PARAPROTEINEMIAS ASSOCIATED WITH SEROUS DETACHMENTS OF THE RETINAL PIGMENT EPITHELIUM AND NEUROSENSORY RETINA

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Background: Serous retinal and retinal pigment epithelial detachments resembling central serous chorioretinopathy developed in three patients who had paraproteinemias.

Methods: The patients in this study were examined at two institutions, and their charts, photographs, and fluorescein angiograms were reviewed by the authors. Two patients had cryoglobulinemia and one had IgA, IgM benign gammopathy.

Results: These patients had decreased central visual acuity and metamorphopsia at the initial examination. All three patients were women. Two patients were taking systemic corticosteroids in tapering doses at the time of the initial examination. The multiple serous retinal pigment epithelial and retinal detachments were unilateral in one patient and bilateral in two patients. Two patients were treated with laser photocoagulation because of chronic visual loss and foveal detachments. At the most recent examination, each patient had visual acuity of 20/30 or better in both eyes and complete resolution of subretinal fluid.

Conclusions: Patients with paraproteinemia may develop multiple serous detachments of the retinal pigment epithelium and of the neurosensory retina. The chorioretinopathy in these patients may have been related to their paraproteinemia, type A personality, corticosteroid use, or a combination of these factors. The final visual acuity in these three patients was good.

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Idiopathic central serous chorioretinopathy typically affects men (90% of cases) who are 20-45 years of age.1 The prognosis is excellent; 95% of patients regain final visual acuity of 20/30 or better, and the disorder recurs in only 20-30% of patients.1,2 Stress and a type A personality often are associated with idiopathic central serous chorioretinopathy.3 Serous retinal and retinal pigment epithelial detachments also have been reported in association with several systemic disorders.4-20 The pathogenesis of the serous detachments of the retinal pigment epithelium and neurosensory retina in these previous reports may have been related to stress, corticosteroid use, systemic hypertension, disturbances in choroidal circulation, or a combination of these factors.4-20

We report the first series of patients with serous retinal and retinal pigment epithelial detachments that resemble central serous chorioretinopathy and that are associated with paraproteinemias. Two of these patients had cryoglobulinemia, and one had a benign IgA, IgM gammopathy. We also review
potential causes of serous pigment epithelial and neurosensory retinal detachments in these patients by focusing on protein-driven fluid shifts in the eye.

Case 1

A 41-year-old woman was evaluated for decreased visual acuity in the left eye that had lasted 1 week. At age 34, the patient first experienced joint swelling and pain. She was diagnosed with Sjögren's syndrome and type II cryoglobulinemia. She had an IgM kappa peak and a positive rheumatoid factor. She was treated intermittently with prednisone, imuran, and other chemotherapeutic agents. At age 38, she was admitted to the hospital with leg ulcers and leg pain, which prevented her from walking. She was treated with multiple sessions of plasmapheresis, which reduced her cryoglobulin level from 97% to 10%. She continued to have recurrent purpuric rashes and anemia that required 3 months of chemotherapy each year. A salivary gland biopsy that was done when the patient was 40 years of age showed a mild lymphatic infiltrate consistent with Sjögren's syndrome.

Three months before she experienced blurred vision, the patient's cryoglobulin level began to rise. She was given an increased dose of prednisone, and treatment with imuran was started. Her prednisone dose had been lowered to 10 mg per day when she experienced decreased visual acuity. Her visual acuity was 20/20 in the right eye with plano correction and 20/25 in the left eye with a +1.25 diptor correction. Her blood pressure was 135/75 mmHg. A slit-lamp examination revealed extensive rose bengal staining of the conjunctiva and cornea in the interpalpebral fissure. An examination of the fundus showed a serous macular detachment, which extended from arcade to arcade in the left eye. A fluorescein angiogram of the left eye confirmed the presence of multiple pigment epithelial detachments, four of which leaked fluorescein into the subretinal space (Figures 1 and 2).

Three months later, the patient's visual acuity had returned to 20/25 in the left eye without correction, but she continued to experience fluctuating visual acuity. Her subretinal fluid had resolved, but she still had a small area of juxtafoveal pigment epithelial detachment. Two months later, the pigment epithelial detachment had resolved, leaving a small area of juxtafoveal pigment epithelial hypopigmentation. She still had visual acuity of 20/25 in her left eye at the most recent follow-up examination (9 months after initial examination); the right eye has remained unaffected.

Case 2

A 60-year-old woman had a 6-month history of blurred vision in both eyes. Ten months before her initial examination, she developed polyarticular arthritis, a rash, low grade fever, and headache. The results of an extensive laboratory evaluation, which included antinuclear antibody, SS-A antibody, SS-B antibody, complement, prothrombin time, activated prothrombin time, renal function tests, hepatitis B, and liver function tests, were unremarkable, except for a mixed cryoglobulinemia with no monoclonal spike (type III). The patient experienced a rash and itching when she was exposed to cold. The patient's systemic problems responded dramatically to corticosteroid therapy.

