

Vasculitis associated with the use of an intrauterine device: A case report

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Abstract. Retinal vasculitis is a complication associated with a local condition or it can be a retinal expression of a systemic inflammatory disorder, which initially may go unnoticed. Drug-associated vasculitis is frequently difficult to identify, because many patients follow treatments with more than one drug and the route of administration varies. A 35-year-old female patient presented with sudden hearing loss, headache and blurred vision that had started two weeks earlier and had become progressively worse. Ophthalmological examination revealed anterior uveitis, bilateral optic disc swelling and retinal vasculitis. The orbito-cerebral MRI, the CT scan and the serological tests were within normal limits. Unable to identify the cause of the retinal vasculitis, the patient's medical history was reviewed. The patient had recently had a gynecological procedure, where a 13.5 mg levonorgestrel intrauterine contraceptive device was implanted. After the device was removed and methylprednisolone treatment started, the patient presented a visible remission of the symptoms and signs. To the best of our knowledge, there is no case of retinal disease and optic disc edema associated with auditory problems caused by an intrauterine device. A proper examination, correlated with a very thorough medical history, could identify rare diseases and associations, in order to provide adequate medical care.

Introduction

Vasculitis is the inflammation of the blood vessel wall secondary to an abnormal immune response (1,2). Systemic vasculitis determines sufferance and fibrinoid necrosis of the endothelial cells, events followed by vascular leakage and blood clot formation with secondary occlusion (1,3). Eventually, all these vascular events determine retinal ischemia and dysfunction of the organ (3).

Retinal vasculitis can be a complication of a local condition or it can be a retinal expression of a systemic inflammatory disorder, which may initially be unnoticed (3-5). The causes of retinal vasculitis are multiple and often overlap, making both the diagnosis and the treatment options challenging (5). Retinal vasculitis is frequently associated with inflammation of the adjacent tissues, such as the choroid or the vitreous, but sometimes, remote ocular structures also appear to be caught in the inflammatory process (6-8).

Retinal vasculitis can be associated with infectious and non-infectious conditions (3-5). The non-infectious causes of vasculitis include ocular disorders and can be drug-induced, i.e., vasculitis associated with a systemic inflammatory disease and vasculitis associated with malignancies (9-11). Drug-associated vasculitis is frequently difficult to identify, because many patients follow treatments with more than one drug and the route of administration varies (12-15). In addition, patients may forget, neglect or hide drug intake. For instance, an intrauterine device (IUD) is considered a medical device. In terms of prevention of an undesired pregnancy, IUDs are usually considered safe with rare side effects, some of which can be severe (16). Currently, there are two types of IUDs available: The copper IUD, which releases copper ions, and the hormonal IUD, which releases a synthetic form of the progesterone hormone, named levonorgestrel (17). The most frequently cited side effects of hormonal IUDs comprise gynecological disorders, headaches, blood-clotting issues, developing acne and breast tenderness, which lead to a higher rate of treatment discontinuation, more than 24% after 1 year and 33% after 2 years (5,17-19). Currently, no previous reports of ocular vasculitis associated with the use of an intrauterine device are available in the literature.

