

Sirolimus-induced severe small bowel angioedema

A case report

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Abstract

Rationale: Drug-induced angioedema has been reported as an adverse effect of many different drugs. But small bowel angioedema associated with sirolimus (SRL) used was barely understood. It must be necessary to report a case suffering from small bowel angioedema with detailed discussion and literature review.

Patient concerns: A 38-year-old Chinese woman presented with generalized gastric pain in the following day after renal transplantation. The patient began to crampy abdominal pain accompanied by nausea, vomiting, and diarrhea on postoperative day 6 (POD).

Diagnoses: We strongly suspected the angioedema was an adverse reaction to SRL.

Intervention: The immunosuppressive regimen was switched from tacrolimus (TAC), SRL, and prednisone to TAC, mycophenolate and prednisone.

Outcomes: The symptoms were relieved within next 48 hours after withdrawing the SRL. One more CT scan showed complete resolution of bowel wall thickening and ascites.

Lessons: This was the first report of small bowel angioedema associated with SRL. Drug-induced-angioedema is a relatively common presentation and is potentially fatal. It must be aware of potential adverse effects.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AIIRA = angiotensin II receptor antagonists, CT = computed tomography, mTORi = mechanistic target of rapamycin inhibitors, POD = postoperative day, PRAs = panel reactive antibodies, SRL = sirolimus, TAC = tacrolimus.

Keywords: adverse drug reactions, renal transplantation, sirolimus, small bowel angioedema

1. Introduction

Angioedema is an area of swelling of the lower layer of skin and tissue just under the skin or mucous membranes. The swelling may occur in the face, tongue, larynx, abdomen, or arms and legs.^[1] There are different causes of angioedema, such as the intake of drugs, allergies, or the lack of the complement C1 inhibitor.^[2] Drug-induced angioedema has been reported as an adverse effect of many different drugs. Among them, the use of angiotensin-

converting enzyme inhibitor (ACEI) was one of the most common causes of severe angioedema presenting at hospitals.

Sirolimus (SRL; Hisun Pfizer Pharmaceuticals Co, Ltd, Shanghai, China) is a macrolide antibiotic with antiproliferative properties that has been proven effective in reducing the risk of acute rejection in renal transplantation.^[3] Because of its effective immunosuppressive effect in organ transplantation and lack of nephrotoxicity, SRL is a very attractive alternative to replace calcineurin inhibitors.^[4] The most common side effects of SRL are thrombocytopenia and dyslipidemia. Angioedema associated with SRL was reported in recent years. But angioedema of periorbital region, floor of mouth, and tongue often occurred.^[5,6] In this report, it presented a case of severe small bowel angioedema associated with SRL used. To some extent, this was the first description of such an association.

2. Case report

2.1. Patient information

A 38-year-old Chinese woman received renal transplantation in November 29, 2017 in our hospital. The etiology of end-stage renal disease was unknown. The patient received a left renal allograft from one 32-year-old cardiac death donor who was dead in a car accident. There were one mismatched human lymphocyte antigen DR (HLA DR), negative repeated complement-dependent cross match test, and 8% donor nonspecific panel reactive antibody (PRA) class I and 0% PRA class II. There was no complication during the transplant procedures. The patient's immunosuppressive regimen included thymoglobulin for induction immunosuppressive therapy, and tacrolimus (TAC), SRL, glucocorticoids for maintenance therapy. SRL was used on postoperative day (POD) 1, with the target trough

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HY and WW contributed equally to this work and should be considered co-first authors.

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital. Informed consent was obtained from the patient for publication of this case report and accompanying images.

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level 1 to 4 ng/mL range. The following day after operation, the patient presented with generalized gastric pain. The symptoms had been worsened over the next 3 days.

2.2. Physical examination and diagnostic assessment

It has been quickly reduced the dose of glucocorticoids in consideration of the side effect of it. At the same time, the patient was inserted with a nasogastric tube for decompression, and treated by omeprazole 40 mg q12 hours IVGTT and placing her on nothing-by-mouth (NPO) status. But the patient began to crampy abdominal pain accompanied by nausea, vomiting, and diarrhea on POD 6. Computed tomography (CT) scan of the abdomen and pelvis revealed a large amount of free intraperitoneal fluid adjacent to the liver capsule (Fig. 1A) and diffuse small bowel wall thickening in the mid-abdomen (Fig. 1B). Ileus was strongly suspected, so exploratory laparotomy was performed immediately to identify the etiology. And it showed small bowel edema which located 50 cm distal from the ligament of Treitz, and no ileus was found (Fig. 2).

2.3. Therapeutic interventions

The patient's medications at that time included TAC 3 mg po bid (trough concentration, 8.9 ng/mL), SRL 1 mg po qd (trough concentration, 3.06 ng/mL), prednisone 25 mg po qd. The patient had no history of gastrointestinal illnesses or drug allergies. SRL was reported to cause angioedema; therefore, the immunosuppressive regimen was switched from TAC, SRL, and prednisone to TAC, mycophenolate, and prednisone.