At the time of her examination, she had blurred vision in both eyes. She was on a tapering dose of prednisone 15 mg daily. Her visual acuity was 20/40 in both eyes. Her blood pressure was 145/90 mmHg. Amsler grid revealed multiple paracentral scotomas and central metamorphopsia in both eyes. An anterior segment examination was unremarkable. An examination of the right fundus showed a serous superotemporal macular detachment with subretinal fibrin, and a pigment epithelial detachment just above the area of fixation. An examination of the left fundus showed a pigment epithelial detachment temporal to the fovea with a superior macular detachment and subfoveal fibrin. There were choroidal folds in both eyes. A b-scan echographic examination showed no choroidal thickening or posterior scleritis.

Fluorescein angiography of the right eye showed a pigment epithelial detachment in the superonasal portion of the macula with leakage on its superonasal border (Figure 3). The left eye had pigment epithelial detachment with fluorescein leakage at the nasal edge of the fovea and in the temporal macula (Figure 4). There were choroidal folds in the superior mid-periphery of both eyes.

One week after initial examination, she underwent laser photocoagulation in the right eye and a subtenon's capsule corticosteroid injection in the left eye to manage her chronic symptoms and the bilaterality of her visual loss. One month later, the serous retinal detachment in the right eye was resolved completely. The left eye had persistent subfoveal fluid that required laser
Fig. 3. Case 2. Fluorescein angiogram of the right eye shows suprornasal pigment epithelial detachment with hypofluorescent leakage on the suprornasal border. Choroidal folds are also present.

Case 3

A 39-year-old woman with a type A personality had a 1-year history of benign mixed IgA and IgM gammopathy accompanied by a mixed neuropathy, including paresthesia in all four extremities and her tongue. Extensive evaluations for malignancy and collagen vascular disease repeated periodically over a 4-year period yielded negative results. The patient had severe osteoporosis and therefore was never treated with prednisone. She also had positive hepatitis B and A antibodies, but not surface antigen, which suggested that she had had previous exposure to the virus, but did not have a chronic infection.

At the time of her initial examination, she had a 4-month history of distortion in her right eye and a 3-month history of distortion in her left eye. Visual acuity was 20/15 in her right eye and 20/20 in the left; there was complete resolution of subretinal fluid in both eyes. The patient was not taking any systemic medications, and had no recurrent systemic symptoms.

Fig. 4. Case 2. Fluorescein angiogram of the left eye shows nasal and temporal pigment epithelial detachment. Note the pigment epithelial leakage in the nasal fovea and temporal macula. Choroidal folds are also present.

Fig. 5. Case 2. Fluorescein angiogram of the left eye. Visual acuity was 20/15. The pigment epithelial detachment superior to the fovea is leaking a minimal amount of fluorescein.

Six weeks later, she experienced central visual acuity loss and had laser treatment in her right eye by her referring ophthalmologist in Argentina. At the time of this laser treatment, the patient had been symptomatic in the right eye for 5 months. One week later, she had visual acuity of 20/70 in the right eye and 20/25 in the left. She had a serous macular detachment in the right eye and a retinal pigment epithelial detachment in the left eye inferior to the fovea. A fluorescein angiogram confirmed the presence of the pigment epithelial detachments in both eyes with minimal leakage of fluorescein (Figures 5 and 6).

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Two months later, the patient was experiencing worsening metamorphopsia in the left eye. Her visual acuity was 20/20 in the right eye and 20/30 in the left. She had subfoveal serous retinal detachment. Because of the chronic nature of her symptoms in the left eye, light argon laser photocoagulation of the retinal pigment epithelial detachment was performed. On examination 2 months later, metamorphopsia was still present. Visual acuity was 20/20 in both eyes. Fluorescein angiography revealed...
Fig. 6. Case 3. Fluorescein angiogram of the left eye. Visual acuity was 20/15. The two pigment epithelial detachments are temporal to the fovea and showed minimal leakage of fluorescein.

persistent leakage of fluorescein from the retinal pigment epithelial detachment in the left eye. This area then was treated again with argon laser.

Three years later she had recurrent metamorphopsia. Visual acuity was 20/20 in the right eye and 20/25 in the left. Fluorescein angiography showed fluid underneath the fovea and a new area of fluorescein leakage in her left eye. This new area of fluorescein leakage was managed with argon laser treatment. At her 1-year follow-up examination, she told the physician that she had difficulty reading. Her visual acuity was 20/20 in both eyes. She had no subretinal fluid.

