Paraproteinemic Maculopathy

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Purpose: Paraproteinemia relates to monoclonal gammopathy-producing pathologic antibodies with serous macular detachment being an uncommon ocular manifestation. We ascertained the clinical course of maculopathy in paraproteinemia and investigated the effect of various therapeutic methods on the resolution of subretinal deposits.

Design: Multicenter, retrospective, observational case series.

Participants: The records of patients with paraproteinemia with optical coherence tomography (OCT) documentation of serous macular detachment were reviewed.

Methods: Data collection included coexisting morbidity, rheology data (immunoglobulin level, hematocrit, and blood viscosity), clinical examination results, and OCT findings.

Main Outcome Measures: Best-corrected visual acuity (BCVA), height and basal area of the serous macular detachment, and systemic versus local therapies.

Results: A total of 33 cases were collected: 10 new and 23 previously reported in the literature. Diabetes was present in 7 patients, systemic hypertension in 9 patients, and anemia in 18. Mean initial immunoglobulin level was 6497 mg/dl, and mean serum viscosity was 5.5 centipoise (cP). Mean logarithm of the minimum angle of resolution initial vs. final BCVA was 0.55 (Snellen equivalent, 20/71) vs. 0.45 (20/56) in the right eye and 0.38 (20/48) vs. 0.50 (20/63) in the left eye. After mean follow-up of 7 months (range, 0-51 months). Systemic therapies included plasmapheresis (18), chemotherapy (30), blood transfusions (2), transplantation of progenitor hematopoietic cells (2), and oral rituximab (10). Immunoglobulin levels normalized in 8 patients and were unchanged in 1 after plasmapheresis, chemotherapy, or both. Ocular therapy in 8 patients included vitrectomy (1), laser photocoagulation (4), intravitreal bevacizumab (5), intravitreal triamcinolone (2), intravitreal dexamethasone implant (1), intravitreal rituximab (1), and sub-Tenon corticosteroid (1). The maculopathy resolved partially or completely in 17 patients and worsened or remained unchanged in 14 patients over median follow-up of 7 months. Maculopathy was unilateral in 9 cases and occurred at a lower initial immunoglobulin level in diabetics. There was a positive correlation between area of the detachment and serum viscosity.

Conclusions: Paraproteinemic maculopathy can be unilateral. Decreasing the blood immunoglobulin level is the primary goal of therapy for paraproteinemic maculopathy, and this can be achieved by a systemic route. Coexisting diabetes facilitates leakage of immunoglobulins at lower levels than in nondiabetics. Ophthalmology 2014;121:1925-1932 © 2014 by the American Academy of Ophthalmology

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Paraproteinemia, or monoclonal gammopathy, is the presence of excessive amounts of a single monoclonal γ-globulin (or paraprotein) in the blood. Monoclonal paraproteins are detected in the sera of 1% of the general population. This is usually the result of an underlying immunoproliferative disorder that includes multiple myeloma (MM), immunocytoma, and Waldenström macroglobulinemia (WM). Waldenström macroglobulinemia is a non-Hodgkin’s B-cell lymphoplasmacytic lymphoma affecting 3.8 per 1 million people annually, approximately 2% of all hematologic malignancies, and involving the elderly with onset around 63 years of age. This monoclonal immunoglobulin M (IgM) paraproteinemia is characterized clinically by signs and symptoms of serum hyperviscosity and hemorrhagic tendency. Ocular manifestations of WM include venous stasis retinopathy, immunoprotein deposition in the cornea and pars plana, and IgM deposits in all layers of the retina. A rare peculiar serous macular detachment in paraproteinemia has been described. Herein, we review our case series and the literature to attempt to understand the causative factors involved in this maculopathy.

Methods
The institutional review board approved the retrospective analysis of data for this observational case series. The records of patients with paraproteinemia and macular pathologic features were reviewed. The following data were collected: Snellen best-corrected visual acuity (BCVA; translated into logarithm of the minimum angle of resolution [logMAR] units), immunoglobulin
level, hematocrit, blood viscosity, associated systemic and ocular comorbidities, and treatment methods and their effects as assessed on optical coherence tomography (OCT). Therapies included various combinations of plasmapheresis (plasma exchange), chemotherapy, intravitreal bevacizumab (off label), triamcinolone or rituximab (off label), and laser photocoagulation after informed consent was obtained.

