Answering Reviewers

The critical comments of the reviewer needing changes in the manuscript have been marked in red

Reviewed by 01436637: "There is no convincing evidence to conclude that the delirium in this patient was the only initial manifestation of sepsis. Both the initial POD and the later SAD could all be presented as the patient emerged from anesthesia and later urosepsis developed."

Authors reply: The authors' state in the discussion that POD was diagnosed initially because "POD is a diagnosis of exclusion". "Based on the clinical presentation and in the absence of suggestive investigations, we initially diagnosed the case as POD, but the subsequent manifestations revealed that we were actually dealing with a patient of sepsis-associated delirium (SAD)". So, initially, by the diagnosis of exclusion we had diagnosed the patient to have POD, but on subsequent manifestations, we realized that it was SAD as the fact that POD by definition "do not have an identifiable aetiology" no longer remained valid as further features of sepsis manifested.

Reviewed by 02445242: 1. The details about delirium are rather sketchy. 2. As reported, "restlessness, agitation, irritability and combative behaviour" are not the central diagnostic criteria, and are therefore not sufficient to make a confident diagnosis of delirium. I would advise the authors to consult a standard text to properly enumerate the diagnostic criteria for delirium. 3. In medical settings, the diagnosis can be made with high reliability by applying very simple, yet precise scales such as the CAM, or its ICU version, the CAM-ICU. This should be stated somewhere in the manuscript, because without the use of such standard scales physicians or surgeons are often likely to miss delirium. 4. The authors are right in stating that post-operative delirium is usually an "interval delirium"; i.e. it generally occurs after a lucid interval (of 24-72 hours) following surgery. The fact that this patient developed behavioural problems so early after surgery casts further doubts on the diagnosis. Unfortunately, the authors do not mention whether he had attentional impairment, altered sensorium and cognitive-perceptual disturbances, which are required to make a proper diagnosis of delirium. 5. To me it appears that this gentleman developed the beginnings of a delirious episode, but both because he was sedated very early, and then went into coma, the episode probably did not get a chance to manifest fully. 6. One of the reasons that delirium is so common in the elderly is that people in this age group frequently have comorbid medical conditions (e.g. hypertension or diabetes), which leads to cerebrovascular compromise. Even a relatively minor brain insult can then set off a delirium. Thus, the past medical history of the patient should be stated. 7. Finally, the authors rightly state that small doses of antipsychotics such as haloperidol are the drugs of choice for treating delirium, and that benzodiazepines are usually avoided except in patients with alcohol withdrawal delirium. This is the standard treatment for delirium due to any cause, and not just post-operative delirium. Despite this the authors chose to use midazolam. Though this is commonly done in ICU settings, this does not gel well with the 'core tips' stated by the authors.

Authors reply: 1. Details about the delirium has been added. “He was disoriented about the time and place, and did not want to acknowledge that he was in a hospital or the fact that he was operated on a few hours ago. He wanted to pull out the intravenous lines, nephrostomy tube and urinary catheter.”

2. A standard text has now been referred to the establish the diagnose delirium: “met all the all four criteria (A–D) required to confirm a diagnosis of delirium as per the “Diagnostic and Statistical Manual of Mental Disorders, 4th edn, text revision (DSM-IV-TR®; American Psychiatric Publishing, Inc., Arlington, VA)”

3. The authors acknowledge that neither CAM nor CAM-ICU was used to diagnose delirium and neither would they like to state it when it was actually not done. The author however establish the diagnosis of delirium by stating that: “Although no formal delirium assessment tools like the Confusion Assessment Method (CAM) or Delirium Rating Scale (DRS) was administered, his clinical manifestations of disturbance of consciousness (agitation), change in cognition (wanted to get up and go home, did not acknowledge that he was in a hospital), its acute onset (he was normally responsive in the immediate post operative period) and the fact that it developed in the postoperative period met all the all four criteria (A–D) required to confirm a diagnosis of delirium” as per the standard textbook referred in clarification point 2.

4. The authors have now stated that the patient “was disoriented about the time and place, and did not want to acknowledge that he was in a hospital or the fact that he was operated on a few hours ago. He wanted to pull out the intravenous lines, nephrostomy tube and urinary catheter”.