Discussion

Serous retinal pigment epithelial detachments and neurosensory retinal detachments associated with paraproteinemias developed in these three patients. Illnesses in patients with paraproteinemias develop from problems that fall into four major categories: 1) autoantibody syndromes, such as cryoglobulins that bind other immunoglobulins and cold agglutinins that bind carbohydrates on the surface of red blood cells; 2) autoimmune disorders, such as peripheral neuropathy and bleeding disorders; 3) disorders related to hyperviscosity resulting from large amounts of circulating immunoglobulin; and 4) idiopathic syndromes resulting from unidentified products, such as systemic capillary leak syndrome, which leads to angioedema, hypotension, and sometimes death. Because paraproteinemias can cause alterations in capillary permeability and significant changes in plasma protein concentrations, they may have caused or contributed to the serous retinal and retinal pigment epithelial detachments in these three patients.

Serous retinal pigment epithelial detachments have been reported in association with pregnancy, systemic corticosteroid use, systemic lupus erythematosus, hemodialysis, organ transplantation, membranoproliferative glomerulonephritis, and endogenous hypercortisolism. Serous retinal pigment epithelial detachments sometimes are seen in patients with toxemia of pregnancy, severe hypertension, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, and Goodpasture's syndrome.

Serous retinal pigment epithelial and neurosensory retinal detachments occur when there is an abnormal collection of extravascular fluid within either the subretinal pigment epithelial or subretinal space. The above disorders, including paraproteinemias, may cause an abnormal excess of interstitial fluid by disturbing the delicate balance between intravascular and extravascular fluid.

There are two major forces that cause fluid shifts between capillaries and surrounding tissues. The capillary hydrostatic pressure, which is generally higher than the interstitial fluid pressure, tends to force fluid out of the capillaries. The plasma colloid osmotic pressure, which is caused by proteins, tends to draw interstitial fluid into the capillaries. In most tissues the small amount of protein that escapes from the capillaries is returned to the venous system by lymphatic vessels.

There are four ways that the regulation of intravascular and extravascular fluid volume in the eye differs from that in most organs. First, the eye does not have lymphatics. Proteins that leak from the choriocapillaris must leave the eye through perivascular channels, diffusion through the sclera, or through Schlemm's canal via the vitreous and aqueous humor. The importance of transscleral outflow of protein is exemplified by patients with uveal effusion who have thickened, abnormal sclera and who develop diffuse swelling of the choroid. Second, choroidal capillary pressure is maintained at a higher level than that of capillary pressure in most other organs. The high capillary pressure is necessary to overcome the high interstitial pressure within the eye that is caused by the intraocular pressure. High capillary pressure is accomplished by the abrupt branching of vessels leading into the capillaries and by the large diameter of choroidal capillaries. Third, the choroid has an unusually high protein content, and the capillaries in the submacular choroid have higher protein permeability than capillaries in the peripheral choroid. The high baseline protein content of the choroid may make it more sensitive to transient increases in interstitial protein.
Finally, the choroidal circulation is regulated by the autonomic nervous system and lacks autoregulation.\textsuperscript{25,27} This makes the choroidal vasculature less responsive to local alterations in capillary and interstitial hydrostatic pressure than other capillary beds. Increased capillary hydrostatic pressure or decreased plasma oncotic pressure can cause increased interstitial fluid, even in the presence of normal capillary permeability. Alterations in capillary permeability that allow excess proteins to leak out of capillaries also can cause tissue edema. Abnormal choriocapillaris permeability probably contributes to the development of retinal and retinal pigment epithelial detachments in many diseases. Autopsy studies and, more recently, indocyanine green angiography, have shown disruption of the choriocapillaris in patients with serous retinal and retinal pigment epithelial detachments. Autopsies of patients with Goodpasture’s syndrome, disseminated intravascular coagulopathy, and thrombotic thrombocytopenic purpura have shown occlusion of small vessels in the choroid, disruption of the choriocapillaris, overlying retinal pigment epithelial injury, and serous retinal detachments.\textsuperscript{14–16} Indocyanine green angiography of patients with idiopathic central serous chorioretinopathy has shown abnormal leakage of indocyanine green from the choroidal vasculature with overlying serous retinal pigment epithelial and retinal detachments.\textsuperscript{28}

