Sudden-onset gallbladder rupture due to Ceftriaxone-associated pseudolithiasis in a patient with acquired hemophilia A

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Abstract

We herein report a 76-year-old man with acquired hemophilia A (AHA) who developed gallbladder rupture due to Ceftriaxone (CTRX)-associated pseudolithiasis. The patient was admitted for an examination of systemic subcutaneous bleeding. A blood test showed a prolonged activated partial thromboplastin time and sequentially revealed low factor VIII activity (<1%) and a high factor VIII inhibitor level of 143 BU/mL. The patient was thus diagnosed with AHA. After admission, he developed a high-grade fever and was administered intravenous CTRX, considering the possibility of psoas abscess or cellulitis. Although his high-grade fever was improved, computed tomography incidentally showed a high-density lesion in the gallbladder, suggestive of CTRX-associated pseudolithiasis without clinical symptoms. Despite cessation of CTRX, the pseudolithiasis never disappeared, and the patient suddenly died after rapid progression of abdominal bloating. An autopsy revealed that the gallbladder was severely swollen and had ruptured with hemorrhaging because of hemorrhagic cholecystitis, caused by CTRX-associated pseudolithiasis with AHA. Our case demonstrated that CTRX-associated pseudocholelithiasis can unexpectedly induce gallbladder hemorrhaging and rupture in a patient with a bleeding diathesis, including AHA. CTRX-associated pseudocholelithiasis can cause a fatal outcome in patients with a bleeding disorder, even if CTRX is ceased as soon as pseudocholelithiasis is detected.

Introduction

Acquired hemophilia A (AHA) is an infrequent autoimmune bleeding disorder caused by autoantibodies against coagulation factor VIII. Hemorrhaging can occur anywhere but most predominantly is seen in subcutaneous and deep muscle [1]. However, gallbladder hemorrhaging in a patient with AHA is extremely rare. Rupture of gallbladder is an infrequent complication, and the majority of cases have resulted from penetrating wall injures. Rupture of gallbladder can lead to fatal consequences, but a rapid diagnosis and treatment are occasionally difficult because of its rare entity and severity[2].

We report a case of sudden-onset gallbladder rupture due to Ceftriaxone (CTRX)-associated pseudolithiasis in a patient with AHA.

Case Presentation

A 76-year-old male patient was admitted to our institution to investigate his left lower back pain and systemic subcutaneous bleeding. On hospital day 1 (HD1), coagulation workup showed no abnormal findings but revealed a prolonged activated partial thromboplastin time (APTT) of more than 300 seconds and a low hemoglobin level of 7.6 g/dL. Computed tomography (CT) showed a low-density lesion, suggestive of left psoas hematoma, and no gallbladder stones (Figure 1a). The APTT level could not be corrected by mixing with normal plasma, which was indicative of the presence of coagulation factor inhibitors. Therefore, intravenous prednisolone 1 mg/kg/day and recombinant activated factor VII (rFVIIa) 90 mcg/kg every

3 h were administered to eliminate coagulation factor inhibitors and to prevent life-threatening bleeding, respectively.

Thereafter, laboratory tests revealed low factor VIII activity (<1%) and a high factor VIII inhibitor level of 143 BU/mL. His bleeding predisposition was attributed to AHA. On the night of HD1, the patient developed a high-grade fever and was prescribed intravenous CTRX 2.0 g every 12 h, considering psoas abscess or cellulitis.

After the bypassing agent therapy was administered, his left low back pain and systemic subcutaneous bleeding were improved. Therefore, we finished administering rFVIIa to the patient on HD5. CT on HD6 demonstrated that the low-density lesion, suggestive of left psoas hematoma, had improved, while a high-density lesion in the gallbladder had emerged (Figure 1b). The patient showed no clinical symptoms of acute calculous cholecystitis, and there were no remarkable changes in his laboratory findings. The patient was diagnosed with CTRX-associated pseudolithiasis, and CTRX was discontinued since his high-grade fever had improved.

Extensive subcutaneous bleeding of the right back occurred on HD10, and rFVIIa was promptly resumed. Since the APTT and low factor VIII activity were not improved and the factor VIII inhibitor level remained high, intravenous methylprednisolone 1 g/kg/day was administered from HD14 to HD16. However, despite the further immunotherapy, his bleeding symptoms and abnormal coagulation-related laboratory data due to AHA were not improved. Furthermore, CT demonstrated that hematoma of the left psoas and the right back had expanded, and the high-density area in the gallbladder remained.

