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Case Report

Exocrine Pancreatic Insufficiency Possibly Related to Atypical Chronic Graft-versus-Host Disease

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Keywords
Chronic graft-versus-host disease · Exocrine pancreatic insufficiency · Pancreatic atrophy

Abstract
We report the case of a 66-year-old woman who presented with diarrhea and weight loss approximately 14 months after unrelated allogeneic bone marrow transplantation for acute myeloid leukemia. Her early post-transplant course was notable for mild acute skin graft-versus-host disease (GVHD) and biopsy-proven upper gastrointestinal (GI) acute GVHD, both of which resolved with treatment. She then developed weight loss and diarrhea treated with prednisolone for what was thought to be GI late acute GVHD. However, her diarrhea and weight loss persisted. Colonoscopy showed a grossly intact mucosa, and stool studies only confirmed steatorrhea. However, an atrophic pancreas was found on an abdominal computed tomography (CT) scan. Exocrine pancreatic enzymes, such as lipase and pancreatic amylase, were markedly decreased, yet pancreatic endocrine function remained intact. The patient's diarrhea and weight loss improved upon treatment with pancrelipase. Therefore, we suggest that her exocrine pancreatic insufficiency was likely partly caused by atypical chronic GVHD.

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Introduction

Graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic cell transplantation (allo-HCT). Chronic GVHD occurs in 30–70% of patients after allo-HCT [1]. The primary target organs of chronic GVHD include not only those primarily targeted in acute GVHD (e.g., gastrointestinal (GI) tract, skin, and liver) but also many other tissues and organs including the oral cavity, the esophagus, the musculoskeletal system, the eyes, the genitalia, and the lymphohematopoietic system [1]. However, the pancreas is not considered a common target organ of chronic GVHD. Herein, we report a rare case of pancreatic exocrine insufficiency and atrophy possibly related to atypical chronic GVHD after unrelated allogeneic bone marrow transplantation for acute myeloid leukemia.

Case Report

A 66-year-old woman approximately 14 months post a human leukocyte antigen-matched unrelated donor allo-HCT presented with diarrhea and weight loss. After achieving a complete remission of her acute myeloid leukemia following standard chemotherapy, she was conditioned using a fludarabine and melphalan-based reduced intensity regimen. Tacrolimus and short-term methotrexate were used for GVHD prophylaxis. Bone marrow aspiration performed on day 25 after allo-HCT showed complete remission and full donor chimerism. On day 25, she developed skin acute GVHD (stage 1, overall grade I) that resolved with topical corticosteroids. The patient then developed persistent nausea on day 53 and was found to have upper GI acute GVHD on histopathologic examination of biopsies obtained during an upper GI endoscopy. Because her nausea improved spontaneously, she did not receive any systemic or topical corticosteroids. Subsequently, her tacrolimus was slowly tapered and discontinued without issue.

After doing well for nearly a year, the patient developed diarrhea that persisted for over a month. She was clinically diagnosed with GI late acute GVHD and treated with 5 mg/day of prednisolone. However, her GI symptoms continued, and she began losing weight. A lower GI endoscopy was performed on day 490, which revealed only fatty stools without any inflammation in the intestinal tract. Therefore, no biopsy was performed. Abdominal computed tomography (CT) and magnetic resonance imaging scans showed a markedly atrophic pancreas (Fig. 1) with approximately 60% volume loss compared to pretransplantation. No pancreatic cysts, tumors, or duct dilatation were detected. Laboratory results showed decreased pancreatic amylase (3 U/L), lipase (6 U/L), and elastase-1 (<80 ng/dL). By contrast, a glucose tolerance test was normal. She denied any history of alcohol consumption. A peripheral blood cytomegalovirus antigenemia test and bacterial cultures were also negative. All other common chronic GVHD target organs were uninvolved. Her symptoms rapidly improved, and her body weight recovered after starting pancreatic enzyme supplementation with pancrelipase. Therefore, we concluded her refractory diarrhea was likely due to exocrine pancreatic insufficiency possibly caused by chronic GVHD. Without a pancreas biopsy, a definitive diagnosis of isolated pancreatic atypical chronic GVHD is not possible.

