Author’s response to reviews

Title: Renal papillary calcification and the development of calcium oxalate monohydrate papillary renal calculi. A case series study

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Author’s response to reviews: see over
Dear editor,

I am sending you a new version of the paper entitled *Renal papillary calcification and the development of calcium oxalate monohydrate papillary renal calculi. A case series study (MS 4985512418764541)*, modified according all reviewer's comments and suggestions. I would greatly appreciate you consider it for publication in the periodical *BMC Urology*. For this purpose I send a Cover Letter explaining point-by-point the changes made, following your instructions.

Being at your disposal,

Prof. Dr. F. Grases
Reviewer: Cecilia Maria Cracco

The authors thanks all interesting comments and suggestion of the reviewer.

**Point-by-point answer to reviewer**

**Major compulsory revisions**

1. A new paragraph has been included (second paragraph on page 3) connecting the precedent information with the Randall’s plaques and urinary stone formation. The last paragraph has been modified declaring the aim of the present study also according reviewer suggestions.

2. According the reviewer suggestions, the title has been modified to *Renal papillary calcification and the development of calcium oxalate monohydrate papillary renal calculi. A case series study.* The Patients and samples subsection has been rewritten. Three new sentences in Discussion section has been added at the end of the section.

3. According the reviewer suggestions the Patients and samples subsection has been rewritten explaining that such patients were not subjected to previous urologic surgery.

4. The origin of COM papillary calculi is now explained in the Introduction section. The morphologic studies of these calculi clearly demonstrates the presence of a zone of union with papillary tissue.

5. The evolution of a lesion into a stone depends on its proximity to the epithelium that cover the papillae and the activity of inhibitors and the immune system (that can reabsorb the hydroxyapatite deposit). A practical clinical consequence is that when papillary COM calculi are identified, the main objective to avoid recurrent episodes, should be the identification and elimination of the cause (or causes) that originates the intrapapillary injury. All these aspects are now commented in the paper.

6. At the end of the Discussion section, new conclusive remarks has been included. The sentence *the higher the number of subepithelial calcifications, the greater the likelihood that some will be transformed into COM papillary calculi* has been removed from the paper.

**Minor essential revisions**

1) In Materials and methods, Patients and samples the term endoscopic nephrolithotomy has been changed by RIRS. This has been also incorporated to the Patients and samples subsection that has been rewritten.

2) Materials and methods. The renal calculi was obtained from spontaneous elimination. This has been incorporated to the Patients and samples subsection that has been rewritten.
3) None of the patients studied exhibited previous infected urine or history of infectious calculi.

4) The COM stones obtained in these patients were only subjected to stereoscopic microscopy observation, infrared spectrometry, scanning electron microscopy and X-ray energy dispersion spectrometry microanalysis, that clearly characterize the renal calculi once obtained from the patient. To avoid excessive irradiation of patients, TC studies were not applied.
The authors find very useful the interesting suggestions from reviewer.

Point-by-point answer to reviewer

1. According the reviewer recommendations, the title has been modified to Renal papillary calcification and the development of calcium oxalate monohydrate papillary renal calculi. A case series study.

2. In the key words section, kidney has been replaced by renal.

3. In the Introduction section, 1st line, dependent on has been replaced by a result of

4. According the reviewer suggestions in the material and methods section, the patients and samples subsection has been rewritten explaining the methodology and pointing out the steps of our study.

5. In the results section, last paragraph of page 5, eliminated has been replaced by retrieved from.

6. In the discussion section, page 7, 2nd paragraph, the spelling of Randall's plaques has been corrected.

7. In the discussion section last paragraph of page 7, a new sentence and reference have been incorporated that provide evidence in support of the theory of injury.

8. References 31-37 has been added in support of the corresponding statement.

9. Reference 39 demonstrates that patients with unilateral single papillary calculus exhibited the same computed tomography attenuation values in both, affected and non-affected kidneys. Nevertheless computer tomography attenuation values of all papillae on the affected side were significantly greater in patients with stone formation than in those without stone formation.
The authors are grateful to the reviewer’s comments that improve the quality of the paper.

**Point-by-point answer to reviewer**

1. This is a descriptive study of association between deposits in renal papillae and the development and morphology of corresponding calcium oxalate monohydrate papillary calculi. This is now pointed out at the end of the Introduction section.

2. The patient inclusion criteria has been now included. We enrolled only four patients due to the difficulty to find patients that fulfill all these criteria.

3. The term *case histories* has been changed to *medical histories*.

4. In the introduction a new paragraph has been introduced explaining to the readers the papillary calculi origin and characteristics.

5. The limitation of the study is specified in a new sentence at the end of Discussion section.

6. The term *intraoperative retrograde ureteroscopy* has been changed to *flexible ureterorenoscopy* according reviewer comment.

7. The presence of subepithelial HAP deposits were considered high when they were superior to three. This has been now included in the text, according to the reviewer comment.

8. The sentence *the higher the number of subepithelial calcifications, the greater the likelihood that some will be transformed into COM papillary calculi* has been removed from the paper. Nevertheless, as it is pointed out in the paper, *An evaluation of Randall’s plaque theory of nephrolithiasis in patients with a unilateral single papillary calculus showed that computed tomography attenuation values (Hounsfield units) of all papillae on the affected side were significantly greater in patients with stone formation than in those without stone formation* (39). These facts demonstrates the linkage between papillae calcification and COM papillary calculi formation.

9. The urine analysis of patients can be important in some occasions. Thus, high oxalate urinary concentrations can be related to oxidative tissular processes that can induce renal injuries responsible of COM papillary calculi formation, as in the patients 2 and 3.

10. The limitation of the study is specified in a new sentence at the end of Discussion section.