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Case Report

Hyperviscosity Retinopathy and Immunogammopathy Maculopahy as New Onset of Multiple Myeloma

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Blood viscosity · Chemotherapy · Immunogammopathy maculopathy · Macular edema · Multiple myeloma · Triamcinolone

Abstract
The purpose is to report a case of immunogammopathy maculopathy and hyperviscosity retinopathy as the presenting feature of new-onset multiple myeloma (MM) in an otherwise healthy man. A 50-years-old man presented with painless visual changes in both eyes for 2 months. Ocular examination revealed bilateral CRVO-like associated with macular edema (ME) and an inferior serous detachment. Hematologic investigation revealed an increased percentage of plasma cells in the bone marrow, reaching the diagnosis of MM IgM/kappa. Clinical support and chemotherapy effectively improved ocular alterations, despite the residual ME. Injection of triamcinolone was carried out, without any response. Bilateral vision reduction with hyperviscosity syndrome-related retinopathy and immunogammopathy maculopathy was the first manifestation of an underlying systemic and potentially fatal disease. This case highlights the need for diligent and thorough investigations for less common systemic conditions associated with retinal vein occlusions.

Introduction

Multiple myeloma (MM) is a hematologic cancer characterized by the accumulation of clonal and malignant plasma cells in the bone marrow that produce monoclonal abnormal immunoglobulins ("paraprotein") [1]. Cases with CRVO-mimicking retinopathy in MM are

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usually associated with hyperviscosity state that is a collection of clinical findings that may reflect increased serum concentration of a monoclonal protein [2].

Here, we describe a patient who presented sudden loss of visual acuity (VA) due to bilateral CRVO-mimicking retinopathy with serous macular detachment (SMD). Appropriate medical workup was conducted, and MM was diagnosed as the underlying cause. We further discuss the possible involved mechanisms and treatment options.

Case Report

A 50-years-old male presented with a sudden painless decreased vision in both eyes (OU) 2 months previously. The patient denied having systemic or ocular diseases. At the time of admission, VA was counting fingers at 1 m in the right eye (OD) and 20/63 in the left eye (OS). Pupillary light reflex, slit-lamp examination, and intraocular pressure were normal in OU. Fundus examination revealed bilateral dilated and tortuous retinal veins, multiple flame-shaped and dot-blot hemorrhages in all 4 quadrants, associated with a wide inferior serous detachment extending to the macula (Fig. 1a, b).

Optical coherence tomography showed macular edema, SMD in the posterior pole and inferior region, as well as hyperreflective material at the outer retina OU (Fig. 2a, b). Fluorescein angiography evidenced engorged and tortuous veins with an irregular pattern of filling, multiple areas of blocked fluorescence, and intravascular abnormal pinpoints (Fig. 1c, d).

Given the atypical bilateral presentation and the patient's age, a broad systematic investigation was chosen. Blood pressure was 110/68 mm Hg. Initial blood work presented anemia (hemoglobin, 5.8 g/dL), high partial thromboplastin time (1.32 s), high international normalized ratio (1.41), hypercalcemia (13.1 mg/dL – normal range: 8.3–10.6 mg/dL), renal insufficiency (creatinine was 2.84 mg/dL) and normal hepatic function. Blood viscosity was 6.4 cP (normal range: 1.4–1.8 cP). Inflammatory and infectious workup was negative. Serum protein electrophoresis showed a monoclonal protein component with peak of 7.0 g/dL (normal range: 0.7–1.6 g/dL) and immunofixation identified IgM/kappa.

The patient was then referred to the hematologist. Computerized tomography survey showed multiple lytic lesions on the bone framework without pathological fractures (Fig. 3a). Also, a bone marrow biopsy showed 55% infiltration with the plasma cells, and a diagnosis of MM IgM/kappa was reached (Fig. 3b). Acutely, the patient underwent plasmapheresis to treat the hyperviscosity syndrome (HVS) and zoledronate to treat hypercalcemia. Subsequently, he received bortezomib (Velcade), cyclophosphamide, and dexamethasone – the VCD protocol.

