Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3740-19
Intern Med 59: 997-1000, 2020
http://internmed.jp

【 CASE REPORT 】

TAFRO Syndrome Presenting with Retroperitoneal Panniculitis-like Computed Tomography Findings at Disease Onset

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Abstract:
TAFRO syndrome is rare, and its pathophysiology remains unclear. We herein report the case of a 66-year-old man who presented at our emergency department with epigastric pain. Contrast-enhanced computed tomography (CT) showed high-density retroperitoneal panniculus with contrast enhancement. He was treated initially with a protease inhibitor and hydration, to little effect. Anasarca, thrombocytopenia, and renal dysfunction developed gradually, and TAFRO syndrome was diagnosed. He was treated successfully with prednisolone and cyclophosphamide, and subsequent CT findings showed improvement. Abnormal CT findings of the retroperitoneum may indicate the early stages of TAFRO syndrome before the presentation of typical ascites.

Key words: TAFRO syndrome, retroperitoneum, computed tomography

(Intern Med 59: 997-1000, 2020)
(DOI: 10.2169/internalmedicine.3740-19)

Introduction

TAFRO syndrome, first reported in 2010, is a rare systemic inflammatory disease characterized by thrombocytopenia, anasarca, fever, bone marrow fibrosis, renal disfunction, and organomegaly (1). The term "TAFRO syndrome" was proposed in 2012 by physicians in Japan (1, 2). The pathophysiology of TAFRO syndrome remains unclear; however, several reports suggest that it is a subtype of multicentric Castleman disease (3) as lymph node biopsy samples obtained from patients with TAFRO syndrome appear identical to those from patients with multicentric Castleman disease (3).

Although an updated diagnostic criterion was established in 2015, it remains difficult to precisely diagnose TAFRO syndrome, not only because of its rarity but also because multiple differential diagnoses need to be excluded (4). Furthermore, patients with TAFRO syndrome present clinically with non-specific symptoms, such as a high fever, epigastric pain, and edema (2, 3, 5). There is no standard therapy for TAFRO syndrome, but in Japan, glucocorticoid therapy is usually administered (4). In cases refractory to glucocorticoid therapy, other immunosuppressants, such as cyclosporin, rituximab, cyclophosphamide (CPA), and tocilizumab, have been prescribed (4-7).

We herein report a patient diagnosed with TAFRO syndrome without massive ascites at the disease onset but with an abnormally high-density retroperitoneum seen on abdominal enhanced computed tomography (CT), which was successfully treated with prednisolone and oral CPA.

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Received: August 1, 2019; Accepted: October 29, 2019; Advance Publication by J-STAGE: December 13, 2019
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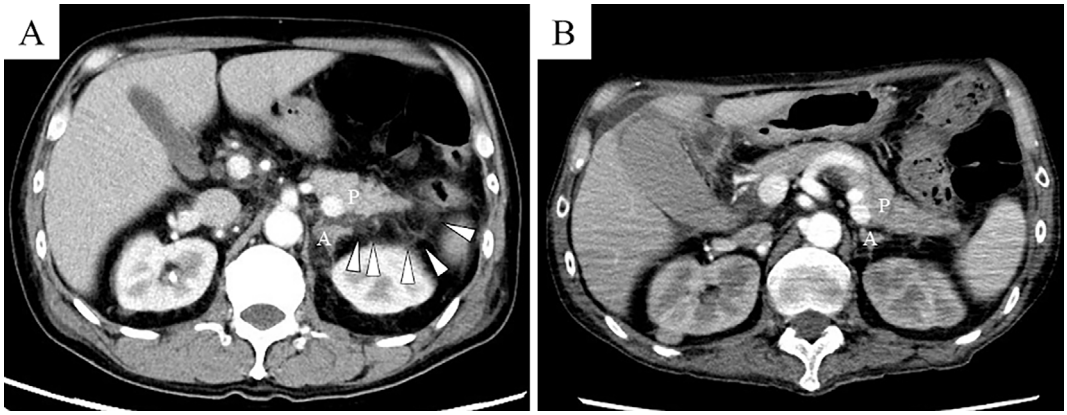

Figure 1. **Contrast-enhanced computed tomography (CT) at the disease onset (A) showed high-density retroperitoneal panniculus surrounding the corpus and tail of the pancreas with a contrast effect (*arrows*). CT also showed perirenal edema. After the administration of therapeutic agents for three months, both the density of retroperitoneal panniculus and perirenal edema decreased (B). P: pancreas, A: adrenal grand**

Case Report

A 66-year-old man was admitted to our hospital via the emergency department with a history of epigastric and back pain that had been present for several days, accompanied by a fever. A physical examination revealed marked epigastric tenderness with muscular defense. He denied any arthralgia and myalgia symptoms, and no skin lesions were noted. His emergency department laboratory test results demonstrate neutrophil-dominant leukocytosis with slight thrombocytopenia. Elevated serum alkaline phosphatase, gamma-glutamyl transferase, and serum C-reactive protein levels were noted. Plain chest and abdominal radiographs appeared unremarkable; however, abdominal contrast-enhanced CT showed slight hepatosplenomegaly and high-density retroperitoneal panniculus adiposus tissue around the pancreatic corpus and tail with contrast enhancement (Fig. 1A). Abdominal CT also showed perirenal edema (Fig. 1A). No lymphadenopathy was detected on neck, chest, or abdominal CT scans. Both pancreatic amylase and lipase levels were within the normal range. Nafamostat mesylate was administered along with wide-spectrum antibacterial agents, to little effect. Pleural effusion, ascites, anasarca, and thrombocytopenia occurred sequentially without any improvement in the patient's symptoms or in subsequent laboratory test results. His renal and liver function test results worsened, and he was started on hemodialysis two weeks after admission.

