Neuro-Ophthalmic Presentation of Hyperviscosity Syndrome Uncovering Multiple Myeloma Diagnosis

Apresentação Neuro-Oftálmica de Síndrome de Hiperviscosidade Conducente ao Diagnóstico de Mieloma Múltiplo

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Abstract:

Multiple myeloma, characterized by uncontrolled plasma cell proliferation in the bone marrow and excessive immunoglobulin production, can lead to hyperviscosity syndrome, posing an oncologic emergency.

We present the case of an elderly woman exhibiting neuro-ophthalmological symptoms such as confusion, frontal syndrome, ataxia and deteriorating vision, alongside retinal hemorrhages. Diagnosis revealed IgG/Kappa multiple myeloma with bone marrow involvement, confirmed through further investigations. The patient was also found to have high blood viscosity. Lumbar puncture and cerebral magnetic resonance imaging (MRI) supported the diagnosis, indicating elevated protein levels and ischemic lesions. Prompt treatment, including dexamethasone pulses, therapeutic plasma exchange and chemotherapy, led to marked improvement.

This case underscores the importance of thorough ophthalmic and systemic evaluations in patients with suspected hyperviscosity, as neuro-ophthalmological symptoms may signal a life-threatening hematologic condition.

Keywords: Blood Viscosity; Eye Diseases; Multiple Myeloma; Retinal Hemorrhage.

Resumo:

O mieloma múltiplo, caracterizado pela proliferação descontrolada de células plasmáticas na medula óssea e pela produção excessiva de imunoglobulina, pode levar a uma síndrome de hiperviscosidade, representando uma emergência oncológica. Apresentamos o caso de uma mulher idosa com sintomas neuro-oftalmológicos como confusão, síndrome frontal, ataxia e deterioração da visão, acompanhados de hemorragias retinianas. O diagnóstico revelou mieloma múltiplo IgG/Kappa com envolvimento da medula óssea, confirmado através de investigações adicionais. A doente também apresentava alta viscosidade sanguínea. A punção lombar e a ressonância magnética cerebral suportaram o diagnóstico, indicando níveis elevados de proteinorráquia e lesões isquémicas. O tratamento rápido, incluindo pulsos de dexametasona, plasmaferese e quimioterapia, resultou numa melhoria acentuada. Este caso destaca a importância de avaliações oftálmicas e sistémicas minuciosas em doentes com suspeita de hiperviscosidade, uma vez que sintomas neuro-oftalmológicos podem sinalizar uma condição hematológica com risco de vida.

Palavras-chave: Hemorragia Retiniana; Mieloma Múltiplo; Oftalmopatias; Viscosidade Sanguínea.

Learning Points

1. Hyperviscosity syndrome (HVS) is an oncologic emergency that occurs due to elevated blood viscosity, most commonly associated with hypergammaglobulinemia.
2. Neuro-ophthalmological symptoms can be the initial manifestation of HVS, advising for thorough ophthalmic and systemic examination of all patients with suspected hyperviscosity.
3. Urgent management is advised for HVS and definitive treatment involves concurrent chemotherapy for the underlying hematologic condition.

Introduction

Multiple myeloma (MM) is a hematologic malignancy caused by the uncontrolled proliferation of neoplastic plasma cells in the bone marrow and the overproduction of monoclonal immunoglobulins (M-protein)[1] MM accounts for approximately 1% of all cancers and 13% of all hematological malignancies[2] and can precipitate a severe condition known as hyperviscosity syndrome (HVS).[3]

HVS constitutes an oncologic emergency arising from elevated blood viscosity, often triggered by irregularities in erythrocyte shape or by pathological increase of cellular or acellular components of blood, notably immunoglobulins.[4,5]