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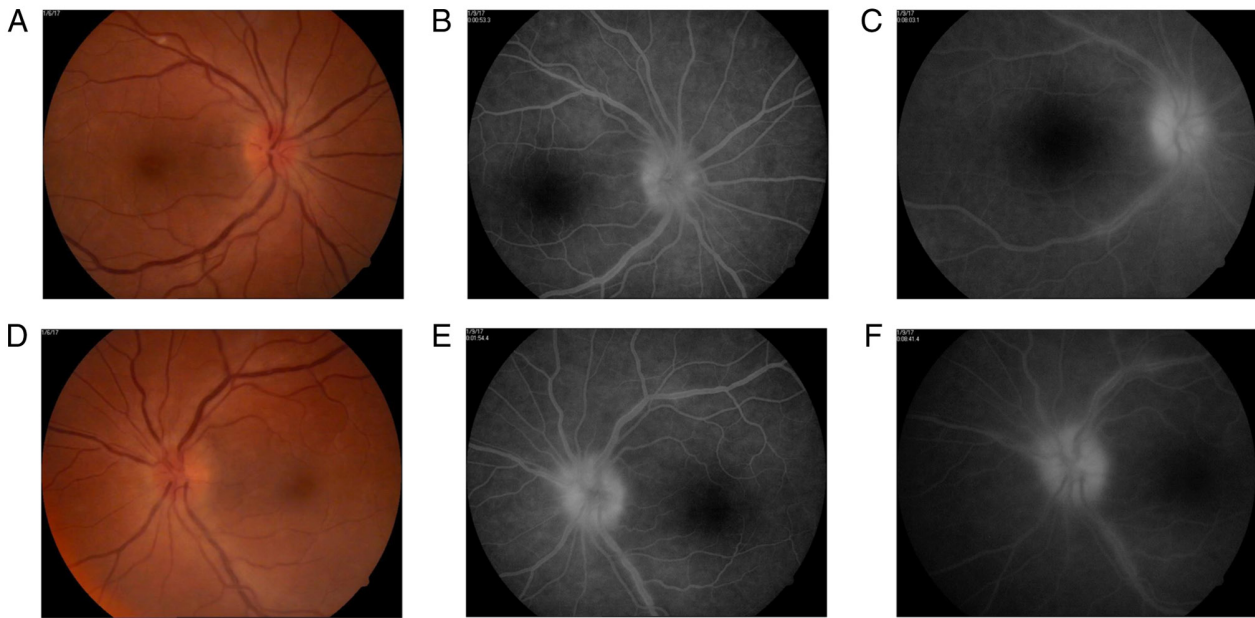


Figure 1. Fundus photography and fluorescein angiography during clinical assessment. (A) The appearance of the posterior pole and (B) fundus angiography in the right eye at 53.3 sec. (C) Fundus angiography in the right eye at 8 min and 3 sec. (D) The appearance of the posterior pole in the left eye on fundus photography. (E) Fundus angiography in the left eye at 1 min and 54 sec and (F) at 8 min and 41 sec.

Case report

A 35-year-old female patient sought emergency care, complaining of sudden hearing loss, headaches and blurred vision that had started two weeks previously and had gotten progressively worse. The headaches were continuous and located in the occipital area, with episodes of increased pain, accompanied by a decrease in hearing and sometimes dizziness. During the previous two weeks before presentation, the neurological exams had not identified any neurological signs. However, non-steroidal anti-inflammatory drugs were prescribed, but without improvement. Furthermore, the patient was examined by an ear, nose and throat (E.N.T.) doctor, but there were no clinical signs to explain the hearing loss.

Based on the patient's medical history, it was identified that she had a multinodular non-toxic thyroid goiter, no drug allergies, she was a non-smoker and had two natural child births. From the Emergency Room of the University Emergency Hospital Bucharest, the patient was admitted into the neurology department, but still without any detectable clinical neurological signs. The dilated fundus examination revealed bilateral optic disc swelling. An orbito-cerebral magnetic resonance imaging (MRI) and a computed tomography (CT) scan were performed, but with no significant findings. In addition, the blood pressure was normal. Therefore, the patient was discharged from the neurological department and referred to the ophthalmologist.

The ophthalmological assessment revealed a slight decrease in the best corrected visual acuity of 20/30 in the right eye and of 20/25 in the left eye. Slit-lamp examination showed a 1+ faint grade of flare in the anterior chamber, accompanied by a few small corneal endothelium precipitates. Color vision, ocular motility and pupillary light reflex were within normal limits.

Fundus examination reveals bilateral optic disc swelling, hyperemia, loss of the optic cup, optic disc vessels drowned in

edema, retinal edema around the optic disc, normal aspect of arteries, but sinuous and dilated veins. The veins also presented a larger diameter than expected and some venous branches were more dilated than others. Their diameter did not constantly decrease towards the periphery, with some medium-sized venous branches greater than the large-sized venous branches (Fig. 1).

