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Maculopathy in a 52-Year-Old Patient With Diabetes

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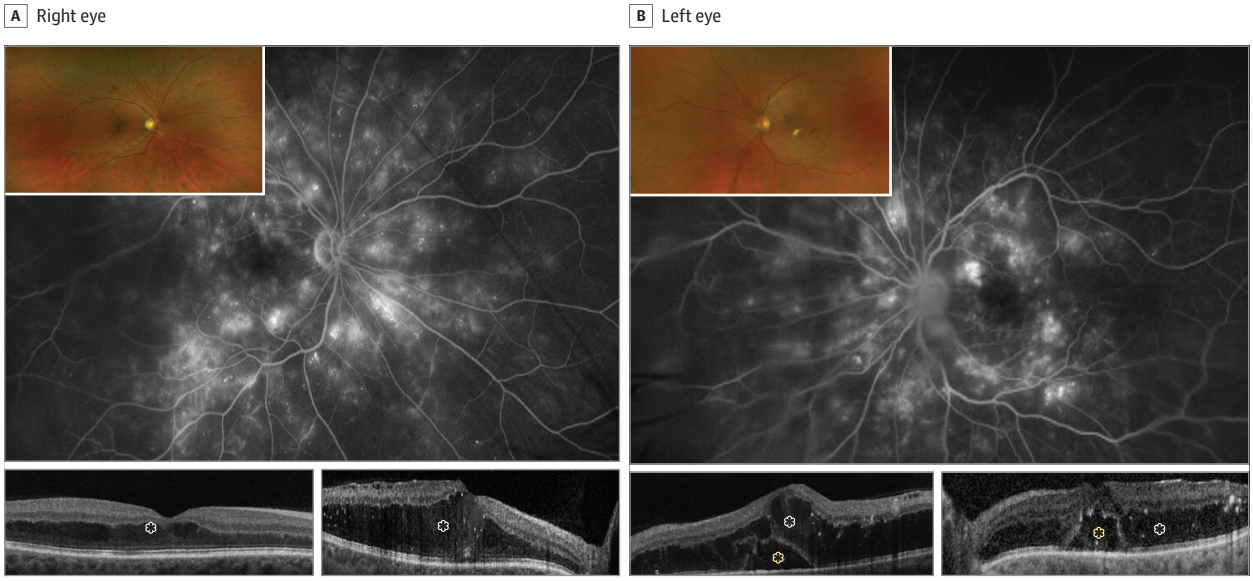

Figure. Widefield late-phase fluorescence angiography images of the right (A) and left (B) eye demonstrating areas of microaneurysms with mild leakage and absence of serious ischemia or capillary dropout. The top left insert in each panel shows the pseudocolor widefield fundus photographs demonstrating retinal hemorrhages, hard exudates, and microaneurysms in the right and left eye. The bottom inserts of each panel show macular optical coherence tomography imaging at presentation (bottom left) and after the patient received intravitreal injections (bottom right) over 6 months. The right eye demonstrates refractory retinal edema. The left eye demonstrates refractory retinal edema with neuroretinal detachment. The white asterisks indicate intraretinal edema; the yellow asterisks indicates neuroretinal detachment.

A 52-year-old woman presented with decreased vision in both eyes. She was diagnosed with type 2 diabetes 3 months before presentation, with a hemoglobin A_{1c} of 13%. At that time, she was given metformin and semaglutide for glucose control. Her visual acuity was 20/50 OD and 20/200 OS. Fundus examination revealed retinal hemorrhages, hard exudates, and microaneurysms bilaterally (**Figure**, A and B). Fluorescein angiography revealed microaneurysms with noncentral leakage in the posterior pole with absence of significant ischemia and capillary dropout. Optical coherence tomography scans from the same day showed retinal edema with intraretinal fluid accumulation in both eyes (central subfield thickness: 320 nm OD, 764 nm OS) with foveal detachment in the left eye. She was diagnosed with severe nonproliferative diabetic retinopathy with macular edema in both eyes. She received 2 and 3 injections of bevacizumab in the right and left eyes, respectively, followed by 2 injections of aflibercept in both eyes with minimal effect on the edema. Blood analysis showed the following values: hemoglobin, 10.4 g/dL; red blood cell count, 3.30×10^6/μL; white blood cell count, 10 470/μL; platelets, 197×10^3/μL; fasting blood glucose, 150 mg/dL (to convert to mmol/L, multiply by 0.0555); normal lipid profile; and creatinine, 1.2 mg/dL (to convert to μmol/L, multiply by 88.4). Hemoglobin A_{1c} decreased to 6.8% at 7 months after presentation.

