CASE REPORT

Acute Macular Neuroretinopathy: An Atypical Hemorrhagic Presentation

Neurorretinopatia Macular Aguda: Uma Apresentação Hemorrágica Atípica

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Recebido/Received: 2021-03-08 | **Aceite/Accepted:** 2021-07-05 | **Publicado/Published:** 2021-09-30

DOI: https://doi.org/10.48560/rspo.23889

ABSTRACT

Acute macular neuroretinopathy (AMN) is a rare disease. We report a clinical case of AMN diagnosed in a 46-year-old, Caucasian female with an atypical exuberant hemorrhagic presentation. She referred unilateral paracentral scotomas started 1 day before admission. Fundoscopy revealed several large, dot-and-blot and flame-shaped intraretinal hemorrhages surrounded by reddish-brown, wedge-shaped lesions pointed towards the fovea. Infrared imaging displayed petalloid dark lesions. Optical coherence tomography showed focal ellipsoid zone disruptions, areas of outer retinal hyperreflectivity and deep intraretinal hemorrhages. Fundus autofluorescence and fluorescein angiography displayed hypofluorescent areas due to intraretinal hemorrhages. One-month after presentation, the patient complained about residual scotomas. Classic reddish-brown, wedge-shaped lesions became well-demarcated and intraretinal hemorrhages almost completely resolved. Tomographic findings partially reversed but converted into outer nuclear layer thinning. Visual field examination displayed paracentral scotomas. Our patient revealed the classic AMN lesions. From our knowledge, this is the first reported AMN case with an extensive hemorrhagic presentation.

KEYWORDS: Macula Lutea; Retinal Diseases; Multimodal Imaging.

RESUMO

A neurorretinopatia macular aguda (NMA) é uma doença rara. Reportamos um caso numa mulher caucasiana de 46 anos com apresentação hemorrágica atípica. A doente referia escotomas paracentrais iniciados 1 dia antes. A fundoscopia revelou múltiplas áreas extensas de hemorragias intrarretinianas em borrão e em chama-de-vela, rodeadas por lesões em cunha apontadas à fóvea. Imagens de infravermelho apresentaram lesões escuras petalóides. A avaliação tomográfica apresentava disrupção focal da zona elipsóide, hiperrefletividade da retina externa e hemorragias intrarretinianas. A autofluorescência e a angiografia fluoresceína mostraram áreas hipofluorescentes causadas pelas hemorragias intrarretinianas. Um mês após, a doente referia escotomas residuais. As clássicas lesões vermelho-acastanhadas em cunha tornaram-se melhor demarcadas e as hemor-

ragias intrarretinianas foram praticamente reabsorvidas. Os achados tomográficos reverteram parcialmente, resultando em atrofia da camada nuclear externa. A campimetria revelou escotomas paracentrais. Esta doente apresentava lesões clássicas de NMA. No nosso conhecimento, este é o primeiro caso reportado com apresentação extensivamente hemorrágica.

PALAVRAS-CHAVE: Doenças da Retina; Macula Lutea; Imagem Multimodal.

INTRODUCTION

Acute macular neuroretinopathy (AMN) is a rare retinal disease, firstly described in 1975 by Bos and Deutman.[1] The hallmark of this condition is the acute onset of paracentral scotomas and photopsias corresponding to the anatomical distribution of macular intraretinal, reddish-brown and wedge-shaped lesions. Classically, the apices of retinal lesions tend to be directed towards the fovea in a petalloid or tear-drop configuration.[1,2] Superficial intraretinal hemorrhages and even macular edema were described in AMN but are uncommonly observed. Mild visual impairment is not infrequently reported at presentation and tends to assume a benign progression. Persistent scotomas occur in 53.2% of cases and can persist for many years. Bilateral involvement was stated in 54.4% of patients.[2]

The exact pathological mechanism of AMN remains unknow. However, the recently published pivotal research data suggests a vascular etiology and identified ischemia involving the deep retinal capillary plexus as a strong correlated mechanism.[3–5]