Therefore, a fundus fluorescein angiography was carried out, with a delay of 2-3 sec in the appearance of the laminar venous flow and an unequal filling with dye of some temporal medium-sized venous branches. The late phase shows optic disc hyperfluorescence due to venous and capillary leakage. Analyzing the venous branches, segmental diffuse hyperfluorescence in the early phases and staining in the later phases of the angiogram were evident (Fig. 1). No additional retinal or choroidal fluorescein lesions were identified.

In this context, the patient's diagnosis was bilateral retinal vasculitis, papilledema and anterior uveitis, headache and hypoacusis. In order to identify the cause of the retinal vasculitis, various blood tests were performed based on the medical history, symptomatology and clinical assessment, trying to avoid unnecessary and exhaustive investigations. The purpose was to identify an immune or infectious cause of the retinal vasculitis. All serological tests for syphilis, tuberculosis, HSV-1, HSV-2, HZV, CMV, HIV, and ELISA for toxoplasmosis were negative. In addition, IgM and IgG anti- β 2-glycoprotein antibodies, IgM and IgG anti-cardiolipin antibodies, lupus anticoagulant, homocysteine level, antibody anti-DNA double catenary, C-ANCA, P-ANCA, anti-Ro/SSA and anti-La/SSB antibodies, ANA, and rheumatoid factor were negative (Table I). Full blood count, biochemical blood profile and cerebrospinal fluid analysis were non-contributory.

Not being able to identify the cause of the retinal vasculitis, the patient's medical history was reviewed, this time focusing on rheumatological diseases, drug intake or other medical procedures undergone in the recent period. As a result, it was

Table I. Specific blood tests performed.

| Immunology | Value | Normal range | Observation |
|--|---|---------------|---|
| Anti-β2 glycoprotein antibodies (IgM) (U/ml) | 3.3 | <5 | Negative |
| Anti-β2 glycoprotein antibodies (IgG) (U/ml) | 1.3 | <5 | Negative |
| Anti-cardiolipin Ab (IgG) (U GPL/ml) | <2 | <20 | Negative |
| Anti-cardiolipin Ab (IgM) (U MPL/ml) | <2 | <20 | Negative |
| Lupus anticoagulant (ratio) | 0.98 | <1.2 | Negative |
| Homocysteine level μmol/l | 10.1 | <10 | Risk for cardio-vascular disease, mild |
| Anti-DNA double catenary antibodies (U/ml) | 6.6 | <25 | Normal |
| Anti C-ANCA antibodies (U/ml) | 1.1 | <5 | Negative |
| Anti P-ANCA antibodies (U/ml) | <2 | <13 | Negative |
| Anti-Ro/SSA antibodies (U/ml) | 2.6 | <15 | Negative |
| Anti-La/SSB antibodies (U/ml) | 3.9 | <15 | Negative |
| ANA | <1:100 | Titer 0<1:100 | Negative |
| Anti-TPO antibodies (U/ml) | 1.44 | <5.61 | Normal |
| Anti-thyroglobulin antibodies (UI/ml) | 1 | <4.11 | Normal |
| Calcitonin (pg/l) | 2 | <5 | Normal |
| Triiodothyronine (T3) (ng/dl) | 0.98 | 0.58-1.59 | Normal |
| Free thyroxine (T4) (ng/dl) | 0.89 | 0.70-1.48 | Normal |
| Parathormone (pg/l) | 37.8 | 11-67 | Normal |
| Erythrocyte sedimentation rate (ESR) mm/h | 13 | <29 | Normal |
| Rheumatoid factor | | | Negative |
| Hematology | | | |
| White blood cells (WBCs) (10 ³ /μl) | 7.4 | 3.8-11.8 | Normal |
| Monocytes (%) | 12.4 | 4.3-10 | High |
| Red blood cells (RBCs) (10 ⁶ /μl) | 4.37 | 3.63-4.92 | Normal |
| Platelets (10 ³ /μl) | 290 | 179-408 | Normal |
| Factor V Leiden | 3.18 | 2.45-3.32 | Normal |
| Protein C (%) | 104.42 | 70-140 | Normal |
| Protein S (%) | 86.9 | 54.7-123.7 | Normal |
| Coagulation | | | |
| International normalized ratio (INR) | 0.91 | 0.8-1.2 | Normal |
| Activated partial thromboplastin time (APTT) (sec) | 24.5 | 22-36 | Normal |
| Fibrinogen mg/dl | 302 | 239-498 | Normal |
| Molecular Biology | | | |
| <i>PAI-1</i> gene mutation | 675 4G homozygote 844A - AA genotype | | Positive (high risk of thrombophilia in association with Leiden V mutation) |
| <i>MTHFR</i> -gene mutation | 677 C 1298 A | | Negative Positive |
| Biochemistry | | | |
| Alkaline phosphatase (U/l) | 52 | 40-150 | Normal |
| Total serum calcium (mg/dl) | 8.76 | 8.4-10. | Normal |
| Serum phosphate (mg/dl) | 3.5 | 2.6-4.5 | Normal |
| Serum magnesium (mg/dl) | 2. | 1.6-2.8 | Normal |
| Serology | | | |
| Anti-HIV-1/HIV-2 antibodies | | | Negative |
| Anti-HCV antibodies | | | Negative |
| Tuberculosis IgG/IgM | | | Negative |
| Antistreptolysin O (ASLO) | | | Negative |
| Venereal disease research laboratory (VDRL) | | | Non-reactive |