We also collected from the literature cases of paraproteinemic maculopathy using Scopus, Google Scholar, and Medline searches through October 2013, searching for macula AND MM, WM, and paraproteinemia, including polyneuropathy organomegaly endocrinopathy M-protein and skin abnormalities syndrome and light-chain deposition disease. Hypertension is defined as a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more. Anemia is defined as hematocrit of less than 40% for males and less than 35% for females. Correlation was carried out using correlation coefficient-adjusted \( r^2 \), 1-way analysis of variance, and standardized \( \beta \) regression coefficients using SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY).

Area of the maculopathy and height were measured on fundus photography (reference being vertical disc diameter [DD]) and OCT (caliper tool; in older machines with no calipers, the macular retinal thickness was assumed at 300 \( \mu m \)), respectively. The horizontal and vertical diameters of the sensory detachment were measured, and the longest of the 2 measurements was taken as the area. Similarly, on OCT, the height of the sensory detachment was measured on the vertical and horizontal scans through the foveola, and the largest value was adopted for the height.

**Results**

The current retrospective series included 10 subjects (Table 1, available at www.aaojournal.org) comprising 7 men and 3 women. Five were white, 1 was Hispanic, and 4 were of unspecified race. The mean age was 59.8 years (range, 40—87 years). Systemic diseases included WM (n = 8), MM (n = 2), diabetes mellitus (n = 4), systemic hypertension (n = 2), and anemia (n = 6). The subretinal fluid under the fovea had a mean area of 2.4 DD for the right eye and 2.1 DD for left eye (range, 1—4 DD) in 17 eyes of 10 patients (Figs 1, 2, 3, and 4). The maculopathy was unilateral in 3 patients.

To perform statistical analyses, we combined the current series with the literature review of 23 cases (Table 1). These 33 cases included 21 men and 11 women; 11 were white, 3 were black, 2 were Asian, and 1 was Hispanic. The mean age was 59 years (range, 37—87 years). Waldenström macroglobulinemia was present in 20 patients, MM was present in 7 patients, benign gammopathy was present in 3 patients, light-chain deposition disease was present in 2 patients, and polyneuropathy organomegaly endocrinopathy M-protein and skin abnormalities syndrome was present in 1 patient. Diabetes mellitus was present in 7 patients, systemic hypertension was present in 9 patients, renal failure was present in 5 patients, anemia was present in 18 patients, and carotid stenosis and systemic lupus erythematosus each were present in 1 patient. Unilateral involvement occurred in 9 patients. Mean hematocrit was 28.6% (median, 29%; n = 14; range, 14.4%—40%). Mean serum viscosity was 5.5 centipoise (cP; median, 4.2 cP; n = 11; range, 2.5—9.1 cP; normal values, 1.5—1.9 cP). Mean initial immunoglobulin level was 6497 mg/dl (median, 5888 mg/dl; range, 306—14,000 mg/dl; n = 24; normal values, 820—2200 mg/dl). The mean diameter of the maculopathy was 2.0 DD (right eye, 2.0 DD [n = 27]; and left eye, 2.0 DD [n = 28]; range, 0.5—5 DD). Mean height of serous detachment was 435 \( \mu m \) in the right eye (range, 71—1167 \( \mu m \) [n = 16]) and 410 \( \mu m \) in the left eye (range, 50—1060 \( \mu m \) [n = 19]). Mean initial BCVA was 0.55 logMAR (Snellen equivalent, 20/71) in the right eye and 0.38 logMAR (Snellen equivalent, 20/48) in the left eye. Final BCVA was 0.45
Figure 2. After 6 weeks, (A, C) serous macular detachment with overlying cystoid macular edema was observed in the right eye, and (B, D) an increase in the subretinal fluid was observed in the left eye. Best-corrected visual acuity dropped to 20/60 in the right eye and 20/200 in the left eye.