Six months after the VCD protocol, VA was 20/32 OD and 20/100 OS. Fundoscopy revealed marked amelioration of intraretinal hemorrhages (Fig. 4a–d), while the SMD persisted OU with reduction in the intraretinal fluid and presence of hyperreflective subretinal deposits, adherent to the retinal surface, as well as at the level of retinal pigment epithelium (Fig. 2c, d). At that point, patient received intravitreal injection of triamcinolone acetonide (Allergan, Inc., Irvine, CA, USA) in the eye with worst VA (OS). One month after the injection, VA remained the same OU, SMD continued in OU (Fig. 2e, f), and the hyperreflective deposits were unchanged (Fig. 2e, f). Fixation assessment by microperimetry showed a slight improvement in OS retinal sensitivity after medication, which may be explained by the improvement of intraretinal cysts (Fig. 1e, f, 4e, f).

One year later, the VA was 20/40 OD and 20/200 OS. He is currently on the sixth chemotherapy cycle, with a partial response, and is a candidate for autologous stem cell transplantation.

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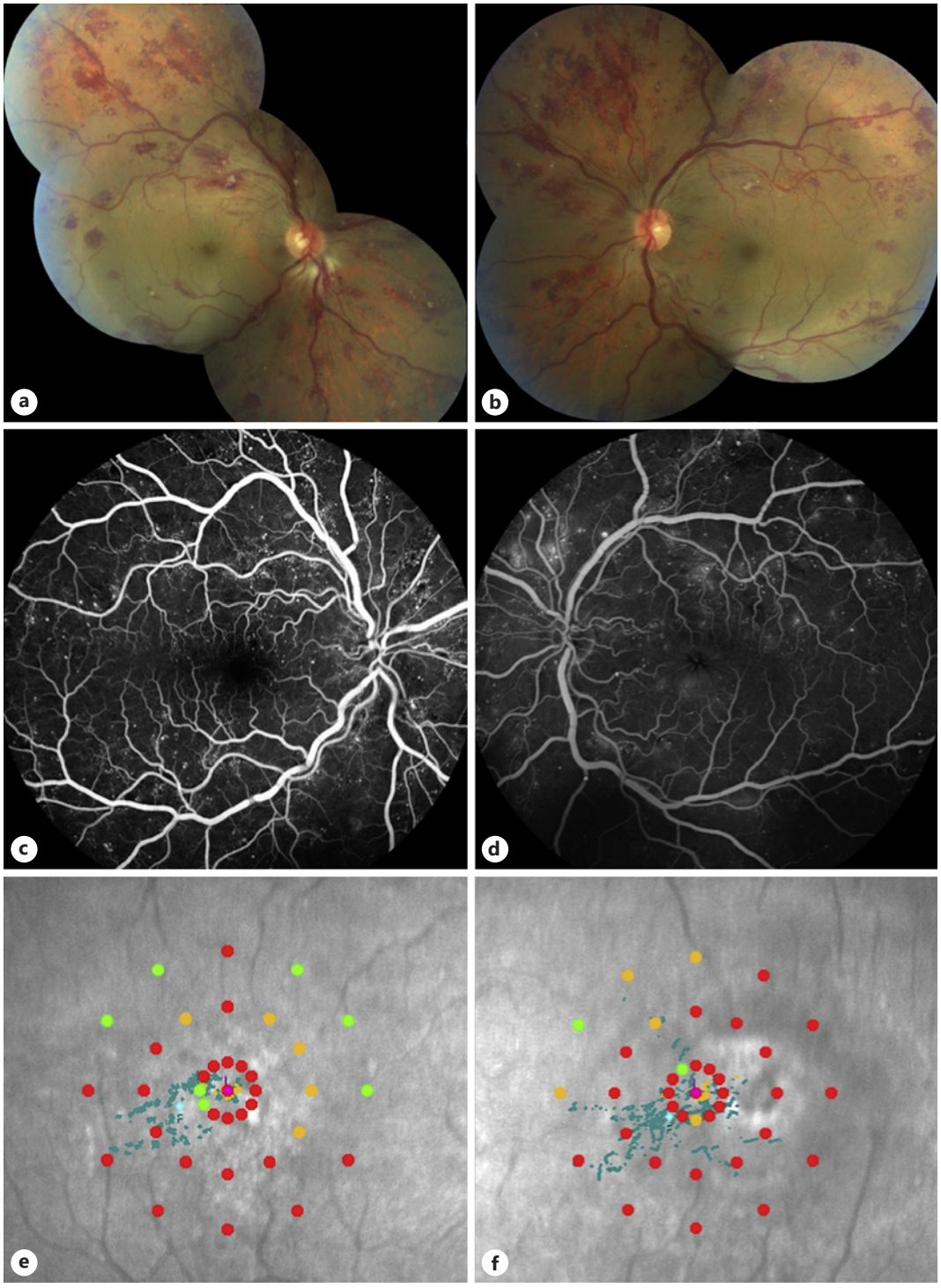

