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Peer Review File

Article Information: https://dx.doi.org/10.21037/acr-21-77

Reviewer A

We feel great thanks for your professional review work on our article. As you are concerned, there are several problems that need to be addressed. According to your nice suggestions, we have made extensive corrections to our previous draft, the detailed corrections are listed below.

Considerations for authors:

Comment 1: What about phlebotomy as first line agents and should be mentioned.

Reply 1: Thank you for your suggestions and we agree with you. We have added the discussion to the article on page 8, line 88-93.

Changes in the text: In terms of treatment, the standard care for PCT involved periodic phlebotomy bloodletting (450 cc/dose) for reducing iron and porphyrin levels. Since phlebectomy is an invasive procedure requiring approximately 5–8 treatment sessions to achieve complete remission, the patient's wishes and financial situation were taken into consideration, and a more moderate antimalarial drug treatment was finally chosen.

Comment 2: Consider adding the standard dose of antimalarials that are used to treat PCT.

Reply 2: As of January 2022, during a telephone follow-up with this patient, he reported that his disease had not recurred, so we are not considering adding medication at this time.

Comment 3: Was serum or urine porphyrins collected?

Reply 3: We collected urine and serum from the patient, but our hospital's equipment is unable to do the tests related to porphyrin levels and typing. Also, the porphyrin test has a time limit for the sample (no more than two days for storage). Therefore, we were also unable to seek the help of a testing institute. Nevertheless, we believe that the detection of porphyrins in blood, urine, and feces is of great importance for diagnosis and assessment of efficacy when conditions support it. We have also added this idea to the article on page 7, line 69-71.

Changes in the text: Quantitative analysis of urinary porphyrins and serum porphyrins could not be performed due to lack of equipment. These two data are more helpful for our assessment of efficacy.

Comment 4: Did the patient have iron overload?

Reply 4: Thank you very much for your correction, we have added the patient's ferritin test results to Table 1 on page 4.

Changes in the text:

Table 1 Ancillary test results and comparison

Test items	Normal	First	Second	Third
Urine porphyrin assay	Negative	Positive	/	/
Fecal porphyrin assay	Negative	Positive	/	/
Aspartate aminotransferase (AST)	0–50 U/L	40 U/L	68 U/L	39 U/L
Alanine aminotransferase (ALT)	0–50 U/L	57 U/L	114 U/L	51 U/L
Gamma-glutamyl transferase (GGT)	0–55 U/L	67 U/L	143 U/L	50 U/L
Alkaline phosphatase (ALP)	40–150 U/L	89 U/L	152 U/L	86 U/L
Ferritin	23–336 ng/ml	403 ng/ml	175 ng/ml	168 ng/ml
Complete blood count, hepatitis C, syphilis, HIV, and tumor marker (AFP, CEA)	Negative	Negative	/	/
CT abdomen	Negative	Negative	/	/

Reviewer B

We feel great thanks for your professional review work on our article. As you are concerned, there are several problems that need to be addressed. According to your nice suggestions, we have made extensive corrections to our previous draft, the detailed corrections are listed below.

While the concept of higher dosages of hydroxychloroquine for shorter duration is very interesting, I would not advise to accept the manuscript in the current state. The reasons are the following:

Comment 1: 1. Urine and fecal porphyrin assays are only given as 'positive'. No

specification of different porphyrins/porphyrinogens is given. However, the type of porphyrins in urine/feces is essential for making the correct diagnosis (as the authors themselves also state in line 55-56). In this form, readers cannot check if the correct diagnosis of PCT is made. Urine and fecal porphyrin assay should be given in detail.
Reply 1: Thank you very much for your correction. In fact, we collect urine, blood and stool from patients for testing, but our hospital's equipment can only do qualitative tests for porphyrins in urine and stool, and cannot test for porphyrin levels or types. Also, the porphyrin test has a time limit for the sample (no more than two days for storage). Therefore, we were also unable to seek the help of a testing institute. Nevertheless, we believe that the detection of porphyrins in blood, urine, and feces is of great importance for diagnosis and assessment of efficacy when conditions support it. We have also added this idea to the article on page 7, line 69-71.
Changes in the text: Quantitative analysis of urinary porphyrins and serum porphyrins could not be performed due to lack of equipment. These two data are more helpful for our assessment of efficacy.