Table I. Continued.

| Immunology | Value | Normal range | Observation |
|---|-------|--------------|--------------|
| Rapid plasma reagin (RPR) | | | Non-reactive |
| Hepatitis B surface antigen (HBsAg) | | | Negative |
| Toxoplasmosis (IgM) Index | 0.1 | <0.499 | Non-reactive |
| Toxoplasmosis (IgG) (U/ml) | 0.1 | <1.6 | Non-reactive |
| Cytomegalovirus (IgM) (S/CO) | 0.05 | <0.85 | Non-reactive |
| Cytomegalovirus (IgG) (AU/ml) | 250 | <6 | Reactive |
| HSV-1 (IgM) (U/ml) | 7.8 | <20 | Negative |
| HSV-1 (IgG) Index | 51.1 | <0.9 | Negative |
| Anti HVS2 (IgM) (U/ml) | 8.4 | <20 | Negative |
| Anti-HVS2 (IgG) Index | <0.5 | <0.9 | Negative |
| Angiotensin convertase enzyme (ACE) (U/l) | 17 | 20-70 | Negative |

HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; HZV, herpes zoster virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; ELISA, enzyme-linked immunosorbent assay for toxoplasmosis; IgM, immunoglobulin M; IgG, immunoglobulin G; aCL, anti-cardiolipin antibodies; C-ANCA, anti-neutrophil cytoplasmic antibodies; P-ANCA perinuclear anti-neutrophil cytoplasmic antibodies; ANA, antinuclear antibodies.