Several environmental factors have been identified as possible triggers for AMN. Nonspecific flu-like illness or fever were associated with classic retinal lesions in 47.5% cases, use of oral contraceptives in 35.6% and exposure to epinephrine or ephedrine in 7.9%. Ocular and non-ocular trauma was observed in 5.9% cases and systemic shock of multiple etiologies in 5.0%. Less commonly, intravenous contrast agents, preeclampsia, post-partum hypotension, anemia, lupus, leukemia, ulcerative colitis, sickle cell disease, and heavy caffeine intake were associated with the onset of the condition.[2,6]

AMN is approximately 6 times more frequent among women with a male/female ratio of 0,16:1. It is typically reported in adults with a mean age of presentation of 29.5 years (ranging from 12 to 65) and 51.5% of cases occur in the third decade of life. Furthermore, this condition has been more often observed in non-Latino Caucasian subjects.[2]

The diagnosis of AMN is clinical and mainly supported by a thorough history exploring the acute onset of visual complaints and a fundoscopic examination typically revealing the distinctive reddish-brown, wedge-shaped lesions. Multimodal imaging techniques have been reported as a powerful tool to further clarify the diagnosis and have provided important insights for the pathogenesis of AMN.

This report describes a clinical case of AMN diagnosed in a middle-aged adult woman with an atypical exuberant hemorrhagic presentation.

CASE REPORT

A 46-year-old, Caucasian female presented to our emergency department with complaints of unilateral paracentral scotomas and photopsias in her right eye with acute onset 1 day prior. The visual impairment started at rest without any apparent precipitating factor. No history of ocular or extra-ocular trauma nor recent acute medical conditions were reported. Drug abuse or recent travels were denied.

This adult woman was born with a congenital upper eyelid ptosis in her left eye. Despite surgical treatment performed during childhood, the patient developed moderate amblyopia. No other previous ophthalmological disorders were reported for the affected and fellow eyes. Additionally, she had no family history of ophthalmological conditions.

The patient had a medical history of a gynecologic cancer 7 years prior and has been under surveillance in the oncologic gynecology clinic, without signs of disease recurrence. She was diagnosed with an endocervical adenocarcinoma IB1 G1 FIGO stage and submitted to radical hysterectomy with pelvic lymphadenectomy followed by adjuvant radiotherapy and brachytherapy. Her medical history had no other remarkable events. She had no medication history (namely, anticoagulants or antiplatelets) at time of presentation nor in the previous 6 months. The patient halted oral contraceptives following hysterectomy. She reported regular consumption of 4 to 5 cups of coffee a day in previous months.

We performed a comprehensive ophthalmologic examination, spectral-domain optical coherence tomography (SD-OCT) (Spectralis®, Heidelberg Engineering, Heidelberg, Germany), fundus autofluorescence (FAF) (Spectralis®, Heidelberg Engineering, Heidelberg, Germany), fluorescein angiography (FA) with infrared (IR) imaging (Spectralis HRA®; Heidelberg Engineering, Heidelberg, Germany) and 30-2 visual field examination (Humphrey Field Analyzer®, Carl Zeiss Meditec, California, USA) at presentation and 1 month after. Additionally, a complete blood test with blood smear was performed at presentation.

Best corrected visual acuity (BCVA) on US equivalent scale was 20/20 in right eye and 20/100 in left eye. The confrontation visual field examination, pupillary light reflexes and ocular motility tests showed no abnormal findings. Anterior segment slit-lamp examination was unremarkable and intraocular pressure measured by applanation tonometry was 14 mmHg bilaterally. Dilated fundoscopic examination of the right eye revealed several areas of large dot-and-blot and flame-shaped intraretinal hemorrhages surrounded by reddish-brown, wedge-shaped and petalloid lesions (Fig.s 1A and 1B). Lesions

were restricted to the posterior pole retina, scattered throughout the macula with the apex pointed towards the fovea and extending to the edge of the foveal avascular zone. The foveal area appeared to be unaffected. No other lesions were clinically observed, with unremarkable peripheral retina. Vascular arcades displayed regular anatomy. The vitreous body was regular and no optic disc oedema was observed. Fundoscopy of left eye was unremarkable.

