Forgotten intrauterine device inducing aseptic peritonitis in newly started peritoneal dialysis

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Abstract
Infectious peritonitis is a challenging condition to continuing peritoneal dialysis (PD) in many end-stage renal disease patients. A cloudy peritoneal effluent or abdominal pain is the most common symptoms of peritonitis, which would be confirmed with peritoneal leukocytosis. However, not all cloudy effluent and peritoneal leukocytosis are infectious in etiology. Here, we report a case of peritoneal leukocytosis related to a forgotten intrauterine device (IUD), where antibiotic therapy failed to achieve a clinical change. This case report and literature review provides insight into a rare but significant presentation of aseptic peritonitis and highlights the need to consider IUD interaction with PD dialysate as a reason for aseptic peritonitis.

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Introduction
Infectious peritonitis is a serious complication of peritoneal dialysis (PD). It accounts for 15% of the mortalities in the peritoneal dialysis (PD) population. In addition, recurrent peritonitis may lead to diminished peritoneal ultrafiltration (UF) capacity causing modality failure and conversion to hemodialysis1. However, not all cloudy effluent and peritoneal leukocytosis are infectious in etiology. Here, we present a case of peritoneal leukocytosis secondary to an intrauterine device and review the available literature.

Case Presentation
A 55-year-old Asiatic female with a history of hypertension, diabetes, and progressive kidney disease stage V, presented to our renal service to establish peritoneal renal replacement therapy. A peritoneal dialysis catheter, the Tenckhoff catheter, was placed by the standard surgical technique without complications. She has finished her PD education after 15 in-center sessions completed within four weeks, after which the patient immediately started her home peritoneal exchanges. The peritoneal dialysate was composed of four exchanges of dextrose 2.5%, each of which was two liters. Three-day exchanges through the daytime were followed by one overnight same dextrose 2.5% concentration. However, she could only achieve a net UF of 500-800 ml/day. Our patient began complaining of shortness of breath and new pitting lower limb edema associated with uncontrolled hypertension. The overnight dwell fluid was changed to icodextrin 7.5% with subsequent improvement of the net UF to 1300cc/day, out of which icodextrin participated with 75% of the net volume. Other quality parameters of PD were acceptable fractional urea clearance (kT/V) of 2.3 and additional urine output of 450 ml. Her medication list also included oral furosemide 40 mg once daily (OD), phosphate binders, paricalcitriol two micrograms three times a week, Lisinopril 20 mg OD and insulin glargine ten units, and insulin aspart five units three times a day. A few weeks after icodextrin started, her symptoms improved, but she began to notice a cloudy peritoneal effluent without pain or fever. Upon clinical examination, there was no abdominal tenderness or other clinical evidence suggestive of peritonitis. The cell count of the peritoneal effluent showed leukocytosis with polymorphonuclear (PMN) predominance (Table 1). The aerobic and anaerobic cultures of the peritoneal fluid were collected, and an empirical intra-peritoneal ceftazidime and vancomycin therapy was started. The microbiology work-up resulted in negative values. An icodextrin was held because an allergic reaction was suspected. The peritoneal effluent was still cloudy after the 10-day antibiotics treatment, and the peritoneal effluent white blood cell (WBC) count continued to trend up slowly to 2.9k cell/mm3 with predominant neutrophils 60-70%
Another set of peritoneal aerobic and anaerobic cultures, fungal culture, adenosine deaminase test, and mycobacterial cultures resulted in negative values. Our patient was still denying any abdominal or constitutional symptoms. She only began to experience a slowly progressive SOB after holding icodextrin over the preceding two weeks. Icodextrin was then resumed to achieve volume control, particularly after the low probability of icodextrin allergy. Antibiotic therapy was completed after 14 days; it was stopped due to the negative results of the cultures. An abdominal x-ray confirmed the appropriate positioning of the PD catheter; however, a metallic shadow appeared in the pelvic region (figure 1). An abdominal computed tomography (CT) showed an intrauterine device (IUD) in the uterus with no other acute pathology (Figures 2,3). When the patient was inquired, then remembered that she had an IUD placed 27 years ago, she had forgotten initially. The antimicrobial therapy did not change the appearance or cellular analysis of peritoneal effluent with raising consideration about IUD-related noninfectious peritonitis versus allergic metal peritonitis. Three weeks later, the IUD was extracted with normal gross pathology. One week after IUD extraction, peritoneal effluent has turned clear, and cell count fell to the normal range. During the whole course of the condition, all systemic inflammatory markers were negative.

