



PEER-REVIEW REPORT

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Title: Hydroxychloroquine-induced renal phospholipidosis resembling Fabry disease in undifferentiated connective tissue disease: A case report

Reviewer's code: 00424850

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor

Reviewer's country: Spain

Author's country: China

Reviewer chosen by: Artificial Intelligence Technique

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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General comments: In my opinion the issue is very interesting. The problem for me is that it is unclear the real/clinical impact of such secondary effect. All along the manuscript, it is clear the pharmacological mechanism explaining histopathological findings, but it is not clear the potential clinical effects (Is the renal effect relevant? Reversible?). On the other hand, the authors indicate that it is a case report and bibliographic review. However, I do not see the part related to the review, not at least in a specific way. In the actual manuscript, it seems to be a qualitative comment of the presented case more than a review. It lacks more specific "numerical" data obtained from existing bibliography. For example, I would like to know how many cases have previously been published as well as the characteristics of the publications, probably with a table with the main aspects of each publication. On the other hand, in the actual manuscript, it is not clear the clinical impact of the pharmacological interaction, nor from the comment of the existing bibliography nor from the case report itself. Probably the manuscript would be more informative if the authors indicate the clinical evolution of the present case after the withdrawal of OH-chloroquine. In my opinion the way for it would be another renal biopsy, although for ethical reasons probably the correct way would be periodical monitoring of proteinuria as well as hematuria, and only in the case of persistence of initial alterations after a reasonable time period (6-12months) to repeat renal biopsy to discard other causes of renal disease. Another point to illustrate when considering published bibliography is the effect and indication of enzyme replacement with pharmacological enzymes. It is not clear in the manuscript, in which in a first time the authors establish that it is indicated but later, when commenting bibliography, it seems that it is not. In relation with formal aspects of the actual text, in my opinion authors repeat too much times the reasons to discard Fabry disease. Specific comments: 1.-Abstract: In the background part some modifications should be done: "Fabry disease is a kind of...". It is an easier and clearer expression. "... can cause symptoms renal



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injury similar to those usually seen in Fabry disease." It is not correct to use "symptom". A symptom is a clinical manifestation of a disease. 2.- Background: It is not correct the expression "X-linked dominant...". Fabry disease is a genetically X chromosome linked disease. I think that probably the background should be more specifically centered on Fabry and kidney as well as differential diagnosis. 3.- Case presentation: Changes to be done: "...of hormone therapy..." This expression is not correct. It is not clear what treatment exactly is referred. It is supposed that it is referred to OHchloroquine. But it is not a hormonal treatment. "... Renal function was normal (Table 1)..." It cannot be said. The correct way to express it is to give any parameter about renal function, that is not normal because there is proteinuria. The table does not give any significant information. Probably it could be interesting a graphic illustrating time evolution of proteinuria as well as estimated glomerular filtration and the relationship with OHChloroquine doses. 4.- Discussion and conclusions: "...diagnosis of Fabry disease depends on the presence of zebra bodies or myelin figures in microscopic tests...". It is an incorrect sentence. This anatomopathological finding is not considered part of Fabry disease diagnosis criteria. This finding is suggestive of this disease, but not a diagnosis criteria itself. It has been in fact what happened in the present case, in which the observation of zebra bodies in the renal biopsy made to the authors to consider this option. "...renal phospholipidosis was ultimately confirmed because of the symptoms...". The correct expression should be "manifestations" instead of "symptoms". Phenotypic expression of a disease can be described with the word "manifestations", that includes "symptoms" and also "signs" "...cumulative dose of 51 g of chloroquine or 18 g of chloroquine can cause renal dysfunction...". It is supposed that one of the times the authors write chloroquine really wanted to write Hydroxichloroquine. In the actual manuscript the conclusion/s is very poor and it is not clearly identifiable as such. I do not know, after reading the actual work which is its originality in the field. I do not know how to manage this finding.



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And, the most important thing is that it is no clear if pharmacological renal lipidosis has any relevant clinical relevance.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- The same title
- Duplicate publication
- Plagiarism
- No

BPG Search:

- The same title
- Duplicate publication
- Plagiarism
- No