Massive pleural effusion then resulted in respiratory failure, and bilateral pleural drainage was performed. Further laboratory test results indicated an increase in fibrinogen, fibrin degradation products, and D-dimer levels; no appearance of autoantibodies; a normal titer of serum immunoglobulins, including IgG4; and no elevation of tumor markers except for serum interleukin (IL)-2 receptor (2,420 U/mL). However, the serum IL-6 (33.2 pg/mL) levels were found to be elevated. Immunofixation electrophoresis of serum and urine showed no evidence of monoclonal gammopathy. Test results for both cytomegalovirus pp65 antigen in his white blood cells and serum beta-D glucan were negative. We performed further chest and abdominal CT but found no additional abnormal findings, such as lymph node swelling or inflammation, other than massive pleural effusion and ascites. Bone marrow aspiration and a biopsy showed an increase in megakaryocytes with reticulin fibrosis. An immunohistochemical analysis for latency-associated nuclear antigen-1 of human herpes virus 8 in the bone marrow yielded negative results. Bacterial and fungal culture results from his blood, urine, and pleural effusion were all negative. Taken together, these physical, laboratory, and imaging findings suggested the possibility of TAFRO syndrome according to the diagnostic criteria (4).

The therapeutic course during admission is described in Fig. 2. We administered intravenous prednisolone (PSL) (1 mg/kg/day), and his symptoms and laboratory findings gradually improved, with a decrease in pleural and peritoneal effusion. During the therapeutic course, *Corynebacterium* species were detected from both blood and pleural effusion samples taken from areas in which percutaneous infection was suspected; therefore, intravenous vancomycin and clindamycin were administered. After 1 week of administration, the PSL dosage was gradually reduced, and CPA (50 mg/day) was added to prevent an inflammatory relapse. After approximately 1.5 months, CPA administration was stopped because of a significant decrease in the patient's neutrophil count and recurrent reactivation of cytomegalovirus, for which ganciclovir and valganciclovir were administered. However, as there was no inflammatory relapse, we reduced the PSL dosage to 20 mg/day at 3 months after starting PSL. His renal function also gradually improved, and hemodialysis was able to be stopped completely. He was discharged from the hospital four months after admission without any disability. Abdominal contrast-enhanced CT performed before discharge showed improvement in the

