

Peer Review File

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Reviewer A

SPECIFIC COMMENTS: The case is well documented in the manuscript, and supported by Chest-x-ray and XR Cystogram and the reasoning for the pathophysiological development of urinothorax in this case is correct in my opinion. However, I believe that pleural fluid characteristics need to be described and commented with more detail than in the present manuscript, as follows:

1. MECHANISMS OF URINOTHORAX PRODUCTION. I fully agree with the author's points of view on this aspect. However, I wonder if abdominal ultrasound examination was performed at any time in this case, to detect possible presence of ascites which could contribute significantly to pleural complications associated with communication between the abdominal and pleural cavities throughout the diaphragm, as the authors themselves recognize. A comment on this specific point (ultrasound examination and possible presence of ascites) would be welcome in the manuscript.

Reply 1: Thank you for your comment. CT abdomen on day of admission revealed a small amount of ascites attributed to postoperative fluid collection. Abdominal ultrasound was performed for evaluation of acute kidney injury and pyuria which also revealed small ascites along with small pleural effusion. Chest radiograph confirmed a large pleural effusion when the patient was in marked respiratory distress.

Changes to the text: We have added mention of this in the manuscript Line 77-82 of the case description "Abdominal ultrasound was performed for evaluation of acute kidney injury and pyuria which revealed small ascites along with small pleural effusion. CT of the abdomen revealed a small amount of ascites attributed to postoperative fluid collection, bibasilar lung atelectasis with no signs of pleural effusion, as well as distended small bowel loops with scattered air-fluid levels likely related to postoperative ileus [Figure 3]."

2. PLEURAL FLUID ANALYSIS. Again, I agree with the relevance of the pleural fluid/creatinine ratio, but also believe that a little more attention to pleural fluid pH measurement should be dedicated in the manuscript. Only an incidental mention to this is given on line 138 (last paragraph in Discussion section).

Since pH of urine is usually low (about 5 in most of the cases), it would be expected that a massive urinothorax presents with a low pH in the pleural fluid also, depending on the actual pH of urine in that patient and the dilution of urine in the pleural fluid. No data on this point is available in the manuscript, and I wonder if pleural fluid pH measurement was made at any time in this patient. I found very few references on this in the existing literature and observed a wide dispersion in the published data. It should be kept in mind that pleural fluid pH measurement should be performed using the same strict anaerobic proper technique than that used for blood gas analysis. Otherwise, an abnormal high pH could be observed in the pleura, then leading to wrong conclusions.

Reply 2: We appreciate your comment and we thought measuring the pH of the urine and the fluid simultaneously would support our diagnosis. As you rightly pointed out, urine pH was 5.5. The pleural fluid analysis at our institution is a ‘send out’. Strict anaerobic environment was not maintained and the delay in the processing of the sample was more than 3 hours. I was unable to find out what technique our laboratory uses to measure the pH. Fluid pH was reported as 7.5. My conclusion is that the fluid pH in this case could not be relied upon to support the diagnosis. In a case series reported, pH greater than 7.5 has been reported in almost a quarter of the cases. PMID: [28616270](https://pubmed.ncbi.nlm.nih.gov/28616270/)

Changes to the text: We have added pH of pleural fluid in line 91 of case description “Pleural fluid analysis showed transudative fluid with pH 7.5, Cr 5.8mg /dl, LDH 172 unit/L, and Total Protein 1170 mg/dl.”. We have also added more explanation regarding this in Line 144-147 “It is worth mentioning that a strict anaerobic environment must be maintained when sending pleural fluid samples for testing and may be unreliable if this is not followed or if processing of sample is delayed.”

Reviewer B

The manuscript submitted by Elizabeth Mikhail et al. describes a case of urinothorax and pseudo-azotemia following total abdominal hysterectomy. This is an interesting and useful contribution to gynecologist, urologist, and pulmonologist. However, I think it needs to be added and corrected in some points.

1. Have you provided any treatment for postoperative ileus? If treatment was not needed, please add an explanation for clarification. (L78)

Reply 1: Thank you for your reply. Postoperative ileus was managed expectantly with

anti-emetics, prokinetics, ambulation, avoidance of narcotics and maintenance fluids with electrolyte supplementation. CT scan did not suggest a mechanical obstruction. Surgery was consulted and they recommended non-operative management.

