CASE REPORT

REVISED Case Report: Recurrent retinal vein occlusion as the first clinical manifestation of systemic lupus erythematosus in a male patient [version 2; peer review: 2 approved with reservations]

Previous title: Case Report: Retinal vein occlusion as the first clinical manifestation of systemic lupus erythematosus in a male patient

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterized by widespread clinical manifestations and immunological disorders. A myriad of ocular manifestations can be seen in patients with SLE. The most vision-threatening complication is vaso-occlusive retinopathy including retinal vein occlusion (RVO). RVO associated with SLE is well described in the literature and its association with antiphospholipid antibodies is recognized. However, RVO as the initial manifestation of SLE is scarcely reported. Herein, we report the first case of recurrent RVO as the revealing manifestation of SLE in a 40-year-old male patient. He had two consecutive episodes of decreased vision. Ophthalmologic examination disclosed a branch retinal vein occlusion the first time and a central retinal vein occlusion the second time. The diagnosis of SLE was established based on clinical and immunological criteria. He was prescribed antiplatelet therapy, hydroxychloroquine at 5.5 mg/kg/day, and intravitreal anti-vascular endothelial growth factor

Open Peer Review

Approval Status

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1. Bouomrani Salem , University of Sfax, Sfax, Tunisia		

(VEGF) antibodies regimen. He slowly improved under treatment.

Keywords

Retinal vein occlusion, Systemic Lupus Erythematosus, Male patient, Intra-vitreous anti-vascular endothelial growth factor antibodies treatment, case report

Military Hospital of Gabes, Gabes, Tunisia

2. **Matias Iglicki** , University of Buenos Aires, Buenos Aires, Argentina

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Ben Brahim M:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Methodology, Resources, Visualization, Writing – Original Draft Preparation; **Arfa S:** Conceptualization, Data Curation, Investigation, Methodology, Visualization, Writing – Review & Editing; **Boubaker F:** Resources, Software, Validation; **Chelly J:** Resources, Visualization; **Ammari W:** Data Curation, Resources, Software, Visualization; **Hammami S:** Formal Analysis, Resources, Writing – Review & Editing; **Arbi F:** Resources, Software, Visualization; **Berriche O:** Formal Analysis, Resources, Writing – Review & Editing

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REVISED Amendments from Version 1

1. Data about the patient medical history was added.
2. We added further details about the laboratory investigations.
3. We have done corrections in the spelling of some words.

Any further responses from the reviewers can be found at the end of the article

Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disorder that, if left untreated, can lead to vision loss¹. Classic risk factors are hypertension, hyperlipidemia and diabetes mellitus². Systemic and inflammatory diseases such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome were found to be associated with the development of RVO³. RVO associated with SLE is well described in the literature and its association with antiphospholipid antibodies is recognized^{1,2}. However, RVO as the initial manifestation of SLE is very uncommon. Herein we report a unique case of recurrent RVO as the initial presentation of SLE in a male patient.

Case report

A 40-year-old Tunisian man, with no family history of autoimmune diseases and a personal medical history of hypertension treated with angiotensin-converting enzyme inhibitor, was admitted to the Ophthalmology Department of Taher Sfar University Hospital with blurred vision in the right eye. On detailed physical examination, he had no fever, arthritis, or chest complaints. On ophthalmologic examination, the best corrected visual acuity was 20/20, and a retinal branch vein occlusion in the right eye was disclosed. He was treated with aspirin (100 mg/day) associated with equilibration of his hypertension.

One year later, he experienced another episode of blurred and decreased vision in the same eye. Physical examination was unremarkable. A skin exam revealed he had an erythema over the malar area. His blood pressure was normal. Fundus examination disclosed central retinal vein occlusion, superficial flame-shaped retinal hemorrhages, and macular oedema (Figure 1). Fluorescein angiography (FA) demonstrated vascular tortuosity, retinal hemorrhage, and cotton wool spots on the right eye (Figure 2). Spectral-domain optical coherence tomography demonstrated cystoid macular oedema (Figure 3). The left eye examination showed normal sizes of the retinal vessels and retina. A refraction study showed a best corrected visual acuity at 20/70 in the right eye and 20/20 in the left eye. On laboratory investigations, a blood test showed platelets: $229 \times 10^9/l$, leukocytes: $9 \times 10^9/l$, and hemoglobin level: 13.5 g/dl. Erythrocyte sedimentation rate was 30 serum creatinine was normal. Moreover, urinalysis did not show proteinuria.