5. The authors exactly want to sate what the reviewer had understood. It was the beginning of delirium. We had inadvertently administered midazolam (instead of the drug of choice in delirium: haloperidol). The authors do acknowledge it in the discussion: “]. However, for treating POD, the drug of choice should have been haloperidol. In fact sedatives like benzodiazepines have the potential to aggravate POD”.

6. All the past medical history is stated. He only had hypertension. We mention in the case report that: “He was evaluated at the out-patient pre-anaesthesia clinic, again on admission before the day of surgery, and was graded as American Society of Anesthesiologists (ASA) Physical Status II. He had a history of hypertension which was controlled on metoprolol 50 mg once and losartan 50 mg once daily. All his routine investigations were within normal limits.”

7. As rightly pointed out by the reviewer, it is often the (wrong) practice in the ICU setting to administer benzodiazepines despite the fact that haloperidol is the drug of choice for treating delirium and to drive home this point, this has been put up as a core tip. Non-psychiatrists need to be educated about this (often done) wrong practice.

Reviewed by 00505635: *This is a rare and very interesting case report*

The authors would like to thank the reviewer for the kind words of appreciation.

Reviewed by 00506103: The authors suspected that delirium was the initial presentation of urosepsis and not a postoperative delirium. The manuscript is well written, however, the authors should explain the mechanism involved in the development of delirium when they affirm that it is the initial presentation of urosepsis particularly in this case characterized from normal hemodynamic, laboratory and ABG parameters.

Authors reply:

The authors have added to the explanation given for development of delirium. "There is experimental evidence to show that in the initial phase of sepsis, endothelial nitric oxide (NO) synthase derived NO demonstrates "proinflammatory characteristics and contributes to the activation and dysfunction of cerebrovascular endothelial cells". Sepsis is also associated with "mitochondrial dysfunction" and early sepsis can cause cytokine, reactive oxygen species (ROS) and NO mediated "decrease in mitochondrial ATP generation". This can result in "neural cell apoptosis and an insufficient energy supply to the neurons". The exact mechanism causing delirium is complex and involves the neurological impact arising out of the immune response causing "prolonged inflammation, brain cells activation, over expression of NO, dysfunction of intracellular metabolism and cell death". However, there is no explanation to the fact as to why other features did not develop early, and that is the significance of this case report.

Reviewed by 00506093: The *structure* appears complete in its sections (*title*, *abstract*, *keywords*, *introduction*, *case report*, *discussion and references*). The *acknowledgements* section lacks and it should be added, if necessary. The *core tips* section is helpful in anticipating the succession of contents discussed, but there is a lack of correspondence with the keywords; in addition, there is a poor correlation between the single points summarized, they seem independent from each other and this is confusing. The tips should be presented in a more logical succession.

Abbreviations are not explained; this section should be added.

We suggest to amplify the list of *keywords*, for example including POD and SAD.

The *title* does not contain all the words then proposed as keywords (*Urosepsis*, *Delirium*, *Nephrolithotomy*). We suggest to change the first half of the title, in order to better clarify the specificity of the case presented (a patient who underwent a nephrolithotomy). The second half of the title is good and underlines the clinical impact of the finding discussed. In its whole, the title is catchy and convincing.

There is just a single *table*, in spite of the redundant references to statystical data, and there are no figures. We suggest finding other tables or figures (e.g. the TC scan showing the obstructing calculi), to better explain the peculiarity of the case discussed.

The *Introduction* section well summarizes the core finding of the study: the early diagnosis of delirium, in patients presenting severe sepsis after PCNL, in the absence of any other clinical or instrumental finding, allows clinicians to promptly treat a potentially fatal condition. On the other hand, the background to these considerations appears a bit confusing. In fact, the

case report is about a specific case of delirium, which is not a consequence of the surgery in itself, but a symptom of a rare complication (severe sepsis) occurring after PCNL. We suggest to better clarify the correlation mentioned.

We suggest some adjuncts in the *case report* section. When coming at the emergency department, did the patient present other symptoms than pain only? Were all the parameters (blood pressure, heart rate, temperature, SpO2) normal? Was there any sign raising suspect of an oncoming infection? Instead, the pre-operative evaluation, the intraoperative and the recovery room periods are well described. Delirium as a fluctuation of the state of consciousness is punctually presented. The conditions leading to tracheal intubation and observation in the CCU are precisely showed.

The POD, with its differential diagnosis, is well discussed. Then, the authors exclude a case of typical POD, beacuse delirium appears in the setting of an ongoing sepsis.