Table 1: Shows the PD fluid cell count follow-up during the course of the illness.

<table>
<thead>
<tr>
<th></th>
<th>Day 1 after noticing cloudy effluent</th>
<th>Day 2</th>
<th>Day 5</th>
<th>Day 10</th>
<th>1 week after IUD removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WBC (cell/mm³)</td>
<td>631</td>
<td>937</td>
<td>1231</td>
<td>2918</td>
<td>8</td>
</tr>
<tr>
<td>Segmented neutrophil (PMN) (%)</td>
<td>73</td>
<td>44</td>
<td>65</td>
<td>77</td>
<td>10</td>
</tr>
<tr>
<td>Eosinophil (%)</td>
<td>11</td>
<td>29</td>
<td>27</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 1: Abdominal x-ray showing a metallic shadow in the pelvic region.

Figure 2: CT abdomen (Transverse view) showing an IUD in place without significant endometrial hyperplasia.

Figure 3: CT abdomen (Sagittal view) section with IUD in place.

Discussion

Over the last decade, the home modalities of dialysis have emerged. Peritoneal dialysis is one of the most common modalities of home-guided therapy. One of the most important reasons for peritoneal dialysis failure is persistent peritonitis [1]. For 50% of peritoneal dialysis patients, the average technical modality success is three years [2]. Infectious peritonitis could be secondary to microbial contamination of the peritoneal dialysis equipment (external exposure) or disseminated from other intra-abdominal foci such as gall bladder, bowel loops, or appendix. Dissemination counts for only 6% of all cases of PD-associated peritonitis [3].
The possible allergic peritonitis related to icodextrin use was investigated, and it was revealed to be related to contamination of some batches of manufactured products with peptidoglycan, which is a pyrogen causing inflammatory reactions, which in turn cause the cloudy peritoneal effluent and eosinophil dominant peritoneal fluid leukocytosis [11]. In a prospective study that included 722 PD patients, it was found that peritoneal dialysis patients receiving icodextrin have neither higher nor lower rates of culture-negative peritonitis or infectious peritonitis rather than non-icodextrin patients [6]. The skin rash is still one of the most important limitations of icodextrin use in peritoneal dialysis [12].

Even though it is more common to have local reactions secondary to the icodextrin solution, dextrose solution-related reactions were also reported. In vitro dextrose solution increases leptin secretion from adipocytes. Omental adipocytes release more leptin after exposure to dextrose solution in the peritoneal dialysis solutions [13]. Leptin is a small molecular weight peptide of 16 kilodaltons (kD), making it easily cleared by the normal kidney. Leptin excretion is decreased in those with chronic renal disease, causing higher plasma Leptin levels. In PD patients, leptin release is more pronounced secondary to omental adipocyte exposure to glucose. Leptin is associated with hyperlipidemia and, subsequently, adverse cardiovascular events among the dialysis population, usually over the long term [14]. This kind of sequelae occurs. In our case, the timeline of the whole process was a few weeks, so it is unlikely to be IUD-related peritoneal dialysate dextrose exposure. Cloudy peritoneal effluent could also be caused by non-cellular components of the peritoneal fluid such as fibrin or lipid. Fibrin filaments are usually seen as clots in the tubes or effluent bags, especially after a dry peritoneal interval, prolonged dwell time, post peritonitis, or constipation [15]. A whitish peritoneal effluent could be caused by lipids, especially triglycerides, in lymphatic obstruction or pancreatitis. Chylous effusion was also reported in some cases with superior vena cava syndrome or amiodopine use [16]. In our case, persistent leukocytosis continued despite ruling out all the previously known etiologies.

