The Editor,

The Baishideng Publishing Group (BPG)

Dear Editor:

We would like to express our sincere gratitude to you and the reviewers for the constructive suggestions to improve the quality of our manuscript entitled " A rare presentation of spontaneous atheroembolic renal disease – a case report and literature review ". We have made all the revisions in accordance with the comments from the reviewers, and we hope the revised version of the manuscript will be more suitable for publication. Our responses to the reviewer's comments are summarized below.

In addition, the revisions or insertions are shown within the manuscript as highlighted (yellow) text in MS Word.

If you have any further question, please do not hesitate to contact me. Thank you very much for your kind consideration, and we look forward to hearing from you soon.

Yours sincerely,

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Reviewers' comments and author's responses (Manuscript NO: 46234)

Reviewer Reports

REVIEWER 1:

Need revisions before publication. Minor revisions:

a) In the title authors put two abbreviations but usually there is no place for abbreviations in the title

Response: Thank you for pointing out an important part. We have removed those two abbreviations and changed the title as mentioned below in manuscript.

Revision (Page 1 Line 7,8) "A rare presentation of spontaneous atheroembolic renal disease – a case report and literature review "

b) In the section „Abstract" authors put abbreviation (AERD) but without explanation.

Response: Thank you for pointing out an important part. We have amended that in manuscript.

Revision (Page 3 Line 68-70) Atheroembolic renal disease (AERD) is caused by occlusion of small renal arteries from embolized cholesterol crystals arising from ulcerated atherosclerotic plaques.

c) The literature is not written in the unique and consistent way. Otherwise the article is interesting for those involved in the management of kidney disease.

Response: Thank you for your valuable suggestion. We have amended that in manuscript. Literature was re written and new information was added. (Discussion Paragraph 3)

Revision (Page 9-11 Line 263-327) - Paragraph 3 to 7 in discussion are dedicated relevant literature review rewritten.

REVIEWER 2

This case report describing AERD with serum cANCA positivity noted by chance is somewhat potentially interesting. However, several concerns are arisen.

1. I understand the reported patient with AERD showed serum cANCA positivity. However, it is unclear how the cANCA positivity influences her clinical status. Was cANCA positivity really involved in the pathogenesis in this patient? This issue should be clearly described.

Response: Thank you for pointing out an important part. We have amended that in manuscript.

Revision (Page 9 Line 263-274) Association of atheroembolism with ANCA positivity is exceedingly rare [11]. A recent literature review done by Zhang J et al mentioned 12 cases (3 with c- ANCA, 6 with p-ANCA, 1 with both, 2 positive ANCA by early indirect immunofluorescence) of cholesterol embolism with ANCA positivity[11]. Out of those twelve patients, average age reported as 69 and ten of them were males with multiple medical comorbidities[11]. One third of the patients found to have spontaneous atheroembolism like our patient[11]. The role of the ANCA in atheroembolic diseases is unclear and yet to be elucidated. Positive c-ANCA without any evidence of systemic evidence of vasculitis at the time of testing were reported previously in literature and various reasons like cross reactivity, non specific neutrophil activating properties, analytical false values etc) are attributed[12].

2. Did the serum titer of cANCA decrease following immunosuppressive therapy? Sequential changes in serum titer of cANCA in this patient should be represented.

   Response: Thank you for pointing out an important part. We have amended that in manuscript.

Revision (Page 9 Line 234-235) ANCA test was repeated twice after her one-month follow up visit and it turned up negative.

3. The discussion section remained irrelevant. Original description contained so many unnecessary general information. This section should focus on the authors' novel observation and speculation. Thus, whole volume of discussion section should be reduced and rewritten.

Response: Thank you for valuable suggestion. We have amended that in manuscript.

Revision (Page 8,9 Line 240-274) Paragraph 1 -3 under discussion was re written to include details relevant to our observation and speculation. Unnecessary general information like surgical management details, history of athero embolic disease description etc were removed from discussion.

4. In abstract section, the description of the conclusion was unlikely.

Response: Thank you for valuable suggestion. We have amended that in manuscript.

Revision (Page 3,4 Line 94-98) In cases like the above where non-vasculitis associated ANCA tests, a high degree of clinical suspicion is required to pursue the diagnosis of spontaneous AERD in patients with clinical or radiological evidence of atherosclerotic burden. Although no specific treatment is available, the potential role of statins and steroids needs to be explored.

REVIEWER 3

There is missing one reference, Please check all references on pubmed.