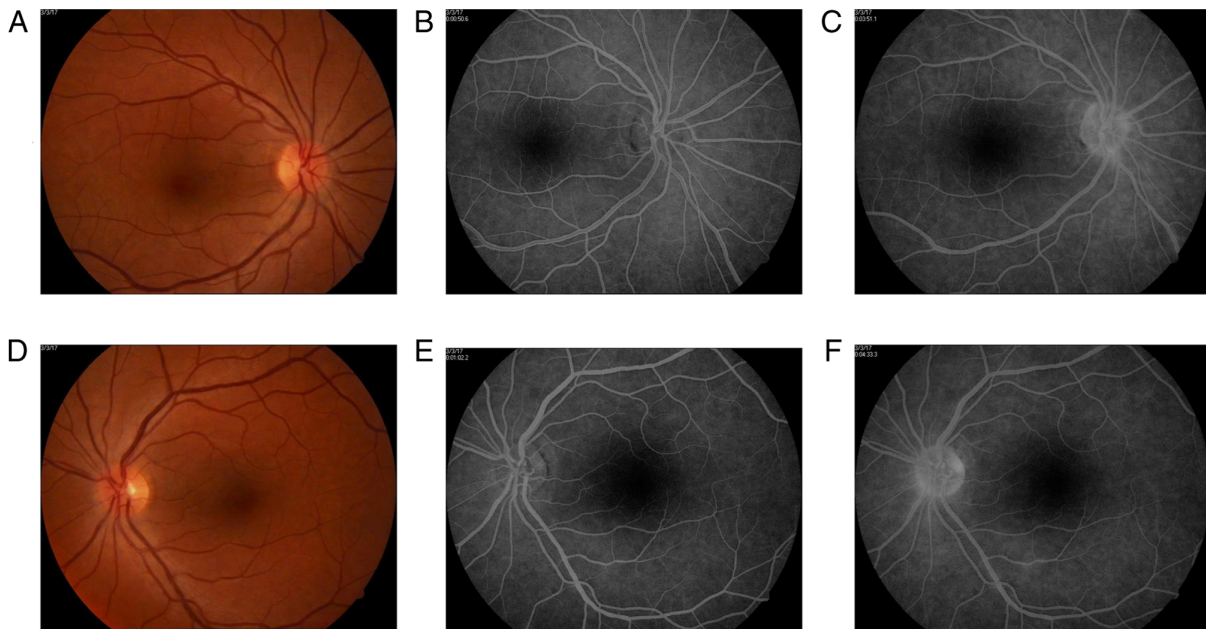


Figure 2. Fundus photography and fluorescein angiography after the IUD was removed and steroid treatment started. (A) The appearance of the posterior pole in the right eye on fundus photography and (B) fundus angiography in the right eye at 50.6 sec (C) and at 3 min and 51 sec. (D) Appearance of the posterior pole in the left eye on fundus photography. (E) Fundus angiography in the left eye at 1 min and 2 sec and (F) at 4 min and 33 sec.

identified that two weeks prior to onset of the symptoms and one month prior to her presentation at the Emergency Room, the patient underwent a gynecological procedure, in which a 13.5 mg levonorgestrel intrauterine contraceptive device (Bayer Inc.) was implanted.

Systemic vasculitis secondary to the IUD was subsequently considered the final diagnosis. After the IUD was removed, treatment with methylprednisolone pulse therapy (MPPT) of 500 mg/daily for 5 consecutive days commenced. Throughout the treatment, the patient was closely monitored for any possible side effects. After the pulse therapy was completed, the patient was discharged from the University Emergency

Hospital Bucharest, Ophthalmology Clinic and continued the oral treatment with methylprednisolone at 0.8 mg/kg/daily with a gradual decrease of the doses every 3 days at home. During the treatment with corticosteroids, the patient also received a proton-pump inhibitor once daily.

One week later, we re-evaluated the patient. All the previous neurological symptoms disappeared and the hearing loss was completely recovered. At the anterior pole examination, there was improvement, the corneal endothelial edema was remitted and the keratic precipitates were reduced in number and size. The fundus examination revealed a decrease of the optic disc edema and in the diameter of the retinal veins

Table II. The Naranjo adverse drug reaction (ADR) probability scale for the intrauterine contraceptive device used.

| Questions | Yes | No | Do not know | Score |
|---|-----|----|-------------|----------|
| 1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | 1 |
| 2. Did the adverse event appear after the suspected drug was readministered? | +2 | 0 | 0 | 2 |
| 3. Did the adverse reaction improve when the drug was discontinued or was a specific antagonist administered? | +1 | 0 | 0 | 1 |
| 4. Did the adverse reaction reappear when the drug was readministered? | 0 | 0 | 0 | 0 |
| 5. Are there alternative causes (other than the drug) that, on their own, could have caused the reaction? | 0 | 2 | 0 | 2 |
| 6. Did the reaction reappear when a placebo was given? | 0 | 0 | 0 | 0 |
| 7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic? | 0 | 0 | 0 | 0 |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | 0 | 0 | 0 | 0 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 1 |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | | | |
| Total | | | | 9 |