Since the authors state that all the cultures were negative, we suggest not to use the term sepsis but SIRS (Systemic Inflammatory Response Syndrome), even if there's a strong suspicion of a septic aetiology.

The discussion section is very interesting, since it clarifies the concept of POD and excludes it could have been occured to the patient. Instead, clinicians diagnosed a case of sepsis associated delirium (SAD), which is an independent predictor of death. Urosepsis is diagnosed in spite of the negative cultures, since pre-operative antibiotic therapy could have altered the bacterial growth. Interestingly, the study underlines a weak pont, consisting in the absence of a culture of the calculi: this prevents clinicians to fully exclude an urinary tract source of bacteria.

This case report is relevant in increasing our knowledge about severe sepsis presentation. It offers a valuable and affordable tool to the early detection of a potentially life threatening condition. It is original, being the only case report of this kind, with no other preceding analyses ever published. Finally, it also raises an interesting question: why delirium appears alone and all the other clinical features of severe sepsis are affected by such a great delay? This delay is the key concept to appreciate the study proposed: delirium only appears soon enough to enable clinicians to start an effective and possibly life-saving intervention.

We suggest to enlarge the *bibliography* section, possibly adding more recent articles (there is just one article from 2014).

Authors reply: The authors would like to thank the reviewer for the detailed feedback to enhance the quality of the paper. All the suggestions have been incorporated in the case report.

Acknowledgement has been added.

Keywords have been added: Postoperative Delirium (POD) and Sepsis Associated Delirium (SAD)

Abbreviations have been added

Keywords have been amplified to include POD and SAD

Title has been modified as suggested by the reviewer: “Postoperative delirium as the only initial presenting symptom of urosepsis in a patient who underwent nephrolithotomy: High index of suspicion and aggressive management can save lives”.

Preoperative KUB X-ray of the patient has been added in the figures as suggested. (Figure 1: A kidney, ureter, and bladder (KUB) X-ray demonstrating the calculi).

The clinical presentation has been modified to better explain that the patient was normal after the surgery in the recovery area and the symptoms developed suddenly. “Over the next 50 minutes of his stay in the post-anaesthesia recovery area he was pain free, interacted normally with the doctors and his relatives and was doing well. Then suddenly he started getting agitated and wanted to get up from the bed and go home.” has been added. This now better explains that delirium is not a part of the surgery but developed after the surgery and recovery from anaesthesia.

The lines “He never developed any fever during his acute onset of symptoms or during the stay in the hospital. His vitals remained stable throughout his admission.” have been added as suggested by the reviewer.

In the Case Report segment, sepsis has been replaced by “Systemic Inflammatory Response Syndrome (SIRS)”as suggested by the reviewer. However in the recent diagnostic criteria by the Surviving Sepsis Campaign’s International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 for diagnosis of sepsis (available at https://www.sccm.org/Documents/SSC-Guidelines.pdf) it is defined as “the presence (probable or documented) of infection together with systemic manifestations of infection”. So, it includes “probable” infection also. For the diagnostic criteria of sepsis, it states “Infection, documented or suspected”. So, “suspected” infection can also meet the diagnostic criteria of sepsis.

The bibliography section has been expanded to include 3 recent additional references (from 2015 and 2016) as suggested by the reviewer.

Answer to chief editor:

Dear Fang-Fang Ji,
please find the attached further edited document.
The authors accept all changes suggested by the Editor-in-Chief. Further shortening of the case description has been done (apart from accepting all those suggested by the Editor-in-Chief). However major shortening could not be done as most of the described parameters/issues were suggested in the review process.

Editor in Chief: "A better and shorter title, which better reflects the content and message of this nice paper could be "Sepsis associated delirium mimicking postoperative delirium as the initial presenting symptom of urosepsis in a patient who underwent nephrolithotomy"

Authors reply: We accept the suggested change.

Editor in Chief: "The case history description is much and much too long. This reviewer made some indications to shorten the text, but should be further shortened."

Authors reply: We accept all the suggested changes (shortening suggested). Further shortening also has been done.

Editor in Chief: "Discussion: The discussion on POD vs SAD is very nice and clear."

Authors reply: The authors would like to than the Editor in Chief for the positive feedback and effort to enhance the quality of the case report.

Thanking you,

Dr.Deb Sanjay Nag