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.[1] 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.[2–10] 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 β 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 μm), 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 sub-retinal 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 μm in the right eye (range, 71−1167 μm [n = 16]) and 410 μm in the left eye (range, 50−1060 μm [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
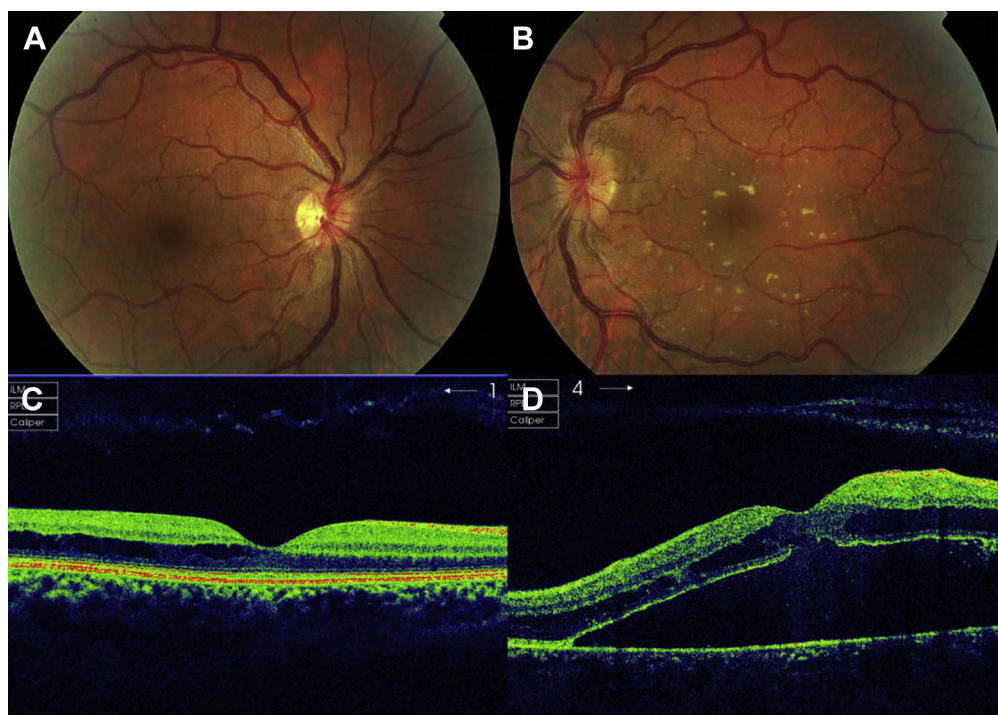
Figure 1. Fundus photographs of the (**A**) right eye and (**B**) left eye and (**C, D**) spectral-domain optical coherence tomography (OCT) images obtained at the initial visit. Venous dilation and tortuosity with peripheral capillary nonperfusion also was observed. The OCT scans show bilateral intraretinal edema and serous detachment of the neurosensory retina of the left eye. Best-corrected visual acuity was 20/20 in the right eye and 20/60 in the left eye.