At presentation, IR imaging showed ill-defined petalloid dark lesions corresponding to the location of the described fundoscopic reddish-brown lesions (Fig. 1C). Tomographic evaluation of these characteristic lesions using SD-OCT revealed areas of ellipsoid zone disruption, hyperreflectivity of the outer nuclear layer (ONL) and the outer plexiform layer (OPL), hyperreflectivity of the Henle layer and hyporeflectivity of the photoreceptor/retinal pigment epithelium complex. Additionally, intraretinal hemorrhages could be observed tomographically as hyperreflective disruptions at the level of the OPL and ONL junction (Fig.s 2A, 2B and 2C). FAF and FA displayed areas of blocked fluorescence corresponding to the intraretinal hemorrhages (Fig.s 1D, 1E and 1F); FA revealed no other areas of hipo or hyperfluorescence on early and late angiograms. Multimodal imaging of the fellow eye was unremarkable.

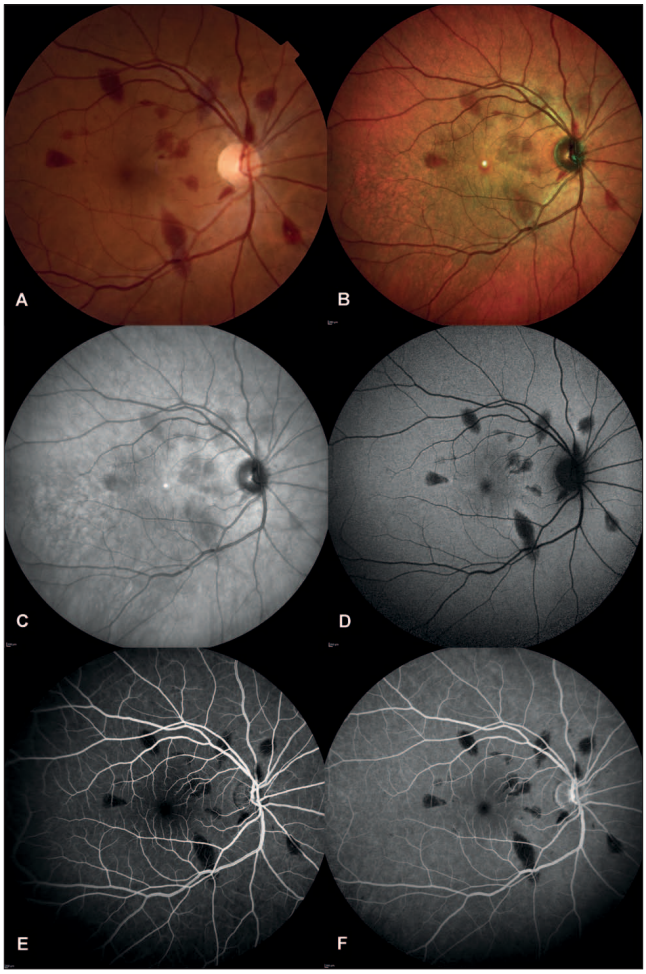

Figure 1. Multimodal retinal imaging at presentation. Fundus image displaying multiple large dot-and-blot and flame-shaped intraretinal hemorrhages restricted to the posterior pole retina (A). Multicolor image showing intraretinal hemorrhages surrounded by reddish-brown, wedge-shaped and petalloid lesions with the apex pointed towards the fovea (B) and infrared image showing the corresponding ill-defined petalloid dark lesions (C). Fundus autofluorescence with areas of blocked fluorescence due to intraretinal hemorrhages (D). Fluorescein angiography at presentation showing areas of blocked fluorescence due to intraretinal hemorrhages without other areas of hipo or hyperfluorescence on early (E) and late (F) angiograms.