WHAT WOULD YOU DO NEXT?

- **A.** Order serum protein electrophoresis
- **B.** Inject intravitreal dexamethasone
- **C.** Switch to ranibizumab, 0.3 mg
- **D.** Stop semaglutide

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Diagnosis

Immunoglobulin (Ig) A multiple myeloma with paraproteinemic maculopathy

What to Do Next

A. Order serum protein electrophoresis

Discussion

The lack of substantial central macular leakage on fluorescein angiography suggests that abnormal vascular permeability was not the major mechanism for the edema, and thus, injection of additional or alternative anti–vascular endothelial growth factor (VEGF) agents (C) or intravitreal corticosteroids (B) would likely not have helped. Although semaglutide (D) has been associated with worsening diabetic retinopathy, the patient had macular edema shortly after starting semaglutide, making it unlikely to be the cause of the macular edema. Additionally, worsening diabetic retinopathy associated with glucagon-like peptide 1 agonists is not commonly associated with worsening macular edema. Although the shape of the foveal detachment in the left eye is unusual for diabetic macular edema, this alone would not warrant workup for a nondiabetic cause of the retinal findings. However, in conjunction with the lack of response to anti-VEGF injections and atypical fluorescein angiography findings, further workup for a nondiabetic cause of the findings is indicated. Baseline laboratory work revealed anemia, elevated white blood cell count, and elevated serum creatinine, raising suspicion for a hyperviscosity syndrome. Thus, serum protein electrophoresis (A) was recommended as the next step in the workup.

This step revealed an M-spike, which prompted quantitative immunoglobin analysis that revealed an elevated IgA result (2441 mg/dL). Bone marrow biopsy revealed 40% to 50% plasma cell infiltration, confirming the diagnosis of IgA multiple myeloma with paraproteinemic maculopathy.

Paraproteinemia describes the presence of excessive monoclonal globulins in the blood, typically due to underlying immunoproliferative disorders such as Waldenström macroglobulinemia or multiple myeloma.[1] Excessive paraprotein in the blood leads to hyperviscosity, which can manifest as venous stasis retinopathy, retinal hemorrhages, and optic disc edema. An infrequent issue in paraproteinemic maculopathy is the presence of serous macular detachment.[1-5] It is proposed that hyperviscosity causes venous stasis and hypoxia of the endothelial cells, weakening the blood-retinal barrier, leading to accumulation of immunoglobulins in the subretinal space. The consequent osmotic gradient created by the immunoglobulins leads to serous macular detachments.[1,5-7] Additionally, risk factors like anemia and diabetes can exacerbate the process by inducing hypoxia and further damaging the blood-retinal barrier, leading to increased leakage of immunoglobulins.[1]

Primary treatment is directed at decreasing blood paraprotein levels through systemic treatments.[8] In a case series of 33 patients with paraproteinemic maculopathy, there was no definitive improvement with intravitreal anti-VEGF or corticosteroid agents. The long-term visual prognosis is guarded, with approximately 40% of cases having unchanged or worsening maculopathy despite adequate treatment of paraproteinemia.[1]

Patients with type 2 diabetes frequently have subclinical diabetes years before being diagnosed. Patients can present with advanced retinopathy shortly after diagnosis, thus making it an important differential to consider. However, this case underscores the importance of considering hyperviscosity syndromes for patients with diabetes and atypical macular edema unresponsive to anti-VEGF treatment. Early diagnosis is crucial because ocular symptoms may be the first indicators of paraproteinemia.

Patient Outcome

The patient was referred to an oncologist and began chemotherapy. Twelve weeks later, her visual acuity improved to 20/40 OD and 20/80 OS. On optical coherence tomography, the central subfield thicknesses changed to 435 nm OD and 406 nm OS. Her IgA level improved to 106 mg/dL.

ARTICLE INFORMATION

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