Autoantibodies tests revealed positive antinuclear antibodies (1: 800), anti-DNA antibodies, anti-nucleosomes antibodies, and slightly positive anti-citrullinated protein antibodies and rheumatoid factors. Antiphospholipid antibodies screening displayed high titer (> 40 UI) of IgG anticardiolipines and

Figure 1. Superficial flame-shaped retinal hemorrhages in fundus examination.

Figure 2. Fluorescein angiography showing vascular tortuosity, retinal hemorrhage, and cotton wool spots on the right eye.

Figure 3. Spectral-domain optical coherence tomography showing cystoid macular oedema.

IgG anti β 2 glycoprotein antibodies. Total blood complement, C3, C4, protein S, protein C antithrombin III, and homocysteinemia levels were normal. The patient was also negative for factor V mutation. Echocardiographie excluded pericardial effusion. The diagnosis of SLE was established based on clinical and immunological criteria including malar rash, positive anti-nuclear antibodies, anti-DNA antibodies, and antiphospholipid antibodies.

The patient was started with hydroxychloroquine at 5.5 mg/kg/day and intra-vitreous anti-vascular endothelial growth factor (VEGF) antibodies regimen, in combination with aspirin (100 mg/day). The patient is still regularly taking his treatment without significant side effects. His vision has slowly improved under treatment. The patient remained under close observation. After two years of follow up, a refraction study showed a stable visual acuity.

Discussion

The atypical clinical presentation of SLE, in a male patient with a medical history of hypertension, and without any clinical objective criteria, led to the delay of the diagnosis of this autoimmune disease. The diagnosis was made after a second retinal vein occlusion. The patient had cutaneous involvement concomitantly with ocular complication. He had immunological criteria including positive antinuclear antibodies, anti-DNA antibodies and antiphospholipid antibodies which made the diagnosis clearer.

SLE is a chronic and autoimmune disease characterized by widespread clinical manifestations and immunological disorders. It occurs in both genders but it is much more common in females than males, with female:male sex-ratio of 8:1 to 15:1³. Male patients have a higher prevalence of life threatening manifestations including lupus nephritis, central neurological system involvement and hemolytic anemia^{3,4}. Regarding immunological features, anti-phospholipid antibodies were found to be more frequent in male SLE patients⁵. Thus, it would be expected that they present an increased risk of thromboembolic manifestations and antiphospholipid syndrome, which could worsen the course of the illness and increase the mortality rates. We report a case of SLE associated with antiphospholipid antibodies in a male patient. He presented a recurrent RVO as the first manifestation of the disease making this case unique.

A myriad of ocular manifestations can be seen in patients with SLE including keratoconjunctivitis, scleritis, episcleritis, retinopathy, choroidopathy, orbital and lachrymal system disorders⁶. The most common ocular manifestation is keratoconjunctivitis but the most visually-threatening is retinopathy. The prevalence of lupus retinopathy varies from 3% to 28%^{6,7}. The

most common manifestations of lupus retinopathy are cotton wool spots, retinal hemorrhage and optic disk oedema⁷. Vaso-occlusive retinopathies is a subset of retinal vasculopathy, including retinal artery or vein occlusions which are a rare but severe complication. The vascular retinopathy in SLE results from immune complex mediated vascular injuries and micro-vascular thrombosis⁸. Patients with retinal vessel occlusion seem to have a poorer visual prognosis.

Patients with SLE have a higher prevalence of developing RVO than the general population. A higher incidence of antiphospholipid antibodies in SLE patients with RVO has been reported. In our case, antiphospholipid antibodies were positive with a high titer^{7,9,10}. Typically, RVO occurs in the first four years follow-up of SLE. Retinal vasculitis was scarcely reported as the initial manifestation of SLE¹¹⁻¹³. As far as we know, this would be the first case of a recurrent RVO as the primary presentation of SLE to be reported in literature.