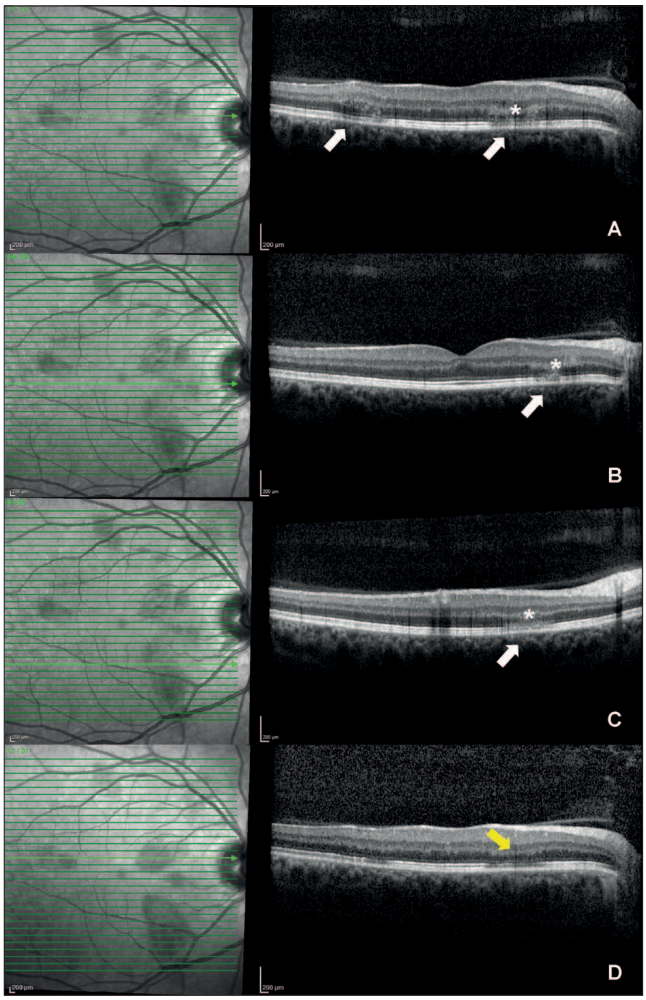

Figure 2. Spectral-domain optical coherence tomography at presentation revealing areas of ellipsoid zone disruption (white arrow); hyperreflectivity of the outer nuclear layer and outer plexiform layer (asterisk); hyporeflectivity of the photoreceptor/retinal pigment epithelium complex (white arrow); and intraretinal hemorrhages at the level of the outer plexiform layer and outer nuclear layer junction (A, B and C). At 1-month evaluation, showing partially reversed ellipsoid zone defects and resolution of outer retinal hyperreflectivity with subsequent mild outer nuclear layer thinning (yellow arrow) (D).

On admission, the patient was hemodynamically stable with normal blood pressure. Laboratory data failed to indicate any systemic disease: a leukocyte count of 6500/mm^3, haemoglobin of 13.5 g/dL and platelet count of 297 000/mm3; blood smear showed no morphologic abnormalities; blood urea was 35 mg/dL and creatinine level was 0,6 mg/dL; C-reactive protein was 1.3 mg/L; total protein count was 7.0 g/dL and protein electrophoresis was normal; coagulation tests were unremarkable. Infectious diseases screening

