise)</td>
<td>5.5</td>
<td>3.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Normal ranges: Total protein = 7 to 8 g/dL; albumin = 3.5 to 4.0 g/dL; gammaglobulin = 1.2 to 1.8 g/dL; IgG = 0.8 to 1.7 g/dL; IgM = 0.05 to 0.335 g/dL; IgA = 0.078 to 0.367 g/dL; cryoglobulin = < 5.8 mg/dL (IgG, IgM, IgA).
and a normal fundus appearance in each eye (Figure). Plasmapheresis was repeated two times based on clinical symptom recurrences 3 and 5 months after the first session. Four months after the last plasmapheresis session, the ocular fundus still had a normal appearance and visual acuity was 20/15 in each eye.

**DISCUSSION**

Our patient presented with mild blurring of vision and funduscopic abnormalities, including serous detachment of the neurosensory macular retina. An osmotic gradient created by deposition of abnormal immunoglobulins has been reported as a possible etiology of the serous detachment. An overcharged vascular system with elevated intraluminal pressure secondary to impaired venous outflow may also contribute to serous detachment, but fluorescein angiography failed to show any leakage before or after treatment. Angiographically silent macular detachment has been described as the hallmark for macular detachment due to immunoglobulinopathy; hyperviscous material (gammaglobulin) in the space overlying the retinal pigment epithelium may block fluorescein leakage in these cases. Hyperviscosity and expanded plasma volume play a major role in vessel dilation. Luxenburg and Mausolf showed that venous diameter is directly related to relative serum viscosity, which is consistent with the evolution of funduscopic changes in our patient: venules progressively returned to normal caliber after treatment.

Treatment for patients with Castleman’s disease associated with hyperviscosity consists of systemic corticosteroids or immunomodulatory therapy to decrease the production of abnormal serum proteins or plasmapheresis to reduce the concentration of these abnormal proteins. Our patient was treated initially with methylprednisolone and cyclophosphamide, which resulted in a partial clinical response. Plasmapheresis resulted in resolution of the systemic and opthalmologic abnormalities, as has been reported for other diseases associated with blood hyperviscosity such as multiple myeloma and Waldenstrom’s macroglobulinemia. Finally, it is important to point out that our patient had no ocular findings of lymphoproliferative tissue development in the orbit, optic disc, or choroid; there was no exophthalmos and no infiltration of the choroid or retinal pigment epithelium. For patients with orbital or intraocular lymphoproliferative disease, other therapeutic modalities such as surgical resection, radiotherapy, and other chemotherapeutic agents should be considered.

**REFERENCES**