Local peritoneal dialysis noninfectious hazards include incisional hernia, exit site leak, hydrothorax, scrotal swelling, and hemoperitoneum. With most of these hazards, The PD exchanges could be continued safely with following the standard management protocols [17]. In our case, we continued the PD exchanges in the same way, given that there was no systemic involvement. Concerns about missed IUD metal allergy supported the collaborative decision to remove the IUD; likely, copper evolved after icodextrin use despite the main cell being PMN (not eosinophils). The interaction between PD and the female reproductive system is well-known in the peritoneal dialysis society. The peritoneal cavity is continuous with the female genital system through the fallopian tube. That explains the bloody peritoneal effluent at the time of shedding endometrial debris during menses. Oppositely, a transvaginal leak of peritoneal dialysate could happen in rare cases when the dialysis catheter is captured in the fallopian tube. In both situations, infectious or sterile peritonitis could occur [18]. Our theory is based on the same anatomical connection, the

The International Society for Peritoneal Dialysis (ISPD) updates the management protocol for preventing and treating PD-associated peritonitis. Generally, empirical antibiotic therapy, with coverage of gram-positive and gram-negative organisms, preferably intraperitoneal, should be started empirically once peritonitis is suspected. Culture-directed antimicrobial therapy should be established as soon as possible. The average duration of antimicrobial treatment is usually 2-3 weeks [1].

The other category of PD associated with peritonitis is noninfectious or sterile peritonitis. Negative bacterial, fungal, and mycobacterium cultures are mandated to establish the diagnosis of sterile peritonitis. Even if negative culture peritonitis, when the clinical and laboratory values improve on the empirical antimicrobial therapy, it could still be considered infectious peritonitis [6]. Peritoneal leukocytosis with cloudy peritoneal effluent could happen in medical conditions rather than infection as in intra-abdominal malignancy [7], especially lymphoma, which could cause atypical cells with or without PMNs dominant cell count. Pancreatitis [8] or exposure to local or systemic amphotericin would also increase PMNs [9]. Peritoneal dialysis catheter placement laparoscopic techniques using CO2 inflation may elicit an allergic reaction with subsequent peritoneal eosinophilia [9]. Peritoneal eosinophilia, or less commonly, monocytosis, could also be caused by potentially allergic conditions such as intraabdominal medications, especially vancomycin or some obsolete patches of icodextrin solutions [10].

Icodextrin-related aseptic peritonitis cases were frequently reported till 2001 [11]. Icodextrin (Extraneal®) is a low carbohydrate load, high molecular weight glucose polymer that induces UF by crystalline osmosis with relatively slow absorption of icodextrin from the peritoneal cavity [11]. Icodextrin is associated with mild to moderate skin rash in 5.5% of the peritoneal dialysis patients, which mostly resolves with discontinuation of icodextrin use [11]. The possible allergic peritonitis related to icodextrin use was
peritoneal cavity/fallopian tube. It conducted the peritoneal fluid to the uterine cavity, where it may have started an inflammatory reaction by the missed IUD causing the cloudy peritoneal effluent.

In our case, the cloudy peritoneal effluent with peritoneal leukocytosis was initially considered peritonitis without a clear etiology, and empirical antibiotic therapy was started. The abdominal imaging guided us to identify the forgotten IUD; we proceeded to remove it, and the effluent improved. Our patient was re-started on the previous PD regime without any reaction. PD fluid cleared, and cell count normalized one week after the removal of the missed IUD without further change in medication, peritoneal dialysis prescription, or daily habits. Our theory could be supported by other reported IUD-associated polymicrobial peritonitis in peritoneal dialysis patients where IUD cultures grew the same pathogen from the peritoneal dialysis effluent [18]. In the same spectrum, our patient’s IUD had been aseptic and long-lasting for 28 years, so the reaction was attenuated without the typical picture of the aseptic or non-infectious peritonitis.

Conclusion
Persistent aseptic leukocytic peritoneal dialysis effluent could possibly be related to an IUD-related reaction with Icodextrin, since the effluent was resolved after the IUD removal without any significant gross surgical pathology or imaging revealed anatomical varieties in the reproductive system as endometrial proliferation or ovarian pathology.

References