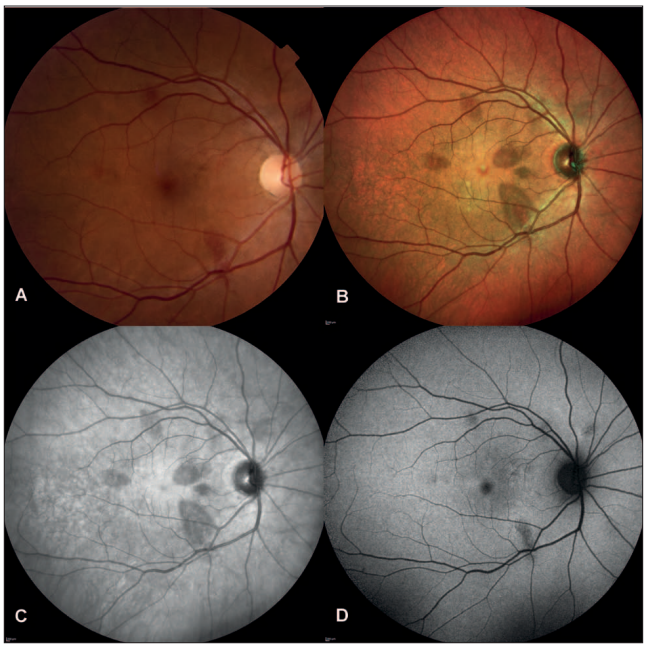

Figure 3. Multimodal retinal imaging at 1-month follow-up. Fundus image displaying the extensive resolution of intraretinal hemorrhages (A). Multicolor image showing well-demarcated reddish-brown, wedge-shaped and petalloid lesions clearly directed towards the foveal area (B) and infrared image showing the corresponding well-defined dark lesions (C). Fundus autofluorescence with a nearly regular retinal autofluorescence (D).

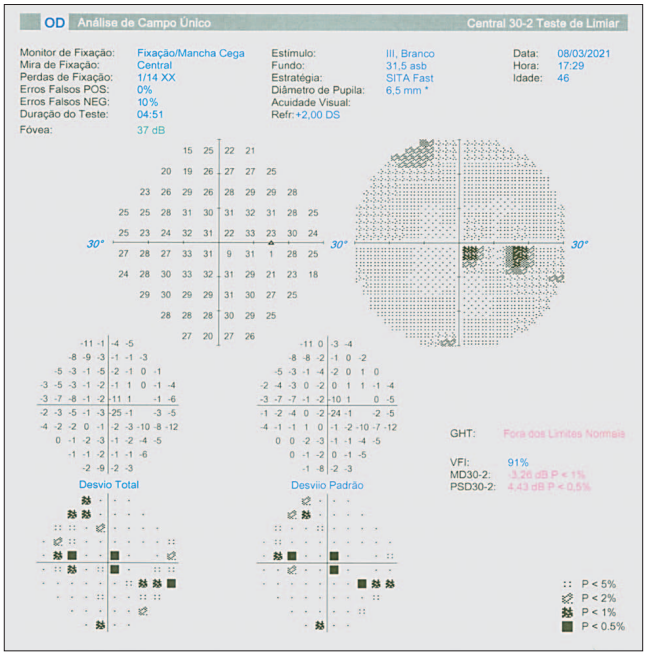

Figure 4. Right-eye, 30-2 visual field examination showing paracentral scotomas correlated to the shape and location of the retinal lesions.

and autoimmune markers were both negative.

Based on clinical findings and supported by multimodal imaging evaluation the diagnosis of AMN was proposed. An observation-only approach was assumed.

At 1-month evaluation, BCVA remained 20/20 in the affected eye and the patient complained about residual scotomas. Dilated fundoscopic examination revealed a nearly complete resolution of intraretinal hemorrhages (Fig. 3A). Better visualized in multicolor images, the posterior pole reddish-brown, wedge-shaped and petalloid lesions became well-demarcated and clearly directed towards the foveal area (Fig. 3B). Likewise, IR images showed well-demarcated wedge-shaped and petalloid dark lesions (Fig. 3C). Structural changes became less prominent; SD-OCT B-scans revealed partially reversed ellipsoid zone defects and resolution of outer retinal hyperreflectivity but displayed mild ONL thinning (Fig. 2D). FAF exhibited an almost normal retinal autofluorescence (Fig. 3D). The patient did not notice any defect on the Amsler chart. However, visual field examination of the right eye displayed paracentral scotomas, closely correlated to the shape and location of the retinal lesions (Fig. 4).