Fig. 1. Baseline of dilated fundus examination (**a**, **b**); fluorescein angiography (**c**, **d**); microperimetry (**e**, **f**).

Discussion

HVS is a severe disorder and it is rare in patients with MM with a reported incidence of 2–6% of the cases [3]. Hemorheological changes in the circulation and vascular disturbances

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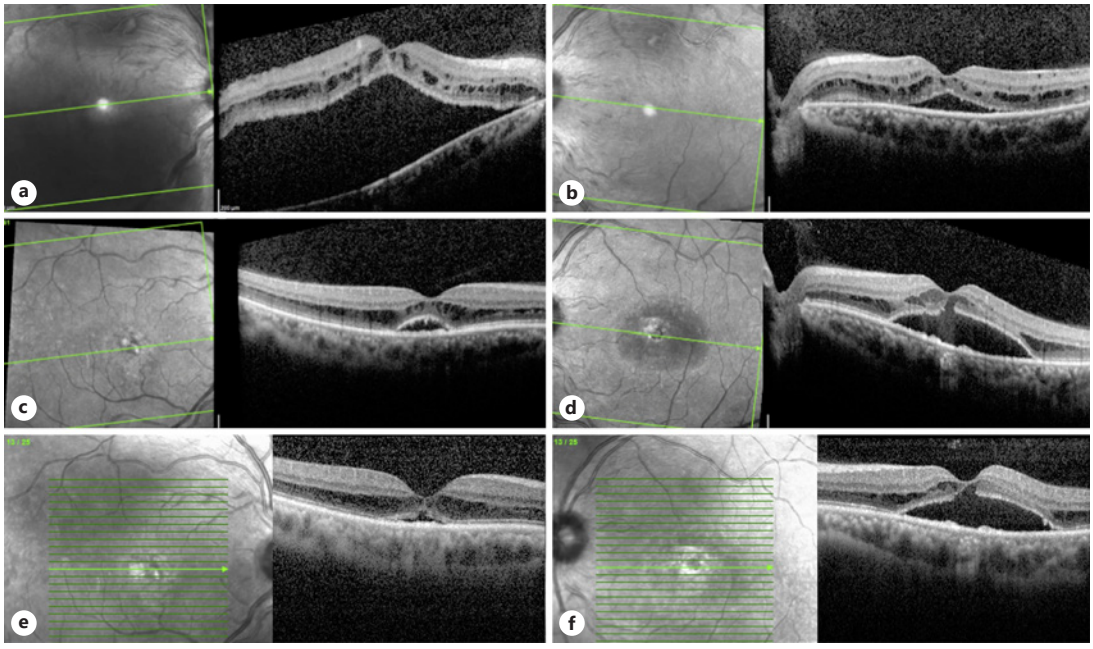

Fig. 2. Optical coherence tomography at baseline (**a**, **b**); 6 months after clinical management (**c**, **d**); 1 month after triamcinolone (**e**, **f**).