Comment 2: 2. Why did the authors choose to treat the patient with hydroxychloroquine twice daily? The first choice would have been to start flebotomy.
Reply 2: Thank you for your advice. The treatment plan was chosen because we had a patient like this many years ago who was also treated with this treatment plan and recovered. This time the choice was made after taking into account the wishes of the patient and his family and our experience, who did not want to undergo an invasive treatment plan. We have also included a discussion of the pros and cons of phlebectomy and the patient's wishes in the article on page 8, line 88-93.
Changes in the text: In terms of treatment, the standard care for PCT involved periodic phlebotomy bloodletting (450 cc/dose) for reducing iron and porphyrin levels. Since phlebectomy is an invasive procedure requiring approximately 5–8 treatment sessions to achieve complete remission, the patient's wishes and financial situation were taken into consideration, and a more moderate antimalarial drug treatment was finally chosen.

Comment 3: 3. As no follow-up urine and feces porphyrin spectrum is given, how do the authors know that the clinical improvement was not due to the instructions given to the patient regarding avoiding sunlight and alcohol discontinuation? Follow-up urine (and fecal) porphyrin assay should be done/given. This is essential for the message of the article.
Reply 3: Thank you for your advice. We also asked the patient about his sun protection during his follow-up visit, and he told us that he was unable to perform full sun protection due to his job. And that 2 weeks of photoprotection does not achieve such an effective treatment effect. Therefore, we believe that it is better to take oral medication to play a more effective role. We have also added this idea to the article on page 7, line 76-78.
Changes in the text: the patient reported that he was feeling better and no new blisters were appearing. However, due to work, complete sun protection is not possible.

Comment 4: 4. In figure 3 it is hard to see the improvement in symptoms.
Reply 4: Thank you for your correction, we agree that a better presentation of the images would allow the reader to fully understand our intentions. We have compared and enlarged the details in image 3.
Changes in the text:

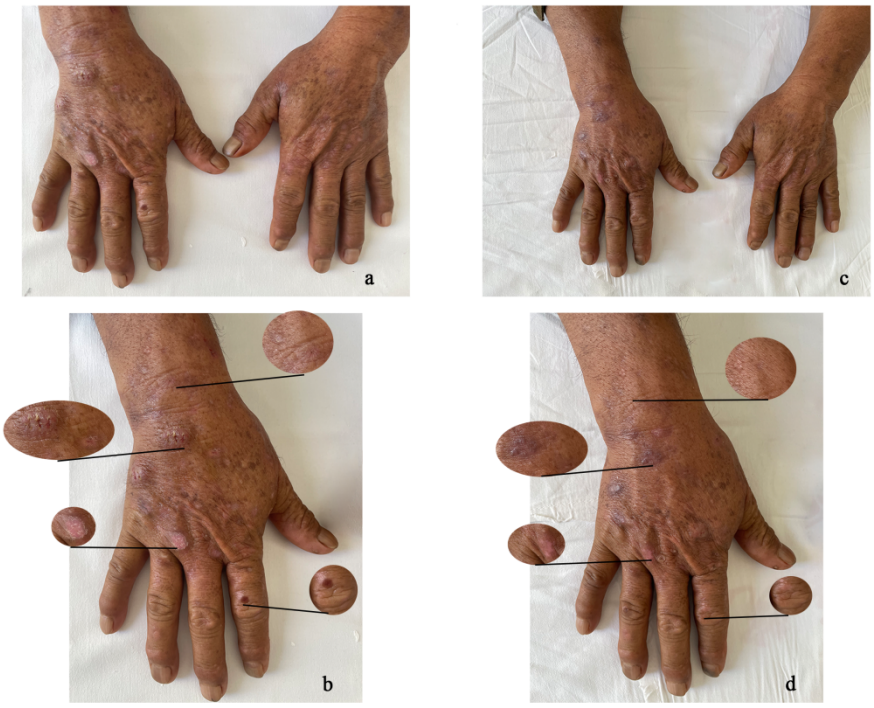

Figure 3. Lesion manifestations. (a,b) Two weeks after oral treatment with hydroxychloroquine, the lesions subsided. (c,d) Two weeks after discontinuation of oral medication, symptoms were better than before and no new lesions appeared.

Comment 5: 5. Line 69: the standard care of flebotomy is not given in this article as an option, while it is the number one treatment choice, even before low dose hydroxychloroquine.
Reply 5: Thank you for your suggestion. We did not choose phlebectomy mainly due to the wishes of the patient and his family, and we have added this perspective to the article page 8, line 88-93.
Changes in the text: In terms of treatment, the standard care for PCT involved periodic phlebotomy bloodletting (450 cc/dose) for reducing iron and porphyrin levels. Since phlebectomy is an invasive procedure requiring approximately 5–8 treatment sessions to achieve complete remission, the patient's wishes and financial situation were taken into consideration, and a more moderate antimalarial drug treatment was finally chosen.