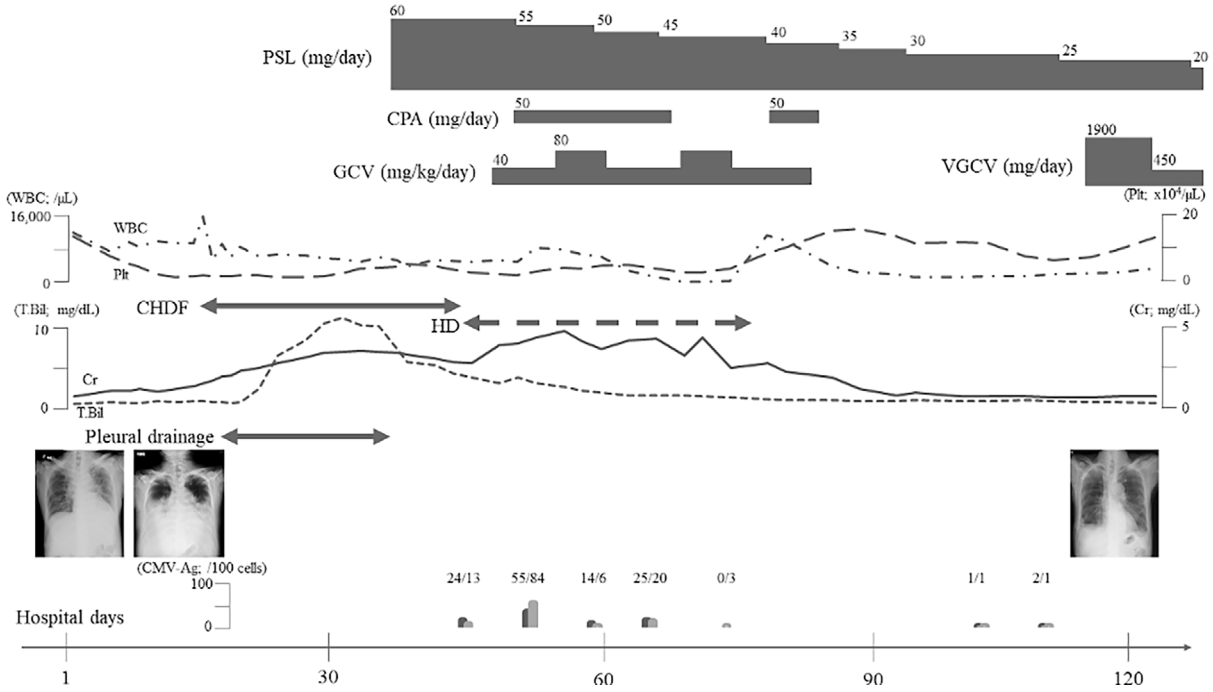

Figure 2. **Clinical course of our patient. Thrombocytopenia, pleural effusion, renal dysfunction, and elevation of total bilirubin (T-BIL) levels were observed after admission. These findings improved following the administration of prednisolone (PSL) and cyclophosphamide (CPA). PSL was subsequently reduced without relapse of the disease status. GCV: ganciclovir, VGCV: valganciclovir, CHDF: continuous hemodiafiltration, HD: hemodialysis, WBC: white blood cell count, Plt: platelet count, Cr: serum creatinine, CMV-Ag: counts of cells positive for pp65 antigen of cytomegalovirus (C10/11)**

retroperitoneal density and an enhancement decrease (Fig. 1B).

Discussion

Between 75% and 95% of patients with TAFRO syndrome present with a low performance status, anasarca, and a fever (8); however, our patient presented with no clinical signs of anasarca. In imaging studies, hepatosplenomegaly and lymph node enlargement accompanied by massive pleural and abdominal effusion are important diagnostic findings of TAFRO syndrome, whereas the CT findings for our patient only indicated mild hepatosplenomegaly without obvious ascites or lymphadenopathy. Contrast-enhanced CT also suggested an increased density of retroperitoneal panniculus surrounding the pancreatic corpus and tail with contrast enhancement. Such characteristics are not recognized as common findings of TAFRO syndrome and mimic the contrast-enhanced CT appearance of acute pancreatitis (9). We were unable to fully rule out the possibility of acute pancreatitis from severe epigastric tenderness and abnormal CT findings at that time, as acute pancreatitis has been reported to occur without any elevation in the serum pancreatic enzyme levels in very rare cases (10, 11).

We first treated this patient with protease inhibitors and antibiotics following an initial treatment for acute pancreatitis, accompanied by a thorough examination, because the therapeutic delay in cases of acute pancreatitis is often fatal. Consequently, the density of the retroperitoneal panniculus on contrast-enhanced CT decreased after treatment with PSL and CPA rather than because of the therapy used to treat acute pancreatitis. This indicated that the appearance of the CT abnormality was a result of inflammation due to TAFRO syndrome rather than acute pancreatitis.

Few previous reports concerning TAFRO syndrome have described the early-phase abdominal CT findings before the appearance of massive ascites, as was the case in our patient. Two hypotheses may explain this abnormal CT finding. One hypothesis is that the finding indicated the initial phase of peritonitis due to TAFRO syndrome, which would eventually induce severe ascites and retroperitoneal edema. Peritonitis is a major symptom of TAFRO syndrome (1), and a high retroperitoneum density may be the result of fluid collection induced by peritonitis. Regarding our patient, there is a possibility that retroperitoneal edema occurred before the development of severe ascites in TAFRO syndrome, which may aid in the early diagnosis and clarification of the pathophysiology of serositis and anasarca in TAFRO syndrome. Retroperitoneal panniculitis is the second potential explanation of the CT findings in our patient, as a contrast effect was observed at the retroperitoneum, indicating inflammation rather than fluid collection radiologically. Retroperitoneal panniculitis is a rare inflammatory status that presents with severe acute-onset abdominal pain, similar

to acute pancreatitis, without any increase in the serum pancreatic enzyme levels, as was observed in our patient (12). No PubMed reports described cases of TAFRO syndrome with retroperitoneal panniculitis as of June 2019; however, panniculitis at other sites, such as the anterior mediastinum, due to TAFRO syndrome has been reported (13). To assess these hypotheses in detail, the collection of further cases of TAFRO syndrome and the thorough confirmation of abnormal findings in the retroperitoneum using CT will be required. If possible, autopsies need to be performed for cases involving TAFRO syndrome and pathological analyses in order to elucidate the exact mechanisms responsible.

In conclusion, a patient was diagnosed with TAFRO syndrome without obvious ascites at the disease onset, showing abnormally high-density retroperitoneal panniculus with contrast enhancement on abdominal CT. This presentation may indicate an early phase of TAFRO syndrome before the development of typical ascites, which may be useful in the early diagnosis and for elucidating the pathophysiology of TAFRO syndrome.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Dr. Rintaro Ohe and Dr. Mitsunori Yamakawa for their great support in relation to the immunohistochemistry of latency-associated nuclear antigen-1 of human herpes virus 8.

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