Figure 3. After 3 monthly 2.5-mg/0.1-ml bevacizumab injections, (A, B) fundus photographs and (C, D) spectral-domain optical coherence tomography (SD OCT) images showed a mild reduction of both intraretinal and subretinal fluid in both eyes. The SD OCT images show refractory edema. Best-corrected visual acuity remained 20/60 in the right eye and 20/200 in the left eye. The SD OCT image from the right eye (C) shows unique stalactite-like projections of the outer retina.
logMAR (Snellen equivalent, 20/56) in the right eye and 0.50 logMAR (Snellen equivalent, 20/63) in the left eye (Table 1).

Regarding therapy for the 33 patients, plasmapheresis was administered in 18 patients, chemotherapy was administered in 30 patients, blood transfusions were administered in 2 patients, and transplant of progenitor hematopoietic cells was performed in 2 patients. Oral rituximab was used in 10 patients. Immunoglobulin levels normalized in 8 patients and were unchanged in 1 patient after plasmapheresis, chemotherapy, or both. Ocular therapy in 8 patients included vitrectomy in 1 patient, laser photocoagulation in 4 patients, intravitreal bevacizumab in 5 patients (Fig 3), intravitreal triamcinolone in 2 patients, intravitreal dexamethasone implant in 1 patient, intravitreal rituximab in 1 patient (Fig 3), and sub-Tenon corticosteroid in 1 patient (Table 1). The maculopathy resolved partially or completely in 17 patients and worsened or stayed unchanged in 14 patients over a median follow-up of 7 months (mean, 19 months; 2 patients had no follow-up). Immunoglobulins were unchanged in 1 patient and likewise for maculopathy after therapy in 1 case. Immunoglobulin decreased markedly, but maculopathy did not improve in 3 patients. Immunoglobulin decreased and maculopathy improved in 5 patients.

There was a strong positive correlation between level of immunoglobulin and serum viscosity ($P = 0.007$). No correlation was present between level of immunoglobulin and hematocrit, diabetes ($P = 0.10$), initial BCVA, area ($P = 0.33$ for the right eye and $P = 0.34$ for the left eye), and height of the macular detachment. There was no correlation between area of the detachment and presence of diabetes, age, or initial BCVA. There was a positive correlation between area of the detachment and serum viscosity ($P = 0.017$ for the right eye and $P = 0.022$ for the left eye). There was no correlation between initial BCVA and height or area of the macular detachment. Visual gain correlated with initial BCVA ($P = 0.001$ for the right eye and $P = 0.021$ for the left eye) and did not correlate with immunoglobulin level, serum viscosity, hematocrit, age, diabetes, or area or height of the detachment. Diabetics versus nondiabetics had the following mean values: age, 67.0 versus 56.7 years ($P = 0.04$); immunoglobulin level, of 4115 versus 7306 mg/dl ($P = 0.10$; normal values, 820–2200 mg/dl); area of macular detachment, 2.2 versus 2.0 DD in the right eye ($P = 0.43$) and 1.83 versus 1.98 DD in the left eye ($P = 0.40$); and hematocrit, 28.6% versus 28.8% ($P = 0.50$). Additional causes of leakage into the subretinal space included (1) disc edema in 1 patient (patient 32), (2) severe ischemic diabetic retinopathy in 1 patient (patient 10), (3) occlusive choroidal and retinal disease in 1 patient (hence failure of the retinal pigment epithelium [RPE] pump; patient 4), and (4) deep retinal leakage sites in 2 patients (2 sites in patient 8 and 1 site in patient 6), possibly related to outer retinal defects, as seen in patient 9. Of note is a peculiar finding of stalactite-like projections in the outer retina in macula of patient 9 (see “Case Report”; Fig 3C).