Comment 6: 6. How long was follow-up? Because 2 weeks of avoiding sunlight does not prove remission of PCT.
Reply 6: Thank you for your question. The patient previously came to the hospital for review every two weeks for a total of three times. Subsequent telephone follow-ups

were conducted every month, and at the most recent telephone follow-up (approximately 3 months after the last hospital review), he told us that his disease had not recurred.

Comment 7: 7. Concluding that short-term oral administration of higher doses could be preferred for the treatment, seems inadequate. It caused liver enzyme elevation, and therefore was discontinued, which is a serious safety issue. This elevation of liver enzymes almost never happens with the lower dosages, so low dose seems safer and just as successful, while almost all PCT patients eventually reach biochemical remission. There is an added safety concern for retinal problems with the higher dosage, which is also not the clinical experience with the lower dosage. So I would be extremely careful to conclude higher dosage could be preferred.
Further in clinical practice we prefer flebotomy, while hydroxychloroquine releases porphyrin from the liver, and therefor may cause a temporary worsening of symptoms. This could be even worse for higher dosage of hydroxychloroquine use.
Reply 7: Thank you for your comments, we also believe that this treatment option needs to be supported by more clinical data and we have added this idea to the article on page 10, line 123.
At the same time, the dose of hydroxychloroquine we administered to the patient was higher than the conventional dose though. But it was still within the range of safe doses. Although the patient's significantly elevated GGT after dosing was indeed associated with hydroxychloroquine, we also found that the patient had a slight abnormality in GGT prior to dosing. Therefore,We suspect that the patient had abnormal liver function prior to treatment. We added this discussion to the article on page 8-9, line 98-102.
Regarding your question about the possibility of retinopathy due to high doses of hydroxychloroquine, we conducted another search for information. We found a meta-analysis entitled "Hydroxychloroquine safety: A meta-analysis of randomized controlled trials" that suggested that retinopathy is mainly likely to occur in patients who have been taking hydroxychloroquine for a long time. Our patient took the medication for two weeks, a period that did not lead to retinopathy.

Changes in the text: However, this treatment option needs to confirm by more research.(Page 10, line 123)

In fect, this dose of hydroxychloroquine falls within the safe dose range. The patient showed an elevation in GGT that could be related to this drug, but we noted that the patient had abnormal GGT before taking hydroxychloroquine. Therefore, it cannot be excluded that hepatic impairment had already occurred prior to the administration of the drug. (Page 8-9, line 98-102)

Comment 8: 8. I would advice the authors to let a native English speaker read and correct the manuscript.
Reply 8: Thank you very much for your correction, we try our best to perform the article better. We will attach the corresponding corrections to the issues you pointed out.

Minor remarks:
- line 10: porphyria instead of porphyrias
Changes in the text: Porphyria Cutanea Tarda (PCT) is a kind of porphyria,

- line 12: leave out 'the' in he was diagnosed with the PCT
Changes in the text: he was diagnosed with PCT.

- line 19: PCT is classified as familial or 'disseminated'. Disseminated does not seem to be the correct term
Changes in the text: Porphyria Cutanea Tarda (PCT) is classified as familial or sporadic forms and is mainly caused by an inherited or acquired deficiency of uroporphyrinogen decarboxylase,

- line 21: 'fecal porphyrinogen'. Is coproporphyrinogen III meant?
Changes in the text: the fifth enzyme in heme synthesis, which catalyzes the decarboxylation of uroporphyrinogen into coproporphyrinogen

- line 24: 'hairiness'. Hypertrichosis seems to be a better term
Changes in the text: Hypertrichosis and hyperpigmentation can occur in exposed areas such as the hands and face.

- Line 69 'antimalarials' is not specific enough. Replace by hydroxychloroquine. (same in line 87).
Reply: Thank you very much for your correction, we have replaced all antimalarials in the text with hydroxychloroquine.

- line 70: 'in the liver', however the symptoms arrive also from porphyrins in the blood
- line 70: does hydroxychloroquine reduce iron levels?
Reply: We express these expressions more concretely.
Changes in the text: The standard care for PCT was long-term oral administration of low-dose hydroxychloroquine (2×100 mg/week) to reduce the level of porphyrin in liver and blood.

- Line 82: 'to have alertness toward liver lesions', in remission, chance of liver lesions is very small.
Reply: Thank you very much for your correction. Although this patient is currently in

remission, we cannot be sure if the disease will recur, so we recommend that he have a routine annual physical exam.

- Line 84: 'PCT is a rare porphyria'. Actually PCT is the most common form among the porphyrias.
Reply: We agree with you and have revised the sentence on page 9, line 116.
Changes in the text: In summary, although PCT is a rare liver disease with skin damage as a manifestation,