Response: Thank you for pointing out an important part. We have amended that in manuscript. All the references are checked in pubmed.

Revision (Page 11,12 Line 318-320, 350-447) Belenfant and co-workers showed improvement in symptoms and nutritional intake with low dose steroid (0.3 mg/kg) in 18 patients with relapsing disease[25].

Authors sometimes used capital letter in the body of statements!!!!

Response: Thank you for pointing out an important part. We have amended that in manuscript.

Revision (Page 8 Line 215) (Page 7, 193) Words like interventional radiology, hepatitis etc changed in to simple letters.

Check again Unneeded abbreviations should be cancelled

Response: Thank you for your valuable suggestion. We have amended that in manuscript.

Unneeded abbreviations were cancelled.

REVIEWER 4

The topic of the manuscript is interesting. Major concerns:

The Case Report description is too long and non-contributory in some instances.

Response: Thank you for your valuable suggestion. We have amended that in manuscript.

Revision (Page 5-8, Line 145-235) - We have re-written the case description under subheadings suggested by editor.

Units (creatinine for instance) are missing.

Response: Thank you for pointing out an important part. We have amended that in manuscript.

Revision (Page 5 Line 150-152, Page 6 Line 179 , Page 8, Line 234) Her baseline

creatinine was 1.5 mg/dL, but had increased to 5.62 mg/dL over a period of 4 months.

Her laboratory examination showed normocytic normochromic anemia, serum eosinophilia (10%), hyperkalemia, metabolic acidosis, elevated creatinine (5.2mg/dl) and elevated BUN (69 mg/dl).

Her renal function continued to improve, and the serum creatinine declined to 2.9 mg/dL at one-month follow up.

Words like didn't are colloquial are have no place in a paper. "....of patient to lie flat". Why do not use the word orthopnea in this situation?.

Response: Thank you for pointing out an important part. We have amended that in manuscript. She was unable to lie flat not due to orthopnea. But as she was obese, she couldn't be in prone position for renal biopsy.

Revision (Page 7, Line 211-214) A renal biopsy was postponed to day 4 after admission due to relative contraindications such as aspirin usage, poorly controlled hypertension, and the patient's inability to assume a prone position due to body habitus.

Please delete words as "lab".

Response: Thank you for pointing out an important part. We deleted the word lab in our manuscript.

Revision (Page 6, Line 177) Her laboratory examination showed….

Discussion is too long and diverted.

Response: Thank you for your valuable suggestion. We have amended that in manuscript. Removed unnecessary details and included some new relevant literature.

Revision (Page 9-11 Line 240-337): Paragraph 1 to 8 – Discussion is rewritten with relevant literature review.

Authors mention "inactive IgA nephropathy changes"...What on earth does that term mean at all?....How can we tell IgAN is inactive from the histopathology?....Oxford classification does not address those concepts, which are impossible to assess with routine histologic techniques.

Response: Thank you for pointing out an important part. This particular case, Renal Pathology was a send out test from our institution, as it required detailed analysis. Professor Helmet Renkke (Head of Pathology, Brigham and Women hospital) had performed immunofluorescence, electron microscopy apart from routine histopathology.

It was our fault not including them in the Figures. We are including them in the revised manuscript. We will upload all the necessary slides as powerpoint for your review.

The word inactive IgAN was in the report from BWH pathology report by Prof Renkke. How ever I have removed the word inactive as per your request.

Patient had eosinophilia. Please introduce this laboratory finding to the discussion and the prevalence in AERD.

Response: Thank you for your valuable suggestion. We have amended that in manuscript.

Revision (Page 9 Line 257, Page 10 Line 299-300): Eventually her biopsy confirmed predominant AERD pathology, and the presence of serum eosinophilia supported the above.

Serum eosinophilia is noted up to 80 % of patients with atheroembolic disease[24].

What do authors mean by AERD being a spectrum of kidney diseases?. I do not agree.

Response: Thank you for your valuable suggestion. We have **removed the word**

spectrum in our manuscript.

Our Explanation – AERD has acute, subacute and chronic forms. In the spectrum of various renal pathologies such as ATN, Interstitial nephritis, glomerular disease, vascular disease such as vasculitis, thrombotic microangiopathies etc , AERD also has a place. It could be differentials to AKI, Sub acute or chronic renal injury in the spectrum of renal pathologies.

We didn't use this word for the first time in literature. Francesco Scolari **(** who wrote many papers on AERD **)** has used this word few times in the literature in the past.