Serous retinal pigment epithelial detachments can develop in patients when an abnormal accumulation of protein is present in the choroid that cannot breach the barrier formed by the intact retinal pigment epithelium. This protein draws fluid into the choroid and the subretinal pigment epithelial space. There are no barriers to protein diffusion within the choroid, and the normal sclera is permeable to proteins. Therefore, the choroid does not swell in response to excess protein because the protein and fluid do not build up enough oncotic force to overcome the normal interstitial adherence of the choroid. If the buildup of protein and fluid beneath the retinal pigment epithelium exerts enough force to separate the retinal pigment epithelium basement membrane from the rest of Bruch’s membrane, it can cause the formation of a protein-rich retinal pigment epithelial detachment (Figure 7). When the choriocapillaris leak heals, the protein-driven buildup of subretinal pigment epithelial fluid is no longer present. Because Bruch’s membrane is fenestrated and does not act as a barrier to protein diffusion, it is unlikely that a loculated pocket of fluid with high protein concentration persists in the subretinal pigment epithelial space. Nevertheless, the structural damage to Bruch’s membrane probably takes many months to heal during which the pigment epithelial barrier may persist.

If excess extravascular protein from a choriocapillaris leak traverses a damaged area of retinal pigment epithelium, it can create a serous retinal detachment. This probably occurs if the retinal pigment epithelial barrier has been damaged by hypoxia or by inflammation.

The serous detachments of the retinal pigment epithelium and neurosensory retina in the three patients in this report may have been related to idiopathic central serous chorioretinopathy. One patient had a type A personality, and all the patients were under stress because of the nature of their systemic illness.\textsuperscript{3} Two patients were taking systemic corticosteroids for their paraproteinemias at initial examination. Although both patients were on a tapering dose, the corticosteroids may have contributed to their ocular disease.\textsuperscript{5,8,11,17–20}

These patients’ paraproteinemias probably contributed to the development of their chorioretinopathy. Paraproteinemias can alter choroidal capillary permeability by causing small vessel occlusion and vasculitis of small and medium vessels.\textsuperscript{29–32} In addition, paraproteinemias may cause increased capillary permeability through poorly understood mechanisms.\textsuperscript{21} These patients had abnormally high concentrations of immunoglobulins in plasma. Because diffusion of proteins across the capillary wall is dependent on the concentration gradient, and these patients had abnormally high intravascular protein concentrations as a result of their paraproteinemia, excessive extravascular protein within their choroid probably developed after a region of capillaries was damaged. This excessive protein and fluid could cause retinal pigment epithelial detachments and, depending on the integrity of the overlying retinal pigment epithelium, also could cause serous retinal detachment.

Because protein flux across choroidal capillaries with abnormally high permeability is probably important in the pathophysiology of serous retinal pigment epithelial detachment and neurosensory retina detachments, treatments aimed at either decreasing capillary permeability or altering the Starling equilibrium may be effective. Laser therapy to areas of leakage probably works by destroying regions of abnormally high capillary permeability. Two patients in this study who experienced visual loss for more than 3 months were treated with laser and had prompt resolution of their symptoms. In addition to lasers, there are several medications that can help decrease capillary permeability. Most of these medi-
Fig. 7. Schematic diagram of a retinal pigment epithelial detachment. The broken lines show boundaries that are permeable to proteins (e.g., Sclera and the deep layers of Bruch’s membrane). The arrows denote the oncotic force caused by a capillary leaking protein. The retinal pigment epithelial detachment occurs because the proteins do not pass through the retinal pigment epithelium.

Circulations, such as mast cell stabilizers and antihistamines, are specific to certain disease processes. Interestingly, corticosteroids, which act in many ways to decrease vascular permeability, seem to worsen the retinal pigment epithelial and neurosensory retinal detachments in patients with idiopathic central serous chorioretinopathy. If more can be learned about the pathophysiology of increased capillary permeability in these disorders, rational treatment options could be tested.

In addition to decreasing capillary permeability, there are several ways to manipulate the Starling equilibrium. Certain cardiac and blood pressure-lowering medications, such as nitroglycerin, lower venous pressure and are particularly effective at decreasing capillary pressure, and therefore might be helpful in these patients. By increasing intravascular oncotic pressure with mannitol, one might be able to draw fluid away from a protein-rich extracellular space.

Because the eye does not have lymphatics, extravascular proteins must leave the choroid through perivascular channels or by diffusion through the sclera or into the vitreous. Laser therapy also may help excessive extravascular proteins gain access to the vitreous and exit the eye through the trabecular meshwork. If there were a surgical procedure that could facilitate the egress of proteins from the choroid through the sclera, such as scleral windows for choroidal effusions, such a procedure might help patients with chronic and severe retinal pigment epithelial detachments and serous retinal detachments. Further studies will help determine which strategies may be helpful for patients with chronic serous retinal pigment epithelial and retinal detachments that do not respond to laser therapy.

Key words: central serous retinopathy, laser, monoclonal gammopathy, paraproteinemia, pigment epithelial detachment, serous retinal detachment.

References