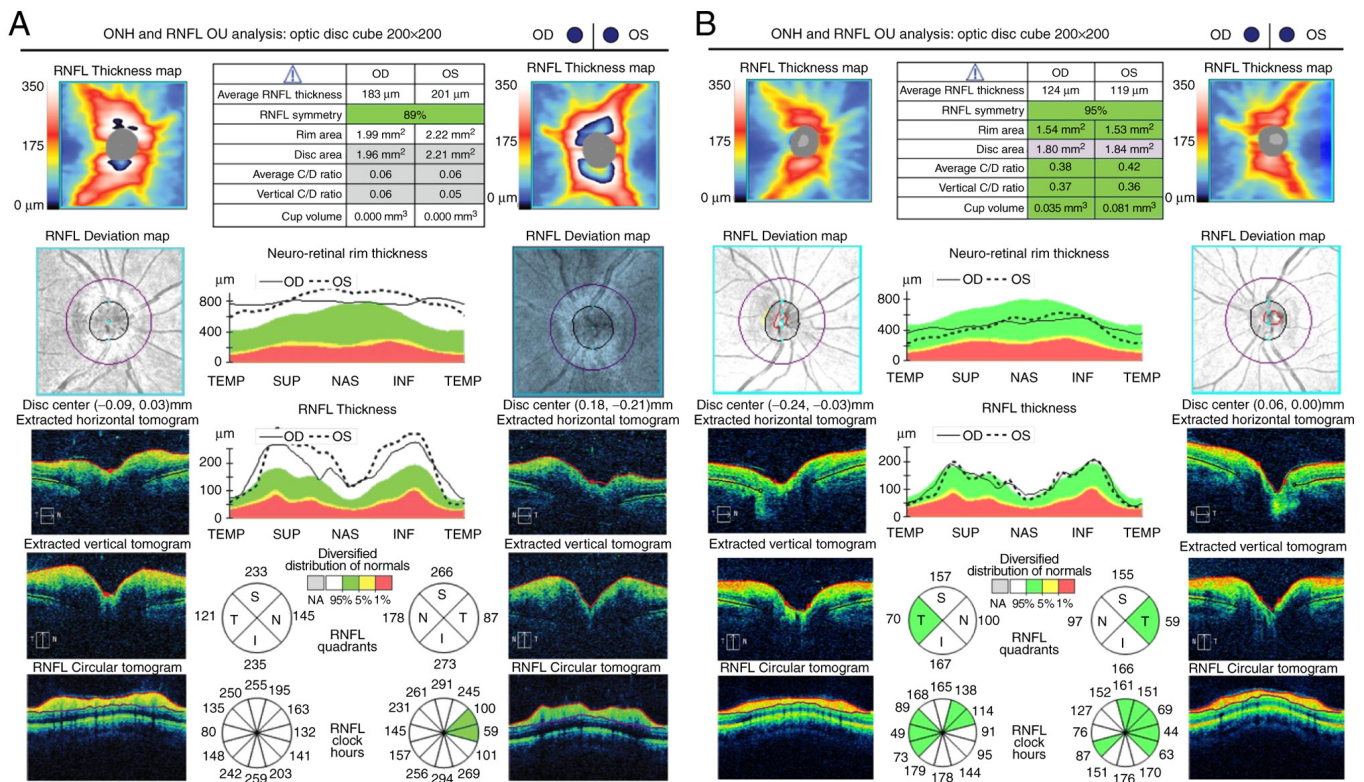


Figure 3. The OCT examination (A) prior to and (B) after one month of treatment.

and their branches (Fig. 2). The optical coherence tomography (OCT) confirmed the identified clinical aspects (Fig. 3). One month later, fundus fluorescein angiography presented with a decrease of the optic disc hyperfluorescence and fewer venous segments of slightly diffuse hyperfluorescence secondary to decreased vascular leakage (Fig. 2).

Ethics approval was obtained from the University Emergency Hospital (Bucharest, Romania). The patient provided written informed consent.