Changes to the text: This explanation has been added to the manuscript Line 82-85

2. When a large right-sided pleural effusion was noted, no ascites was observed?

(L80) If so, please add an explanation and clearly indicate. I think it is better to show CT.

Reply 2: Thank you for your comment. CT abdomen on day of admission revealed a small amount of ascites attributed to postoperative fluid collection. Abdominal ultrasound was performed for evaluation of acute kidney injury and pyuria which also revealed small ascites along with small pleural effusion. Chest radiograph confirmed a large pleural effusion when the patient was in marked respiratory distress. No pleural effusion was noted on admission.

Changes to the text: We will add a figure of the CT abdomen for reference. We have added mention of this in the manuscript Line 77-82 of the case description “ Abdominal ultrasound was performed for evaluation of acute kidney injury and pyuria which revealed small ascites along with small pleural effusion. CT of the abdomen revealed a small amount of ascites attributed to postoperative fluid collection, bibasilar lung atelectasis with no signs of pleural effusion, as well as distended small bowel loops with scattered air-fluid levels likely related to postoperative ileus [Figure 3].”

3. As a differential diagnosis, can complications of pleural endometriosis be ruled out? (L72)

Reply 3: Thank you for your comment. According to the literature, complications of pleural endometriosis include pneumothorax and hemothorax that are commonly catamenial in nature. In the case of our patient, pleural fluid developed acutely after surgical removal of endometriosis and pleural fluid was yellow in color, effectively ruling out complications of pleural endometriosis.

Changes to the text: We have made mention of this in the discussion section of the manuscript Line 160-166. “Differential diagnoses that were effectively excluded in this case include, gastric and esophageal perforation and, pleural effusion secondary to ascites, which was substantiated by presence of minimal ascites and no pleural effusion

noted on CT scan of the abdomen done at the time of admission. Furthermore, the prospect of complications associated with pleural endometriosis, including hemothorax, was effectively ruled out since these are mostly catamenial and pleural fluid analysis revealed straw colored fluid that was transudative in nature.”

Reviewer C

The case report a very rare complication after hysterectomy. It is very important to report the management of such rare complications to give some useful indications to physicians. However, in my opinion could be useful to understand if in the three precedent cases reported the damage was to the bladder or ureters.

furthermore one might think that laparotomic hysterectomy could increase the risk of urothorax (perhaps an increase in peritoneal permeability caused by the laparotomy itself) even if the data are insufficient.

Although it is always difficult to prevent a lesion of the urinary tract during a hysterectomy, in the discussion it could be proposed (In consideration of the serious complications) the use of ureteral stents in patients most at risk or in those in which the lesion is suspected or could be caused by excessive devascularization of the urinary tract even during surgery(10.1016/j.ejogrb.2020.05.032.)

Reply 1: Thank you for the interesting comment. Review of literature revealed an article with the following conclusion “Current evidence indicates that prophylactic ureteral catheter placement has the advantages of reducing ureteral injury, shortening the operative time and reducing the amount of bleeding. It might serve as a routine preoperative preparation choice for laparoscopic gynecological surgery, especially with pelvic adhesion. Further large volume, multicenter well-designed trials are warranted before making the final clinical guidelines.” Prophylactic ureteral stents are used in hysterectomy for placenta accreta spectrum.

The husband also provided information the surgeon was shaving tissue at the bladder wall and was careful to avoid any injury to the bladder.

Changes to the text: We have made mention of this in the discussion section of the manuscript Line 168-175. “Although urinothorax is a rare occurrence of a commonly performed gynecologic procedure, it is imperative that physicians be prepared to effectively address such medical complications. Careful review of the literature revealed that prophylactic placement of ureteral catheters has several merits, including the reduction of ureteral injury risk, a decrease in operative duration and mitigation of intraoperative hemorrhage. Considering these potential benefits, prophylactic ureteral

catheters may serve as a viable preoperative strategy prior to gynecologic surgeries particularly when dealing with pelvic adhesions (10).”

In addition, two of the precedent cases indicated injury to the bladder (Amro et al., and Goto et al.) and one indicated injury to the left ureter (Chan et al.) We have made mention of this in the Table of comparison. (Table 1)