For example please refer this paper 1. **Scolari F**, Ravani P, Gaggi R, Santostefano M, Rollino C, Stabellini N. The challenge of diagnosing atheroembolic renal disease: clinical features and prognostic factors. Circulation. 2007; 116(3): 298-304. [PMID: 17606842 doi: 10.1161/circulationaha.106.680991]

Why do authors think the patient had an elevated ANCA titer?.

Response: Thank you for pointing out an important part. We have removed the word elevated in the manuscript.

Revision (Page 7 Line 209) positive titer of ANCA

Explanation – We wanted to highlight that ANCA positive has some significance, as it remained positive after many serial dilutions. In our patient the titre was 1/320. Mayo clinic laboratories suggests ANCA titre remain positive after 2 serial dilution to be considered significant.

How can they link a positive ANCA titer with a thromboembolic event?.

Response: Thank you for pointing out an important part. We have amended that in manuscript.

Revision (Page 9 Line 263-274) Association of atheroembolism with ANCA positivity is exceedingly rare [11]. A recent literature review done by Zhang J et al mentioned 12 cases (3 with c- ANCA, 6 with p-ANCA, 1 with both, 2 positive

ANCA by early indirect immunofluorescence) of cholesterol embolism with ANCA positivity[11]. Out of those twelve patients, average age reported as 69 and ten of them were males with multiple medical comorbidities[11]. One third of the patients found to have spontaneous atheroembolism like our patient[11]. The role of the ANCA in atheroembolic diseases is unclear and yet to be elucidated. Positive c-ANCA without any evidence of systemic evidence of vasculitis at the time of testing were reported previously in literature and various reasons like cross reactivity, non specific neutrophil activating properties, analytical false values etc) are attributed[12].

What is the role the damaged endothelium may play in both situations so as to present with ANCA positivity?.

Response: Thank you for pointing out an important part. It's a valid interesting question.

Both ANCA vascultis and AERD are known to involve damaged endothelium. In case of ANCA vasculitis whether damaged endothelium occurring before or after the development of ANCA antibodies is not entirely clear. More recent literature supports pathogenic role of ANCA in the endothelial damage.

Halbwachs L, Lesavre P. Endothelium-neutrophil interactions in ANCA-associated diseases. *J Am Soc Nephrol*. 2012;23(9):1449–1461. doi:10.1681/ASN.2012020119

We have very limited literature/research related to AERD. Future research needs to address this question further.

Was the vascular inflammation evaluated in the kidney biopsy?.

Response: Thank you for pointing out an important part. This particular case, Renal Pathology was a send out test from our institution, as it required detailed analysis. Professor Helmet Renkke (Head of Pathology, Brigham and Women hospital) had performed immunofluorescence, electron microscopy apart from

routine histopathology.

It was our fault not including them in the Figures. We are including them in the revised manuscript. We will upload all the necessary slides as PowerPoint for your review.

References do not follow WJN instructions.

Response: Thank you for pointing out an important part. We have amended that in manuscript references and we included doi and Pubmed ID. (Except a Few articles that were published before year 2000 didn't have DOI)

Figure 1 is non-contributory.

Response: Thank you for pointing out an important part. We have amended that in manuscript. We have amended the figures and included new figures that are relevant. (Immunofluorescence and electron microscopy)

REVIEWER 5

In this manuscript, the authors report on an unusual case of spontaneous atheroembolic renal disease (AERD) mimicking ANCA-associated glomerulonephritis. This paper is clinically interesting, but one point need to be addressed.

Minor comment: The authors should describe the influence of ANCA on the onset of AERD in this case.

Response: Thank you for pointing out an important part. We have amended that

in manuscript.

Revision (Page 9 Line 263-274) Association of atheroembolism with ANCA positivity is exceedingly rare [11]. A recent literature review done by Zhang J et al mentioned 12 cases (3 with c- ANCA, 6 with p-ANCA, 1 with both, 2 positive ANCA by early indirect immunofluorescence) of cholesterol embolism with ANCA positivity[11]. Out of those twelve patients, average age reported as 69 and ten of them were males with multiple medical comorbidities[11]. One third of the patients found to have spontaneous atheroembolism like our patient[11]. The role of the ANCA in atheroembolic diseases is unclear and yet to be elucidated. Positive c-ANCA without any evidence of systemic evidence of vasculitis at the time of testing were reported previously in literature and various reasons like cross reactivity, non specific neutrophil activating properties, analytical false values etc) are attributed[12].