Regarding the treatment of RVO in patients with SLE, anticoagulation and anti-platelet therapies have contributed to the stabilization of the retinal occlusion and the prevention of recurrent thrombosis either used separately or combined. The use of an immunosuppressant is still controversial due to the lack of evidence about its effects in improving the visual acuity and the retinal vascular occlusion recurring⁷. Intravitreally administered anti-VEGF antibodies were introduced in the treatment regimen of RVO. Its main desired effect is to reduce the macular edema, which is the major cause of decreased visual acuity in patients with RVO¹⁴. Our patient received a combination of anti-platelet therapy and anti-VEGF antibodies. Clinical improvement was achieved under this treatment.

Conclusion

SLE in males may have an atypical presentation. This often leads to a diagnostic and therapeutic delay. In this paper, we have reported a unique case of SLE in a male patient presenting with a severe and sight-threatening ocular complication. The diagnosis was overlooked, as the patient did not have any clinical criteria of SLE initially. Our case report's core contribution is to raise awareness about the possible atypical and severe presentation of SLE in men.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Data availability statement

All data underlying the results are available as part of the article and no additional source data are required.

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Open Peer Review

Current Peer Review Status: ? ?

Version 2

Reviewer Report 06 December 2021

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- The corrections requested for the "Discussion" section have not been made.
- Similarly, the suggested bibliographical references, dealing with the subject of this paper and very useful for enriching the discussion, have not been used.

This version should be revised in accordance with these suggestions.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Connective tissue disease, autoimmunity, immunogenic.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 14 Dec 2021

Marwa Ben Brahim, Taher Sfar University Hospital, University of Monastir, Mahdia, Tunisia

Dear Reviewer;

The requested corrections for the discussion section are now made as you previously suggested.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 23 September 2021

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Matias Iglicki

Private Retina Practice, University of Buenos Aires, Buenos Aires, Argentina

Marwa Ben Brahim *et al.* present an interesting study about Retinal vein occlusion (RVO) as the first clinical manifestation of systemic lupus erythematosus (SLE) in a male patient. The study results certainly suggest to some degree that the RVO as the initial manifestation of SLE is scarcely reported.

Besides how the magnitude of these data add new findings compare to the current standard can not be determined only based on this study. The results are encouraging and further study is warranted.

Here some relevant points:

1. Please add on keywords - these do not match with the manuscript.
2. The authors should express why it is relevant for an RVO patient to link Retinal vein occlusion as the first clinical manifestation of systemic lupus erythematosus in a male patient? What does it change for the current standard of care?
3. The authors should explain why their findings make a difference for ophthalmologists around the world and for the readers of *F1000Research*.
4. The authors should explain the source of the information and what criteria they used for adding it to the paper. Were the assessors masked? What was the ICC (Inter class Correlation) between them in order to analyze the data? Was the randomization digitalized?
5. Please add in the introduction that papers have been published showing how the Optical Coherence Tomography (OCT) and new devices lead us to proper diagnoses in Retinal diseases - add one line in the introduction of this and also in the discussion section. These papers should be described in the general considerations. See references^{1,2,3}.
6. Please add how and how long takes for a retina specialist to link and ask the patient about SLE and other Rheumatology and Rheumatic Diseases.
7. Results could be misinterpreted - add a short summary of the similarities in different devices and also add different OCT modalities, etc., and what can be improved in the process of detecting RVO is mandatory in the discussion section i.e wide-field angiography, different types of OCT modalities OCT angiography (OCTa).

8. Please apply correction for misspelling and English grammar.

References

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: DME, RVO, NAMD and retina surgical cases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Jun 2022

Marwa Ben Brahim, Taher Sfar University Hospital, University of Monastir, Mahdia, Tunisia

1. Keywords: they match the manuscript
2. Since systemic lupus erythematosus is a chronic inflammatory disease with a periodic evolution it may require anti-inflammatory and/or immunosuppressant treatments in addition to symptomatic treatments of visceral manifestation such as the case of RVO how required Hydroxychloroquine, aspirin, and antiangiogenic treatment as well as long term follow-up in order to reduce relapses.