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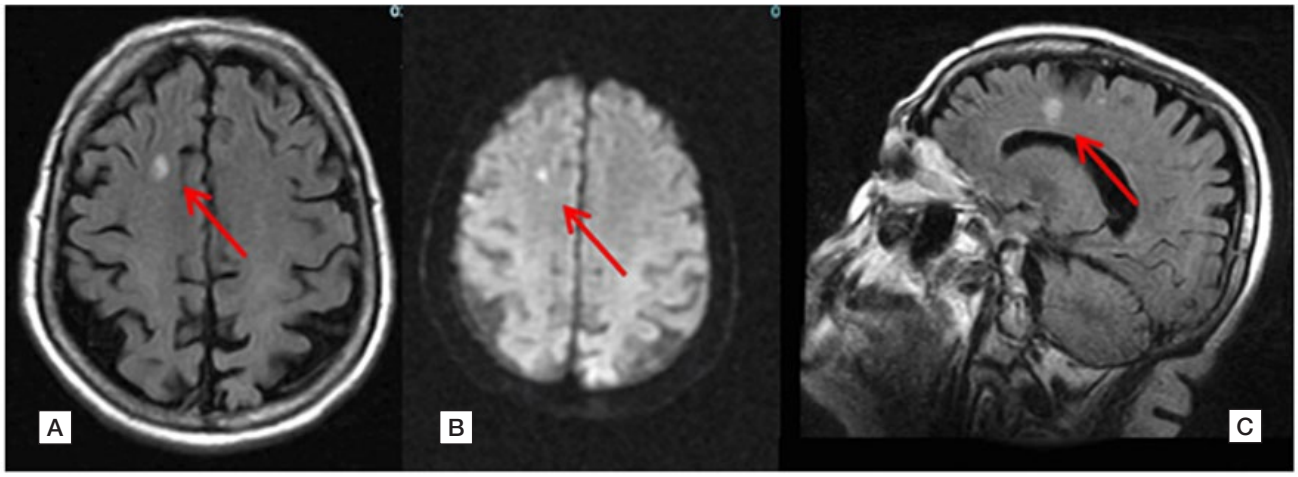

Figure 1: MRI findings: **[A]** - Axial T2-weighted FLAIR image showing a hyperintense lesion in the right frontal subcortical white matter (red arrow); **[B]** - Axial diffusion-weighted imaging (DWI) demonstrating restricted diffusion in the same region (red arrow), consistent with an acute ischemic lesion; **[C]** -Sagittal T2-weighted FLAIR image revealing a hyperintense lesion in the right frontal subcortical white matter (red arrow).

As such, the most common causes of HVS are hypergammaglobulinemia, particularly in Waldenström macroglobulinemia (WM), and MM - out of which 25% are accounted for IgA MM, whereas IgG MM leads to HVS in under 5% of cases.[3,6,7] The clinical triad of HVS includes mucosal bleeding (epistaxis, gum bleeding), visual abnormalities (blurring, papilledema, retinal bleeding, arterial or venule thrombosis), and neurological abnormalities (drowsiness, ataxia, increased risk for both cerebral bleeding or ischemia).[8] Despite its rarity, HVS poses a life-threatening risk, particularly in older patients, and correlates with poorer survival outcomes in MM.[9]

We present a case where a constellation of neuro-ophthalmologic symptoms prompted investigation into an underlying systemic condition, revealing HVS secondary to IgG/kappa MM.

Case Report

A 69-year-old white female, with a relevant past medical history of degenerative musculoskeletal pain, recently diagnosed pre-diabetes (HbA1c 5.9%) and undergoing investigation for newly found anaemia, presented in the Emergency Department with an altered mental state, characterized by confusion, incoherent speech, restlessness, and complaints of visual impairment. She reported blurred vision and hypovision worsening over the previous months, particularly in the weeks prior.

On initial assessment, the physical exam was unremarkable, but neurological examination revealed a frontal lobe syndrome marked by inattention, disinhibition, and flight of ideas. Additionally, it showed cerebellar dysfunction with axial predominant ataxia. Ophthalmologic evaluation demonstrated miotic pupils, minimally reactive to light. Fundoscopic examination revealed candle flame hemorrhages and a small adjacent cotton-wool spot near the lower temporal arcade in the right eye, along with small temporal hemorrhages in the left eye, in addition to previously known cataracts.

Regarding the neurological findings, an electroencephalogram (EEG) revealed no focal or paroxysmal slow activity. At the same time, brain magnetic resonance imaging (MRI) (Fig. 1) displayed a small subcortical hypersignal focus in the right frontal high convexity, suggesting an acute-subacute ischemic vascular lesion, alongside a probable vascular lacuna in the right hemipons.

Considering the patient's clinical presentation, including ophthalmological involvement (blurred vision, retinal hemorrhages) and neurological symptoms (subacute ischemic cerebral infarction, ataxia), hyperviscosity syndrome was considered and later confirmed, with assessment of blood viscosity (2.73 cps, for reference value 1.50-1.72 cps).