**Case Report**

A 47-year-old white man with no significant medical history was referred to our clinic for blurry vision in the left eye. Baseline BCVA was 20/20 in the right eye and 20/60 in the left eye. Slit-lamp biomicroscopy results were unremarkable, and intraocular pressure was 12 mmHg in the right eye and 14 mmHg in the left eye. Fundus examination showed mild venous dilation and tortuosity in both eyes and a serous macular detachment with yellow subretinal exudates in the left eye (Fig 1). Optical coherence tomography revealed bilateral cystoid macular edema and detachment of the neurosensory retina. Fluorescein angiography showed peripheral vaso-occlusive disease with significant capillary nonperfusion. Six weeks after initial presentation, BCVA...
decreased to 20/60 in the right eye and 20/200 in the left eye, and OCT showed neurosensory detachment with overlying cystoid macular edema and bilateral disruption of the outer retina (Fig 2). The patient’s blood pressure was 130/90 mmHg. Hyperviscosity syndrome was suspected, and blood tests revealed severe anemia (hemoglobin, 7.9 mg/dl; normal values, 13.5–17.5 mg/dl) and a total serum protein level of 19.2 mg/dl (normal values, 6.0–8.0 mg/dl), with elevated monoclonal IgM of 10 500 mg/dl (normal values, 45–153 mg/dl). Bone marrow biopsy showed massive lymphoplasmacytoid infiltration. A diagnosis of WM was made. Computed tomography of the abdomen showed multiple retroperitoneal lymphadenopathies (iliac and inguinal). Plasma- pheresis was performed, followed by 8 cycles of systemic polychemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and steroids and 2 cycles of cladribine. Systemic rituximab was not given until IgM levels decreased to less than 5.0 mg/dl because rituximab is associated with sudden increase in IgM levels and should be avoided in patients with hyperviscosity. Simultaneously, 3 monthly 2.5-mg/0.1-ml intravitreal bevacizumab injections were administered in both eyes. Best-corrected visual acuity remained 20/60 in the right eye and 20/200 in the left eye, and OCT demonstrated a slight bilateral decrease in neurosensory detachment (Fig 3). At that time, the IgM level dropped to 3925 mg/dl. Two months after the last intravitreal bevacizumab injection, 3 monthly intravitreal injections of rituximab (1 mg/0.1 ml) were administered in both eyes. Best-corrected visual acuity remained unchanged and OCT demonstrated a slight bilateral decrease in the amount of subretinal fluid (Fig 3). At that time, the IgM level dropped to 2943 mg/dl. After 2 years of follow-up, complete remission was not reached; BCVA was 20/60 in the right eye and 20/400 in the left eye, and OCT showed no significant improvement.

Discussion

Serous macular detachment is an uncommon ocular manifestation of paraproteinemia.2–27 The absence of angiographic leakage within the macular detachment does not support the theory of angiographic exudation from the retinal or choroidal vasculature. In a few cases, there was leakage in the deep retina (Table 1). Some investigators have focused on the presence of IgM in the subretinal space,11,12 suggesting that an increased osmotic gradient causes fluid accumulation under the retina. In support of this hypothesis, several histopathologic reports documented immunoglobulins in the subretinal space.11–13 High-molecular-weight immunoglobulins lead to an osmotic gradient. Because IgM antibodies are the largest antibodies found in the blood and the lymph fluid, they rarely accumulate in pericardial, peritoneal, and pleural effusions.28,29 Immunoglobulin M antibodies consist of a heavy chain, a light chain, and 5 base units with a molecular mass of 970 kDa in its pentamer form (molecular weight, 0.6–1 000 000 kDa). Because IgM antibodies are very large molecules and cannot diffuse well, they are found in the interstitium in extremely low quantities. When such large, positively charged IgM molecules are present in excess, they bind electrostatically to red cells, aggregating and forming rouleaux, with subsequent increase in the blood viscosity. As the IgM protein concentration in the serum increases, the blood viscosity increases exponentially. It is somewhat intriguing to explain how IgM antibodies reach the subretinal space (Fig 4). According to Klaassen et al,30 the central mechanism of the altered blood–retinal barrier results from the altered permeability of retinal endothelial cells caused by elevated levels of growth factors (such as vascular endothelial growth factor), cytokines, and loss of pericytes (as occurs in diabetes). Subsequently, both paracellular and transcellular transport across the retinal vascular wall increase via opening of the endothelial intercellular junctions and increase in endothelial caveolar transcellular transport. There is histologic evidence that the blood–neural barrier (which is similar to the blood–retinal barrier) is affected in paraproteinemia. Kanda et al31 reported the pathologic findings in a patient with sensorimotor neuropathy associated with WM and monoclonal IgM, particularly in relation to blood–nerve barrier defects. A sural nerve biopsy specimen revealed gaps between adjacent endothelial cells of small endoneurial vessels as well as the absence of some of the tight junctions between adjacent endothelial cells. Similarly, in a sural nerve biopsy from a patient with benign monoclonal IgM kappa gammopathy and sensory-motor demyelinating neuropathy, Lash et al32 found that many endoneurial capillaries were lined by fenestrated endothelium, indicating the breakdown of the normal blood–nerve barrier. The endoneurium contained large amounts of extracellular proteaceous material containing IgM kappa gamma globulin.