DISCUSSION

In this report, we describe the clinical case of a 46-year-old, Caucasian female that presented with an acute onset of unilateral paracentral scotomas and photopsias and no visual impairment. Funduscopic examination revealed the distinctive macular reddish-brown, wedge-shaped lesions pointed towards the fovea classically described in AMN, that corresponded to dark petalloid areas on IR imaging. Tomographic evaluation of those lesions showed the characteristic areas of ellipsoid zone disruption and hyperreflectivity of the ONL and OPL, which partially reversed and were replaced by mild ONL thinning 1 month later. The occurrence of intraretinal hemorrhages in AMN was previously reported in literature; however, typically of minimal extension and only described in 3.2% of the cases.[2,7] Our patient showed an atypically pronounced hemorrhagic presentation of AMN, with multiple large areas of deep, dot-and-blot and superficial, flame-shaped intraretinal hemorrhages scattered throughout the macular region. The hemorrhages were well-defined at presentation and showed an almost complete resolution at 1-month follow-up.

In 2003, Turbeville *et al* hypothesized that a vasogenic mechanism could unify the retinal findings of AMN.[8] Currently, the exact etiology remains to be further elucidated.

In the last decades, the advent of modern multimodal retinal imaging techniques highlighted the characteristic findings of AMN and enhanced our understanding of the relevant pathophysiologic mechanisms. It is now apparent that AMN is largely the result of non-inflammatory ischemia.[2,9] Typical localization of the lesions to the outer retinal layers in the macula including disruption of the ellipsoid and interdigitation zones in association with abnormalities at the junction between the OPL and ONL have been described by multimodal imaging. This pattern of changes implicates local compromise and ischemia of the deep retinal capillary plexus which provides retinal perfusion to the vulnerable watershed zone between the retinal and choroidal circulations.[4,5] Persistent scotomas often observed in AMN may be related to permanent thinning of the ONL that ensues after the initial hyperreflective infarct of the junction between OPL and ONL. Furthermore, the co-

existent ellipsoid and interdigitation zone disruption may be explained by the partial contribution (10%) of the deep retinal capillary plexus to the photoreceptors' oxygen supply. This ischemic concept is strongly supported by formerly identified risk factors, including non-specific flu-like illness or fever, use of oral contraceptives, exposure to epinephrine or ephedrine, caffeine abuse, trauma, and systemic shock – that could directly or indirectly influence retinal capillary perfusion.[2]

The advent of OCT angiography (OCT-A) allowed for enhanced visualization of the intermediate and deep capillary plexuses. Due to the possible vascular dysfunction as a major factor in the development of AMN, OCT-A is a valuable tool to further characterize the pathological mechanism behind this rare retinal condition. In AMN lesions, OCT-A revealed reduced flow in deep capillary plexus, reinforcing focal ischemia of the photoreceptor axons in the OPL as the major etiologic factor. Variable recovery of capillary flow was noted during follow-up; however, the damage inflicted to the photoreceptor units induces atrophy with long-term ONL thinning.[3–5]

The patient described in this report showed unilateral, classic AMN lesions on fundus examination, IR imaging and SD-OCT B-scans. To the best of our knowledge, this is the first case report of AMN with an extensive hemorrhagic presentation. Multimodal retinal imaging revealed several large, intraretinal deep hemorrhages located at the junction of the OPL and ONL. Other causes of deep retinal hemorrhages were considered in the differential diagnosis. The patient had no history of diabetes nor high blood pressure. She was not pregnant. Retinal vein and artery occlusions were excluded as the vascular arcades showed regular configuration and angiographic arteriovenous filling was unremarkable. No history of trauma was noted. Given the previous history of gynecologic cancer submitted to adjuvant radiotherapy and brachytherapy, a possible hematologic disorder was ruled-out since blood counts were regular with no morphologic abnormalities reported in the blood smear. No signs of systemic infection were observed. Autoimmune markers failed to identify a possible immunologic disorder. In 2016, Spaide has proposed that the deep capillary plexus may have a critical role in retinal fluid homeostasis.[10] We hypothesized that severe deep capillary plexus dysfunction and ischemia – that seems to be the key factor in the pathogenesis of AMN – may cause significant breakdown of the inner blood–retinal barrier leading to extensive intraretinal blood leakage observed in our patient.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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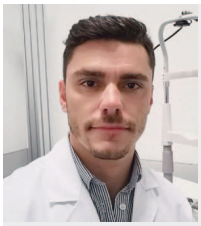

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