Furthermore, the peripheral blood smear showed erythrocyte stacking also suggestive of viscosity. Serum protein electrophoresis showed a monoclonal gamma peak, which immunoelectrophoresis further identified as monoclonal gammopathy of IgG/Kappa type. Urinary assessment was irrelevant, without proteinuria and unmeasurable free light chains. A myelogram was then performed, showing hypercellularity (>50%) of atypical plasma cells, mostly with immature characteristics, and immunophenotyping identified plasma cells strong CD38+, CD138+, CD19-, CD56+, CD10-, CD20-, weak CD117+, CD45-. Immunoelectrophoresis of oligoclonal bands in the cerebrospinal fluid (CSF) yielded identical results to those found in the blood, supporting the presence of a systemic disease with neurologic involvement. Onconeural antibodies in the blood and anti-NMDA in the CSF were negative.

All laboratory results can be found on Table 1.

As such, the patient was diagnosed with IgG/Kappa MM, ISS stage III, with bone marrow involvement and hyperviscosity

Table 1: Laboratory parameters.

	Results	Reference Range
Blood sample		
Hb (g/dL)	7.9	12.0-16.0
Reticulocyte index (%)	0.14	0.5-2.0
Leukocytes (/µL)	2 060	4 000-11 000
Erythrocyte sedimentation rate (mm/1st hour)	122	0-30
Peripheral blood smear	Erythrocyte stacking, anisochromia Confirmed neutropenia, very rare lymphoplasmacytic cells	
Urea/Creatinine (mg/dL)	19/0.7	21.0-43.0/0.6-1.1
Total proteins/Albumin (g/dL)	10.1/3.0	6.4-8.3/3.4-4.8
LDH (IU/L)	380	125-220
Total calcium (mg/dL)	7.8	8.9-10.0
IgG (mg/dL)	4684	up to 1631
IgA (mg/dL)	13	up to 69
IgM (mg/dL)	18	up to 33
Serum electrophoresis	monoclonal gamma peak	
Serum immunoelectrophoresis	monoclonal gammopathy of IgG/Kappa type	
Serum free light chains	kappa/lambda free ratio of 4.73	
ß2-microglobulin (mg/L)	6.15	0.97-2.64
24-hour urine		
Proteins (mg/24h)	66.3	<300.0
Free light chains	unmeasurable	
Urine electrophoresis	no abnormalities	
Cerebrospinal fluid		
Proteins (mg/dL)	67.4	15.0-45.0
Myelogram		
Histology	Hypercellularity 50+% of atypical plasma cells, mostly with immature characteristics	
Immunophenotyping	24% of cells: plasma cells Strong CD38+, CD138+, CD19-, CD56+, CD10-, CD20-, weak CD117+, CD45-	

syndrome, presenting with neuro-ophthalmological manifestations. Cytogenetic analysis by OncoFISH revealed del(17p) in 17% of analysed cells and a 4p16.3 (FGFR3) alteration in 14%.

The patient was started on dexamethasone pulses (20 mg/day for 4 days), which led to improved laboratory parameters. Therapeutic plasma exchange (TPE) was associated and led to a noticeable clinical improvement.

Within days, the patient demonstrated more coherent speech, absence of memory deficits or attention impairment, and reduced verbosity. While maintaining a broad-based gait, she no longer required assistance from others. Despite persistent asymmetric hypovision in the left eye due to dense cortical nuclear cataracts, fundoscopic examination revealed marked improvement in retinal hemorrhages, with only one flame-shaped hemorrhage observed near the lower temporal arcade of the right eye. Serial monitoring of blood viscosity showed a gradual decrease to normal values.

Concurrently, the patient commenced chemotherapy with a three-drug combination of bortezomib, cyclophosphamide, and dexamethasone.

Throughout the first 10 months of follow-up, the patient exhibited sustained improvement in both ophthalmologic and neurologic symptoms, alongside stable hematologic parameters. At that time, she showed biochemical relapse, and was started on daratumumab, lenalidomide and dexamethasone (Dara-Rd regimen). Her clinical course was then promising,

with notable advancements in her overall well-being. However, tragically, approximately 5 months later, the patient succumbed unexpectedly to an unknown cause, possibly related to a thrombotic event. Despite the diligent efforts of the medical team and the patient's positive response to treatment, her untimely demise remains a poignant reminder of the unpredictability inherent in certain medical conditions.