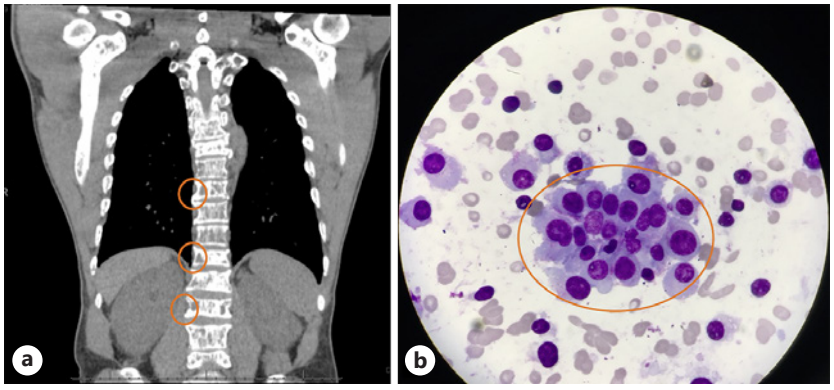

Fig. 3. Computerized tomography with multiple lithic lesions (**a**). Myelogram with increased percentage of plasma cells (**b**).

during HVS trigger a distinctive CRVO-mimicking retinopathy. Increased serum viscosity within the retinal vessels is believed to result in greater intraluminal pressure that would lead to (1) compensatory arterial and arteriolar dilatation and tortuosity, and (2) pathological changes in the junction complexes between endothelial cells, breaking through the internal retinal barrier, resulting in a leakage of vascular content, creating the retinal hemorrhages. In addition, due to impaired RBC transit, there would be static hypoxia that would explain the areas of nonperfusion observed in cases of HVS-related retinopathy [4, 5].

Apropos of SMD, it is described as an uncommon ocular manifestation of paraproteinemias and is characterized as an immunogammopathy maculopathy. This entity has rarely been reported in patients with IgM MM, being much more common in patients with Waldenström

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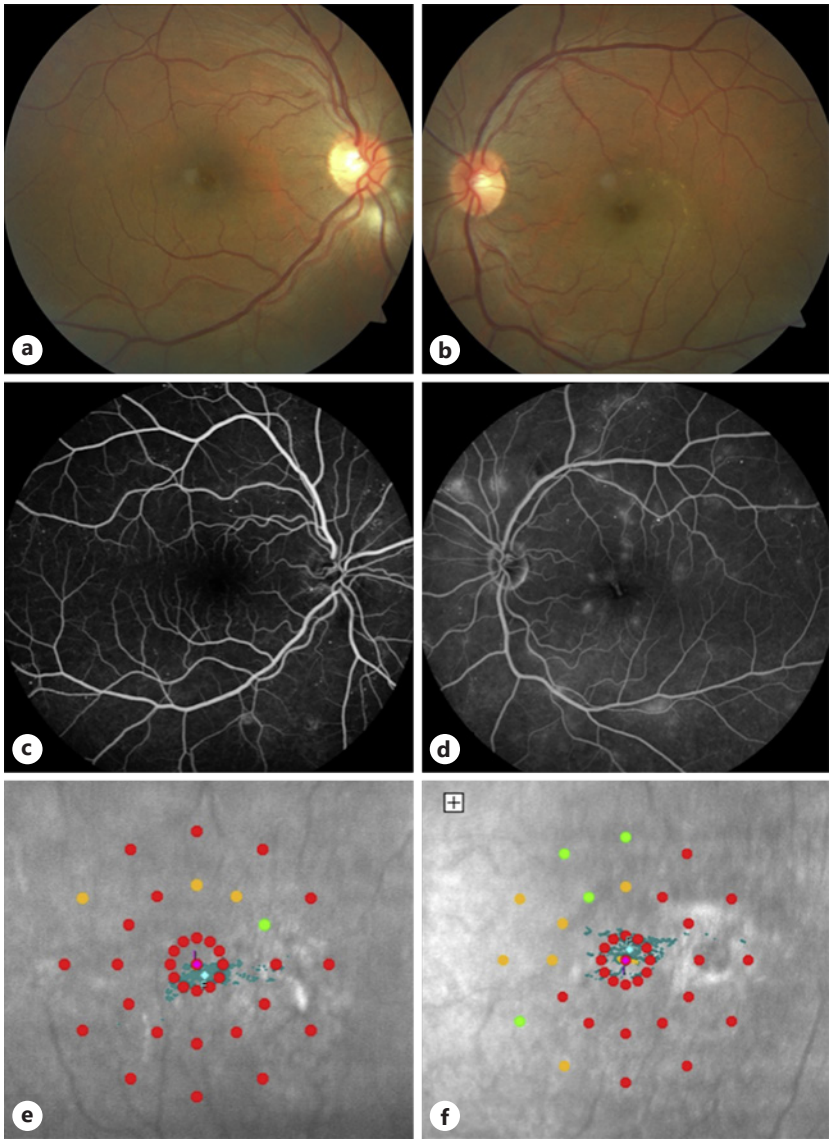