Brody et al33 suggested that macular exudative detachments from diabetic maculopathy can lead to increased leakage of immunoglobulins into the subretinal space. In a case with polyneuropathy organomegaly endocrinopathy M-protein and skin abnormalities syndrome, Okada et al3 proposed that the high vascular endothelial growth factor level probably induced the retinal microvascular hyperpermeability, leading to leakage of immunoglobulin in the subretinal space. The maculopathy resolved 1 month after hematopoietic surgery, when serum vascular endothelial growth factor level decreased in response to autologous peripheral blood stem cells. The sera of WM patients are known to be associated with increased levels of angiogenic cytokines, such as angiogenin, vascular endothelial growth factor, and basic fibroblast growth factor.34 In normal bone marrow, angiopoietin-1 consistently activates tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains-2 and stabilizes vessels by promoting interactions between endothelial cells and surrounding pericytes. On the contrary, during the malignant process in WM, increased angiopoietin-2 levels block tyrosine kinase with the immunoglobulin-like and epidermal growth factor-like domains-2 receptor and lead to vessel destabilization by loosening endothelial–periendothelial cell interactions and degrading the extracellular matrix. The primary source of angiopoietin-2 is endothelial cells because angiopoietin-2 is stored in vesicles known as Weibel-Palade bodies and is released rapidly in response to hyperglycemia and ischemia. Angiopoietin-2 seems to be an important mediator in the alteration of the blood–retinal barrier in diabetes and other retinal vascular disorders.30

Ashton35 as well as Foos and Allen36 were among the first to describe retinal and RPE detachment histologically in patients with MM. The subpigment epithelial fluid is derived from choroidal vessels. The platelets can no longer fulfill their normal function of maintenance of endothelium because they
become covered by paraprotein. Moreover, the hyperviscosity can cause stasis and hypoxia, leading to endothelium decompensation. There is secondary breakdown of the blood–retinal barrier, in addition to the RPE decompensation from the underlying deposit and hypoxia. Coexisting anemia, diabetes, and hypertension are additional risk factors for retinal vascular endothelial damage and ischemic injury, enhancing leakage and breakdown of the blood–retinal barrier. Dumas et al. explored the contribution of plasma viscosity and the endothelial cell monolayer to oxygen molecular transport processes using a fluorescence inhibition method. They found hypoxia induced by hyperviscosity plasmas from patients with WM to have increased intercellular adhesion molecule 1 expression on the surface of endothelial cells, which could be the cause of vascular disorders through the implication of polymorphonuclear neutrophils.

Baker et al. demonstrated complete disruption of the outer retina within the detachment and proposed that these focal outer retinal defects (Figs 2 and 3) slowly progress over time, eventually allowing a so-called track for intraretinal IgM. Our study was not aimed at estimating the presence of such outer retinal defects. A pathologic communication between the optic disc, the subarachnoid space, and the subretinal space was proposed by Feigl et al and Khan et al. Feigl et al found a finger-like extension to the optic disc from the macular detachment by indocyanine angiography and proposed the disc as the cause of the macular detachment, similar to optic pit maculopathy.