Discussion

While the exact pathogenesis of MM is not yet fully understood, the production of soluble factors by the myeloma cells is widely implicated and plays a central role in end-organ injury. Per the established diagnostic criteria for MM by the International Myeloma Working Group (IMWG),[1] the most significant complications are chiefly encompassed by the CRAB features - hyperCalcemia, acute or chronic Renal insufficiency, Anemia, and Bone lesions, with rapid skeletal dissolution - as well as a heightened susceptibility to infections, which together with biomarkers of malignancy that reflect imminent organ damage. Our patient met the “A” CRAB criterion (anemia) in addition to >50% plasma-cell infiltration, supporting the diagnosis of active, newly diagnosed multiple myeloma (NDMM). Although cytogenetic abnormalities were detected, with del(17p) in 17% of cells, this value falls below the thresholds typically used to define high-risk cytogenetics, as the GEM group considers del(17p) clinically relevant only when >20%.[10]

NDMM patients presenting with HVS characteristically exhibit high M-protein burden and elevated β2-microglobulin levels, lower albumin levels, increased bone marrow plasma-cell infiltration, and frequently present with higher ISS stage III rates, higher INR, and diminished fibrinogen compared to counterparts without HVS.[9]

HVS represents a critical, life-threatening risk, particularly pronounced in older patients, and significantly worsens long-term outcomes across all patient demographics.[11,12] Clinical manifestations of HVS encompass a spectrum of symptoms, including headache, fatigue, visual disturbances, retinopathy, dementia, and cerebral infarction. Additionally, presentations may include other end-organ damages such as heart failure and myocardial infarction, occasionally presenting as inaugural symptoms,[13,14] illustrating the heterogeneous nature of early symptoms. Our patient demonstrated both ophthalmic involvement - candle-flame hemorrhages and cotton-wool spots - and neurological manifestations - including frontal disinhibition, ataxia, and MRI evidence of an acute–subacute ischemic lesion. This constellation is well aligned with previously reported MM-associated HVS presentations in the literature.[7,11,13]

Ophthalmic manifestations of HVS may manifest as visual changes and retinopathy, often presenting as blurred vision and diplopia, attributed to microvascular complications such as thrombosis or hemorrhage. Although fundoscopy images were unavailable for publication, this limitation is acknowledged, as the findings were clinically pivotal for early suspicion. Timely eye examination is imperative when HVS is suspected, facilitating prompt diagnosis and treatment.[4]

Neurological sequelae, ranging from headache and confusion to more severe neurologic syndromes, stupor, coma, dizziness, ataxia, hearing impairment, seizures, and stroke syndromes, are commonly observed due to compromised blood flow to the central nervous system and deposition of paraproteins in peripheral nerve myelin sheaths.[5,6]

Because HVS is an emergency, prompt treatment is essential. Therapeutic plasma exchange (TPE) is recommended for HVS, as it can effectively reduce serum viscosity by 20% to 30% per session, depending on the immunoglobulin isotype, thereby facilitating the resolution of most clinical manifestations.[6] However, definitive treatment also requires chemotherapy for the underlying hematologic condition, often initiated concurrently.[6] In fact, in the absence of effective chemotherapy for MM, a rebound phenomenon linked to persistent M-protein production has been noted.[14] Management of HVS should prioritize symptom severity over the measured viscosity levels, with initial therapeutic strategies encompassing supportive measures such as hydration.

In our case, early initiation of high-dose dexamethasone followed by prompt TPE resulted in rapid clinical improvement, enabling resolution of most neurological and ophthalmic manifestations and normalization of viscosity.

The initial chemotherapeutic regimen (bortezomib–cyclophosphamide–dexamethasone) reflected the standard of care at the time this patient was treated; current EHA-ENM (European Haematology Association and European Myeloma Network) guidelines[15] instead recommend Dara-VRd (daratumumab + bortezomib + lenalidomide + dexamethasone) as the preferred first-line regimen for transplant-eligible patients and (Dara-)VRd as a preferred regimen for older or non-transplant-eligible patients. Nonetheless, we updated the discussion to acknowledge this temporal discrepancy and reflect present-day standards of therapeutic decisions for contemporary readers. Despite initial hematologic and clinical stabilization, the patient experienced biochemical relapse at 10 months, under bortezomib (V), and subsequently received Dara-Rd regimen with good clinical response. Her unexpected death several months later, likely thrombotic in nature, underscores the ongoing high morbidity of MM and the prothrombotic environment associated with both disease and treatment. Ultimately, we aim to highlight the need to conduct a thorough ophthalmic, neurologic and systemic examination in patients presenting with signs and symptoms suspicious of hyperviscosity, as neuro-ophthalmological manifestations may constitute the initial signs of a potentially life-threatening hematologic disease. In older patients, these mild nonspecific complaints are very common and can easily go unnoticed - early recognition and referral can lead to timely diagnosis and appropriate management. ■

Contributorship Statement

RNS and AF – Case review and manuscript preparation.

PS, AA and AF – Case review and critical revision of the manuscript.

All authors approved the final version to be published.

Declaração de Contribuição

RNS e AF – Revisão do caso e elaboração do manuscrito.

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