Fig. 4. One year after systemic management and triamcinolone injection: dilated fundus examination (**a**, **b**), fluorescein angiography (**c**, **d**), and microperimetry (**e**, **f**).

macroglobulinemia. The exact pathogenetic mechanism of this maculopathy remains unknown. Some authors suppose it to be a HVS-independent entity [6], a hypothesis contended by others [4]. It is speculated that infiltration of the neurosensory retina and subretinal space by excess of immunoglobulins creates increased osmotic pressure gradient toward the extracellular space, which may result in increased transudation of subretinal and intraretinal fluid. The transudation of fluid cannot be surpassed by the retinal pigment epithelium (RPE) pump and, therefore, macular edema with SMD occurs [6].

Also, histopathologic reports from patients with Waldenström macroglobulinemia or MM have documented immunoglobulins intraretinally, in the subretinal space and the RPE [4, 7]. Initially, optical coherence tomography images show a thick irregular border of hyperreflective material on the undersurface of the detached retina likely representing degenerating photoreceptor outer segments. With time, this layer decreases on the outer retinal surface and a pre-RPE layer of granular hyperreflective material develops. This significant

accumulation of material may represent degenerated outer segments, precipitation of immunoglobulin, or a combination of both [8].

Classically, fluorescein angiography demonstrates no fluorescein leakage in the macula, and this "angiographically silent" macular detachment distinguishes immunogammopathy maculopathy from other types of serous macular effusion [5–7]. This indicates that the blood-retinal barriers at the macular area are intact or at least that the disruption of the blood-retinal barriers is not the primary mechanism for subretinal fluid accumulation [6].

In these cases, targeted treatment underlying systemic disease is recommended. Therefore, early initiation of systemic chemotherapy associated with plasmapheresis can effectively reduce the levels of hyper secreted serum immunoglobulins and serum viscosity [9]. That way, this remains the mainstay of therapy for immunogammopathy maculopathy [3, 4, 6]. Based on that our patient was treated with the association of systemic chemotherapy and plasmapheresis. However, the SMD persisted OU though reduced in size when compared to the first visit.

According to some authors, the slow response of maculopathy to systemic chemotherapy may be due to 3 factors: (1) unknown period that IgM may persist in the subretinal space, either through direct accumulation or osmotic effects; (2) the degree of continued RPE and/or choriocapillaris dysfunction contribute to the pathogenesis [8]; and (3) long-standing SMD associated with intraretinal cysts. All 3 factors combined would lead to permanent vision loss as a result of RPE and photoreceptor degeneration [5].

In the presented case, the decision to treat the patient with intravitreal injection of triamcinolone represented an attempt to protect the retina, photoreceptors, and RPE from possible degeneration until chemotherapy was fully effective. It was also an attempt to regulate any possible inflammatory factors that might contribute to immunogammopathy maculopathy pathogenesis. Nonetheless, there was no improvement in VA or SMD.

These SMD have been variably treated with intravitreal injections of anti-vascular endothelial growth factor antibodies, dexamethasone implants, and panphotocoagulation without much improvement in the subretinal fluid. Reduction of intraretinal fluid was the only improvement attained [4, 5, 7, 8].

Thus, HVS-retinopathy improves after plasmapheresis and systemic chemotherapy [10], but there are no known effective treatments for immunogammopathy maculopathy. SMD persists in most patients for an extended period even after successful reduction of IgM levels and viscosity with plasmapheresis [4, 6].

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and all of the accompanying images (Ethics Committee: 93300518.0.0000.5505).

Conflict of Interest Statement

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Author Contributions

All the authors attest that they meet the current ICMJE criteria for authorship. Study concept and design: da Cruz, Milhomens Filho, and Moraes. Acquisition, analysis, or interpretation of data: all the authors. Drafting of the manuscript: da Cruz, Milhomens Filho, Ferraro, and Polizelli. Final revision and submission: Moraes and da Cruz. Final approval of the version to be published: all authors.

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