There is a lot of overlap between the pathogenesis of central serous retinopathy (CSR) and paraproteinemic maculopathy. Unilaterality of the maculopathy is one common finding in paraproteinemia and CSR, as found in the current series. In CSR, Printe and Flammer detected capillary or venous congestion after ischemia in 1 or more choroidal lobules, and this finding may be the reason for choroidal hyperpermeability. Nicholson et al. documented the presence of a thickened and engorged choroid in CSR by enhanced depth OCT and proposed that these hyperpermeable choroidal vessels produce increased tissue hydrostatic pressure, promoting the formation of RPE detachments, overwhelming the barrier function of the RPE, and leading to fluid accumulation between the retina and the RPE. Optical coherence tomography also may show an anatomic defect (microrip) in the RPE associated with fluid that is leaking into the subretinal space. Likewise, there is venous congestion in the choroid and retina in paraproteinemia, leading to choroidal ischemia and hyperpermeability, which leads to CSR (Fig 4). Zamir and Chowers reported a patient with paraproteinemia who had CSR in the right eye and branch retinal vein occlusion in the left eye, with normal maculae. Although CSR could be the primary cause of the ocular condition, one could argue that paraproteinemia could have induced a CSR-like condition, as previously discussed.

Early treatment is necessary to prevent irreversible visual loss, especially with the currently lengthened expected life span. Paraproteinemic maculopathy becomes symptomatic when IgM levels exceed 4000 mg/dl in diabetics and 7000 mg/dl in nondiabetics (Table 1) and serum viscosity exceeds 5.5 cP. Prompt referral to a hematologist or oncologist is necessary for systemic monitoring and treatment. The visual loss in paraproteinemic maculopathy may be similar to the visual loss in CSR, with proteinaceous subretinal fluid. Landa et al. found a correlation between the subfoveal thickness of the protein deposit layer and visual acuity at baseline in 38 patients with CSR. No such relation was found in our series, possibly because of the retrospective nature of the study and the small size of the study group.

Usually, no treatment is indicated for asymptomatic disease. Indications for initiating treatment include blood hyperviscosity and ocular disturbance. The cardinal therapies include plasmapheresis (for patients with symptomatic hyperviscosity), rituximab (anti-CD20 antibody, that is, genetically engineered human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes), and chemotherapy (purine nucleoside analogs, alkylating agents, thalidomide, and bortezomib). Plasmapheresis is very useful in reducing serum hyperviscosity and rapidly improving most ocular manifestations. According to Menke et al., plasmapheresis resulted in significant reductions in serum IgM (by 46.5%) and serum viscosity (by 44.7%), and venous stasis retinopathy improved in all patients after plasmapheresis. Paraproteinemia-related venous stasis retinopathy mimics a central retinal vein occlusion-like appearance (no thrombus) with normal retinal blood flow. In our review, the area of the macular detachment correlated with serum viscosity, and many eyes did not demonstrate resolution of the maculopathy despite improvement in both the serum viscosity and the venous stasis retinopathy. One possible reason could be the short follow-up in the current review; these immunoglobulins need a long time to resolve. Besides plasmapheresis, chemotherapy, especially with rituximab, remains the mainstay of therapy. Various intravitreal injections (bevacizumab, triamcinolone, rituximab) failed to show a definite benefit in the current series.

In conclusion, this case series, along with the literature review, provide further evidence of the direct correlation between IgM levels in the blood and the degree of subretinal fluid accumulation under the fovea in these patients. Clinical improvement clearly correlated with a decrease in serum IgM. Maculopathy of paraproteinemia can mimic diabetic retinopathy, adult vitelliform dystrophy, and CSR, especially in the many patients with diabetes. Unilateral localized macular detachment is noted commonly in patients with elevated serum IgM levels associated with WM. Paraproteinemic maculopathy often becomes symptomatic when IgM levels exceed 7000 mg/dl (4000 mg/dl in diabetics) and serum viscosity exceeds 5.5 cP. Therapy should be directed toward decreasing the serum immunoglobulin level and the serum viscosity.

References


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; cP = centipoise; CSR = central serous retinopathy; DD = disc diameter; IgM = immunoglobulin M; logMAR = logarithm of the minimum angle of resolution; MM = multiple myeloma; OCT = optical coherence tomography; RPE = retinal pigment epithelium; WM = Waldenström macroglobulinemia.

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