Thus, rFVIIa was switched to activated prothrombin complex concentrates (APCC) 100 IU/kg every 12 h on HD16. Thereafter, the systemic subcutaneous bleeding improved, and the dose of APCC was reduced to 100 IU/kg every 12 h on HD21. On the same day, however, the patient developed a high-grade fever, so piperacillin and tazobactam were administered. On HD22, the patient complained of abdominal pain in the right upper quadrant. Enhanced CT with intravenous contrast demonstrated not only a high-density area, indicative of CTRX-associated pseudolithiasis but also pericholecystic stranding, a thickened gallbladder wall, and extravasation of contrast into the gallbladder, indicative of hemorrhagic cholecystitis (Figure 1c, d). Several hours later, the patient suddenly died after rapid progression of abdominal bloating.

At the autopsy, the gallbladder was severely swollen and ruptured with hemorrhaging and contained a large amount of hematoma. Intra-abdominal blood clots were connected to the gallbladder, and the primary source of hemorrhaging was thought to be the gallbladder (Figure 2a, b). Histology of the gallbladder demonstrated hemorrhagic and necrotic changes with focal neutrophilic cell infiltration and fresh thrombi (Figure 2c).

Discussion

CTRX, a third-generation cephalosporin antibiotic, is used worldwide to treat infectious diseases, including lower respiratory tract infections, bacterial meningitis, and skin and soft tissue infections, since it can penetrate tissues. CTRX-associated pseudolithiasis is a known complication, reported mainly in children. The mechanism is ascribed to a high CTRX concentration in the gallbladder bile, which is 20- to 150-fold higher than that in the serum. When the CTRX concentration in the gallbladder exceeds its threshold, CTRX can precipitate by binding to calcium ions secreted along with bile acids. Since CTRX can precipitate with calcium, CTRX-associated pseudocholelithiasis is principally composed of calcium-CTRX complexes [3].

Subcutaneous, deep muscle, and retroperitoneal bleeding are predominant bleeding sites in patients with AHA [1]. However, gallbladder hemorrhaging and rupture are extremely rare entities, with only a few previously reported cases, even in patients using anticoagulants or with bleeding disorders. According to reports, mechanical irritation of the gallbladder wall due to preceding repeated cholecystitis can result in hemorrhaging from the gallbladder and its rupture [4,5]. Yoshida et al. reported on the outcomes with CTRX-associated pseudocholelithiasis. The median intervals from CTRX administration to the diagnosis of CTRX-associated pseudocholelithiasis and from CTRX cessation to pseudolithiasis resolution were 10 days and 69 days, respectively. Events related to pseudocholelithiasis occurred in 29% patients, but most of the cases were improved

with conservative treatment with CTRX cessation[3]. CTRX-associated pseudocholelithiasis can induce the development of cholecystitis, but no cases with fatal outcomes, including gallbladder hemorrhaging and rupture, have previously been reported.

In our case, AHA was a predisposing factor, leading to gallbladder hemorrhaging and rupture. The gallbladder is not structurally tolerant of ischemia, since it is maintained by the cystic artery, which is a terminal artery. Thus, high artery pressure due to a hematoma, boosted by AHA and local ischemia from massive blood loss caused an ischemic gallbladder wall, can trigger gallbladder rupture.

In conclusion, our case demonstrated that CTRX-associated pseudocholelithiasis can unexpectedly induce gallbladder hemorrhaging and rupture in a patient with a bleeding diathesis. Clinicians should be alert for CTRX-associated pseudocholelithiasis, which can cause a lethal outcome in patients with a bleeding disorder, even if CTRX is ceased as soon as pseudocholelithiasis is detected.

Statements

Statement of Ethics

Written informed consent for publication was obtained from the patient's wife.

Disclosure Statement

There are no conflicts of interest, financial or otherwise, to disclose for any the authors.

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Author Contributions

All authors contributed the management of the patient, reviewed the manuscript, and reviewed the literature.

Figure Legends

Figure 1. (a) On day 1 after admission, abdominal computed tomography with intravenous contrast showed no gallbladder stone. (b) On day 5 after admission, plain abdominal computed tomography showed a high-density lesion in the gallbladder, indicative of ceftriaxone-associated pseudolithiasis. (c, d) On day 22 after admission, abdominal computed tomography with intravenous contrast showed a high-density biliary sludge pattern and iodinated contrast material extravasation into the gallbladder (arrow).

Figure 2. (a, b) The autopsy revealed gallbladder rupture, resulting in a massive hematoma. (c) Final pathology demonstrated hemorrhagic and necrotic changes with focal neutrophilic cell infiltration and fresh thrombi (hematoxylin-eosin staining ×400).

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