Author's response to reviews

**Title:** Vitamin C-induced hyperoxaluria causing reversible tubulointerstitial nephritis and chronic renal failure: a case report

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**Author's response to reviews:** see over
Dear Editor:

We thank you for your careful review of our case report titled “Vitamin C-induced hyperoxaluria causing reversible tubulointerstitial nephritis and chronic renal failure: a case report”. We would like to submit a revision following the suggestions of the reviewers.

We appreciate the recommendations of Drs. Galesic and Rayner, which form the basis of our revision. Specific responses to their comments are as follows.

Dr. Galesic (Referee 1):

"1. The authors should discuss the possible etiopathogenesis of chronic diarrhea in described patient.”

As listed, at home, our patient was taking several over-the-counter medications which are known to be cathartic. These include the high-dose MgO, niacin, and high-dose vitamin A. We believe his chronic diarrhea was medication related because the in-patient work-up with upper and lower endoscopy uncovered no organic lesions, and because within one week of admission when all these unprescribed medicines were stopped, his diarrhea resolved. We have expanded on this deduction in the revision.

"2. In the first line of Background the authors wrote «In man, oxalate is an end product of metabolism». Oxalate is also end product of metabolism in women. Thus, it is better to say in humans oxalate is an end product of metabolism.”

We agree and therefore changed “man” to “humans” in the revision.

"3. Normal range of laboratory data need to be presented (normal range for each value especially some of these data, for example Ca 10.4 mg %). In Europe, we usually express Ca in mmol/L).”

In the revision we have included the normal range of the abnormal lab tests our patient exhibited.

"4. The renal ultrasonographic findings in this case revealed normal size kidney. This is really unusual because in chronic interstitial nephritis the kidney is always smaller. The authors should discuss this data and give an explanation why the kidneys are of the normal size. ...”

The exact sizes of his kidneys on ultrasound were 10.1 x 4.7 x 5.1 cm on the right and 10.6 x 3.8 x 5.0 cm on the left, although due to space constraints these dimensions were previously not stated in the paper. We have now added these dimensions.

Although in the clinical arena, radiologists typically allow for a normal range between 10.5 to 13 cm kidney lengths in the caudad-to-cephalad direction, given his male
gender, a height of 5’ 11” and a body mass of 70 kg, most clinical nephrologists would consider his ultrasound renal sizes to be somewhat small. We generally expect a perfectly normal kidney in such a man to be 12 to 13 cm, not below 10.5 cm. The renal biopsy findings are consistent with the clinical impression of underlying chronic kidney disease, which is corroborated by many serial creatinine measurements both before and after his admission. Although the acute component of his renal failure largely recovered, his serum creatinine never dropped below 1.7 mg/dl, suggesting some chronicity and relative irreversibility.

"... The patient described in this article had chronic diarrhea, which could cause an acute renal failure. The patient was dehydrated, his specific gravity of urine was 1020, these data support that dehydration (chronic diarrhea) could be the possible cause of acute renal failure."

We fully concur that our patient could have been volume contracted on admission due to chronic diarrhea. Indeed we had given him a vigorous therapeutic trial with several liters of saline solution the first week, assuming salt depletion could contribute to the acute component of his renal failure. However, this possible cause of acute renal failure was not supported by our failure to correct his elevated creatinine or to attenuate the relentless rise during the first 10 hospital days by very generous IV saline infusion. He had gained 7 kg of fluids by serial daily weights and cumulative external fluid balances. In fact his blood BNP had risen to 2217 pg/mL by day 7 (from a baseline of < 200) and his chest X-ray began to show some vascular congestion. Despite such vigorous hydration, his serum creatinine had remained above 10 mg/dL until we removed excess oxalate by dialyses, stopped his vitamin C, and prescribed a low-oxalate diet and metolazone. Parenthetically, throughout the entire hospital stay, he had maintained perfectly normal blood pressure (systolic >120 & diastolic >70 mm Hg). He appeared to have some element of inappropriate ADH secretion based on his admission serum Na of 130 mM and all subsequent serum Na concentrations (consistently remained <130 throughout his hospitalization). We are not able to explain his high urine specific gravity on admission or the consistently low serum Na levels even after discharge that are compatible with excessive ADH. We do know, however, that extensive tumor work-up had failed to uncover any evidence for this possibility.

"5. In this article myeloma as a cause of hypercalcemia was excluded by serum and urine protein electrophoresis. Electrophoresis of urine and serum protein is not enough for diagnosis of light chain disease (type of myeloma). Imunoelectrophoresis, and bone marrow biopsy are needed for diagnosis of this type of myeloma."

We agree that the combination of SPE and UIE would make the diagnosis of multiple myeloma in only about 95 % of the cases. We did not mean to sound so dogmatic in our brief report as suggesting definite exclusion of this possibility. It was the totality of the other findings like a negative bone marrow (as part of the work up for weight loss, anemia and hypercalcemia), absence of myeloma casts in the kidney biopsy, and his sustained and steady renal function improvement on a low-oxalate diet and abstinence from vitamin C which made us feel reasonably comfortable that myeloma was an unlikely etiology of either his spontaneously resolved hypercalcemia or renal failure. Had these problems persisted, we would have measured his plasma free light chains as recently published and recommended by the Mayo Clinic group. In the revision, we have softened the initial statement to reflect our original reservation.
Dr. Rayner (Referee 2):

"This is a well written paper but in the current format it is a little long and can be shortened."

We have identified some redundancies and have shortened the paper.

"The authors should acknowledge that there was no proof of malabsorption in this case (although quite suggestive) and hypocitraturia."

Hypocitraturia, as mentioned in the paper, was documented 11 and 30 days post discharge (respectively, 14 mg and 18 mg per gram of creatinine; normal being ≥ 250), though we did not measure urine citrate during his peak renal failure since severe metabolic acidosis is expected to non-specifically suppress excretion. We agree that we did not specifically test for malabsorption in this case, although we too thought that there were suggestive signs like hypocitraturia (and hyperoxaluria despite anorexia and minimal intake, which per se has been reported to reflect intestinal malabsorption). We have now acknowledged this reservation in the revision.

"I have had the slides reviewed by our renal histopathologists who report evidence of oxalosis in the vessels, and the authors may want to include this data."

We appreciate the kind offer and insights based on the slides review by Dr. Rayner’s histopathology colleagues. To include this observation, we wonder if they would be kind enough to insert a pointer or two in the involved vessels and email us the specific slides as a file through the Journal Editorial office. Of course we would want to acknowledge in the text and footnote, the expert assistance by the reviewers in identifying these abnormalities.

In summary, we have responded to the comments and concerns of both reviewers, as outlined above. We have also followed their specific recommendations in re-writing the revision. We hope it is now acceptable for publication. Thank you for the opportunity to re-submit to the Journal.

Sincerely,

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