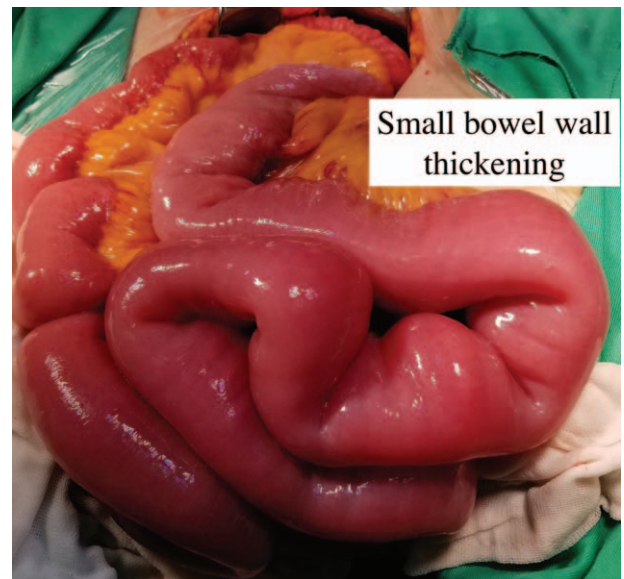


Figure 2. Small bowel edema found by exploratory laparotomy.

2.4. Follow-up and outcomes

The symptoms were relieved for the next 48 hours after withdrawing the SRL. One more CT scan obtained 7 days later, showed complete resolution of bowel wall thickening and ascites (Fig. 3). Then the patient discharged.

3. Discussion

Angioedema is a self-limiting swelling that occurs in the deeper cutaneous and mucous membrane layers.^[5] Most cases of angioedema resulted from a reaction to food or drugs, but some episodes had no identifiable trigger. Penicillins, ACEI, sulfonamides, aspirin, and nonsteroidal anti-inflammatory drugs are the most common drug classes related to angioedema.^[5]

In this case, the patient suffered from severe crampy abdominal pain accompanied by nausea, vomiting, and diarrhea, but the patient had no history of gastrointestinal illnesses. CT scan and exploratory laparotomy revealed severe small bowel angioedema. The patient was treated by omeprazole 40 mg q12 hours IVGTT and placing her on NPO status. The patient's medications included TAC, SRL, and prednisone at that time. The patient

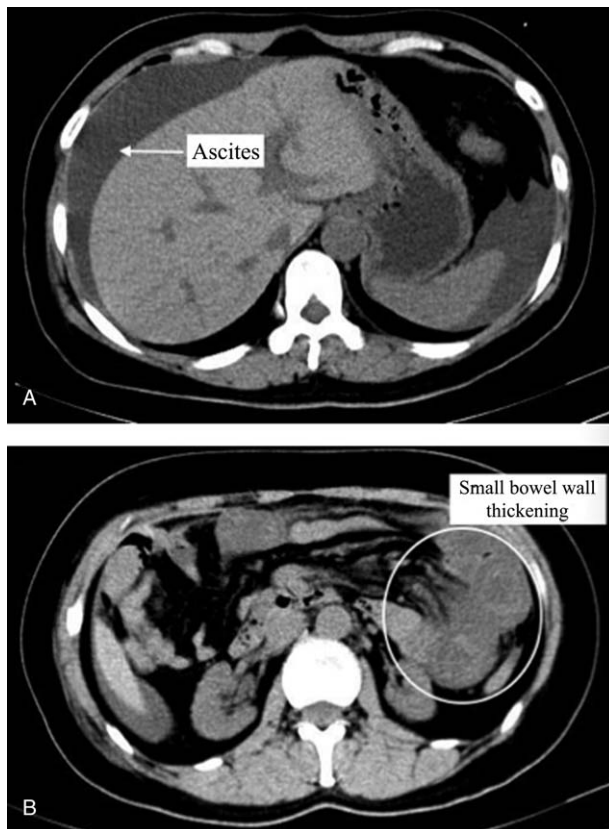


Figure 1. Computed tomography scan of the abdomen and pelvis.



Figure 3. Computed tomography scan after withdrawing the sirolimus.

stopped taking the SRL for the reason that SRL had been reported to cause angioedema.^[5-7] The symptoms were relieved for the next 48 hours. In previous reports on angioedema associated with SRL, the event occurred in 2.2% to 9.6% of the patients.^[7] Angioedema of the face, periorbital region, floor of mouth, and tongue often occurred.^[5,6] This patient suffered from severe small bowel angioedema. It might be related with forbidding early postoperative mobilization.

Angioedema can be mediated by histamine, bradykinin, or other mechanisms.^[8] Histamine-mediated angioedema, also called allergic angioedema, is a type I immunoglobulin E-mediated hypersensitivity immune response of mast cell degranulation.^[1] Bradykinin-induced angioedema is the most common cause of nonhistamine-mediated angioedema. From the practical guide about angioedema published in 2017, bradykinin-mediated angioedema includes 3 distinct types: hereditary angioedema, acquired angioedema, and ACEI-induced angioedema. Several case reports implicated the increased incidence of angioedema when mechanistic target of rapamycin inhibitors (mTORi) were added to ACEI in the solid organ transplant setting.^[9] ACEI or angiotensin II receptor antagonists (AIIRA) and TAC had been identified the triggering factors of SRL-reduced angioedema in the literatures.^[10] But the patient did not take ACEI and AIIRA at that time. The participation of SRL in the pathogenesis of angioedema in RTRs is possible. In previous studies, SRL was reported to cause impaired, endothelium-dependent relaxation in response to bradykinin. It suggested that SRL interfered with the bradykinin pathway.^[3]

Although, no medication was approved for ACEI-induced or acquired angioedema by US Food and Drug Administration. Plasma-derived/recombinant C1-INH, ecallantide, and icatibant were proved to play a broader role in treatment of bradykinin-mediated attacks in patients who did not have hereditary angioedema in recent and ongoing research.^[1]

The case report was the first report of small bowel angioedema induced by SRL. Drug-induced angioedema is a relatively

common presentation and is potentially fatal. It must be aware of potential adverse effects.

Author contributions

HY and WW wrote the first article draft. All authors were involved in the care of the patient. All authors participated in the interpretation of the data and writing of the final article and all authors approved final article.

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