3. In fact, publishing this case report may raise awareness about this severe sight-threatening manifestation of SLE in men patients.
4. Dear reviewer, I do not think that interclass correlation could be applied in a case report.
5. Optical coherence tomography (OCT) allows the visualization of retinal layers and early diagnosis of the small retinal lesions.
6. Although the scarcity of ophthalmological manifestations as the primary manifestation of SLE, retina specialists should keep this diagnosis in mind and carefully look for other signs of an autoimmune systemic disease.
7. Done.

Competing Interests: No competing interests were disclosed.

Reviewer Report 17 August 2021

<https://doi.org/10.5256/f1000research.58746.r91272>

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The authors provide an interesting and original Case Report of retinal venous occlusion revealing systemic lupus erythematosus in a man. This observation is distinguished by the initial atypical clinical manifestation, male sex, and recurrence of retinal occlusion. This case is therefore the first to report recurrent retinal venous occlusion as an initial manifestation of lupus.

Some comments are however useful to improve the quality of this manuscript:

1. Title:

- Replace the proposed title with "recurrent retinal vein occlusion as..." to highlight the recurrent character which is the originality of this observation.

2. Abstract:

- Replace "primary" by initial or revealing.

3. Keywords:

- Adapt the list of keywords to international standards: remove "patient" from "male patient",

remove "case report", remove "intra- vitreal and treatment" from "Intra-vitreous anti-vascular endothelial growth factor antibodies treatment".

4. Case Report:

- Specify the anti-hypertensive treatment received by the patient (possibility of induced lupus)?.
- Replace "caucasian" by "Tunisian".
- Remove "s" from "rheumatoid factors",
- Add, if possible, a photo of the patient's malar erythema.
- If possible, give the results of the explorations made to support the diagnosis of systemic lupus erythematosus: cardiac ultrasound (lupus pericarditis? which is asymptomatic in 30% of cases), cerebral MRI (infra-clinical neurolupus? Especially the association with retinal vasculitis is noted in more than 70% of cases¹), and urinalysis?.
- Specify, if they were carried out, the results of the following tests: factor V mutation? (main thrombophilia causing venous thrombosis in Tunisia), and homocysteinemia? (hyperhomocysteinemia may be an added risk factor for retinal vein occlusions during SLE (1 patient/3 in Kumar K *et al* series²).

5. Discussion:

- Replace "primary" by initial or revealing.
- Discuss the significance of anti-CCP antibodies in this observation: associated rheumatoid arthritis? (positive anti-CCP antibodies and positive RF: Rheumatoid syndrome?) Or a simple positivity of anti-CCP which can be seen in 10-15% of patients with SLE³?

6. Conclusion:

- Rephrase "delay in making the diagnosis..." by "diagnostic and therapeutic delay".
- Replace "article" by "paper".
- Correct "typical" by "atypical".
- Emphasize the recurrent and revealing nature of the retinal venous occlusion which is the originality of this case.

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Connective tissue disease, autoimmunity, immunogenic.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Sep 2021

Marwa Ben Brahim, Taher Sfar University Hospital, University of Monastir, Mahdia, Tunisia

1. Done

2. Done

3. Done, the keyword "case report" was kept because it has to be mentioned.

4. We, unfortunately, do not have any pictures of the patient's malar rash. Since the patient had not had any neurological symptoms, we did not demand a Brain-MRI. We have added further details about the laboratory investigation.

5. Done. The patient had slightly positive anti-citrullinated protein antibodies and rheumatoid factor without bone erosion or joint stiffness or deformity evoking the diagnosis of rheumatoid arthritis. In fact, the positivity of anti-CCP can be seen in 10-15% of patients with SLE without an association to rheumatoid arthritis.

6. We rephrased "delay in making the...." as you suggested. We corrected typical by atypical as you suggested. We have emphasized the recurrent and revealing character of the retinal vein occlusion in all parts of the paper.

Competing Interests: No competing interests.

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