Discussion

First, the predominant optic disc edema accompanied by very fine ocular signs suggested a neurological condition, misleading the clinicians. However, a careful examination related to ancillary tests including fundus fluorescein angiography and OCT provides the information necessary for a proper diagnosis (4,20). Rarely, retinal vasculitis may be isolated, and idiopathic without any other signs. Typical, retinal vasculitis

is a manifestation of a systemic disease or of a retinal inflammatory condition. We followed up the guides in order to determine the cause of the disease; however, the tests did not offer the information required. A very thorough examination of the medical history supplied the missing piece of information that was necessary to elucidate the cause. To the best of our knowledge, medical literature has not previously reported any case of retinal vasculitis related to Jaydess® 13.5 mg levonorgestrel intrauterine contraceptive device (21). However, some studies in literature indicate the occurrence of vasculitis related to oral contraceptive administration, but with mild vascular involvement (16,18,22,23). Mosovich *et al* published a case of necrotizing vasculitis caused by the Microgynon pills (levonorgestrel, 0.15 mg and ethinyl-oestradiol, 0.03 mg) (13).

The diagnosis of generalized vasculitis with retinal involvement is, similar to other drug-induced vasculitis, based on the temporal relationship between the drug administration and the appearance of the clinical signs of disease (24). In addition, the absence of other causes that could explain the clinical picture, as systemic autoimmune diseases or infectious diseases (the ancillary test was negative or non-reactive), the remission of the disease after the device has been removed and the positive response to the systemic steroid therapy also indicate a direct relationship between the IUD and disease.

In addition, we focused on thyroid disorders in order to exclude a secondary cause, being aware of the possible relationship with primary or secondary ANCA vasculitis. The test results excluded other retinal vasculitis associated with systemic inflammatory diseases, such as systemic lupus erythematosus, Wegener granulomatosis, microscopic polyangiitis, antiphospholipid syndrome and ANCA-associated vasculitis (25,26).

As the patient was complaining of hearing dysfunction, and in the context of a mild anterior uveitis, Cogan syndrome was suspected (27). However, in the absence of any cardiac signs, normal blood level of leukocytes, a slight increase of the erythrocyte sedimentation rate, a normal C-reactive protein, we excluded this syndrome (27,28).

Finally, the Naranjo adverse drug reaction (ADR) probability scale was performed and suggested an outcome to our clinical evidence (29,30) (Table II). The last question is slightly contentious, since it was based on the patient's response. The patient claimed that when she was previously under treatment with similar drugs, such as oral contraceptive (similar to levonorgestrel), she presented a low intensity similar response, but could not provide medical evidence to support these aspects.

The Naranjo criteria classifies the probability that an adverse event is related to a specific drug therapy, based on a list of weighted questions, which examine factors such as the temporal association of drug administration and the event, alternative causes that can explain the event, drug levels, dose-response relationship and the patient's previous experience with that drug (29-31). If ADR score is ≥ 9 , the adverse drug reaction is considered as definite, if the score is between 5 and 8 it is interpreted as probable, possible for a score between 1 and 4, and doubtful if the score is 0 (31). The Naranjo criteria does not take into account drug interactions. Drugs are evaluated individually for causality, and points are deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.

In conclusion, to the best of our knowledge no previous case of retinal disease and optic disc edema associated with auditory problems (possible vascular) caused by an intrauterine device has been reported. A proper examination correlated with a very thorough medical history could identify rare diseases and associations, in order to provide adequate medical care.

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Availability of data and materials

Further information regarding the case is available from the corresponding author upon reasonable request.

Authors' contributions

AMG had a substantial contribution to the conception and design of the work, analyzed and interpreted the data being also the first investigator and coordinator of the article. AMG also gave the final approval of the version to be published. CA collected all the data from the patient's medical history and produced the figures and tables. SI performed ocular coherence tomography, fundus fluorescein angiography, and verified that the information and data were accurate. AE performed the Naranjo adverse drug reaction (ADR) probability scale and revised the paper. ACG was responsible for literature research of the current data, drafted the study, and revised it critically for important intellectual content. AMG and ACG assessed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the University Emergency Hospital, 050098 Bucharest, Romania. The patient provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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