Discussion

Chronic GVHD is a major long-term complication of allo-HCT that occurs in 30–70% of patients and can significantly impact their quality of life [1]. It is diagnosed and staged according to the National Institutes of Health (NIH) consensus criteria [2]. The most common targets of chronic GVHD include the skin, oral mucosa, eyes, genitalia, GI tract, liver, lungs, musculoskeletal

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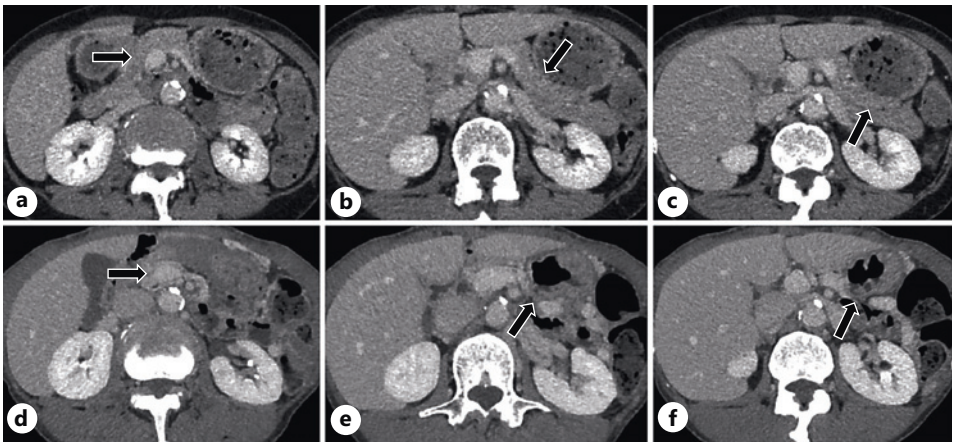

Fig. 1. Abdominal computed tomography (CT) of the pancreas showed a head width of 10.3 mm (**a**), a body width of 12.9 mm (**b**), and a tail width of 11.4 mm (**c**) before allogeneic hematopoietic cell transplantation (allo-HCT). On day 637 after allo-HCT, the pancreas was atrophied with a head width of 3.2 mm (**d**), a body width of 5.2 mm (**e**), and a tail width of 6.2 mm (**f**).

system, and hematopoietic system. Isolated chronic GVHD of the pancreas leading to atrophy and exocrine insufficiency is rare and may be a manifestation of atypical chronic GVHD. The 2020 NIH Consensus Project defined atypical chronic GVHD as an alloreactive or autoimmune response in a nonclassical chronic GVHD target organ or an atypical presentation in common chronic GVHD organ. This Consensus Project noted that atypical features often manifest upon tapering or discontinuing immune suppression and can occur with minimal or no features of classical chronic GVHD [3]. As for our case, pancreatic atrophy was observed in the absence of other common chronic GVHD manifestation after discontinuation of tacrolimus. Thus, it is possible that the pancreatic atrophy in this case was due to atypical chronic GVHD.

The differential diagnosis for pancreatic atrophy includes chronic pancreatitis, autoimmune pancreatitis, pancreatectomy, immune checkpoint inhibitor therapy, type 2 diabetes mellitus, and pancreatic GVHD [4–8]. Chronic GVHD presenting with pancreatic atrophy is rare, and its natural history and pathophysiology are poorly defined. However, published reports are suggestive of its existence. For instance, Brook et al. [9] reported that among allo-HCT recipients, those with chronic GVHD had greater pancreatic atrophy, especially atrophy of the pancreatic head, than those without chronic GVHD. Okada et al. [10] found that 32.4% of patients after allo-HCT had pancreatic atrophy, which was significantly associated with inferior overall survival and an increased risk of non-relapse mortality. Nakasone et al. [11] showed that 16.7% of patients after allogeneic peripheral blood stem cell transplantation had pancreatic atrophy, which correlated with liver and GI chronic GVHD. These reports suggest that chronic GVHD may cause pancreatic atrophy. However, chronic GVHD is often preceded by acute GVHD [1], but none of these reports demonstrated biopsy-proven acute GVHD preceding the onset of pancreatic atrophy. By contrast, our patient was diagnosed with biopsy-proven GI acute GVHD on day 53. Her acute GVHD symptoms completely resolved before she then presented with steatorrhea, weight loss, and pancreatic atrophy. Hence, her clinical course suggests that her pancreatic atrophy and exocrine insufficiency may have been related to her prior acute GI GVHD.

Foulis et al. [12] performed autopsies on 14 allo-HCT recipients with acute GVHD. Four patients had pathological changes, including epithelial cellular atypia and lymphocytic infiltration of exocrine ducts. The authors also found that class I and II major histocompatibility complexes were overexpressed in the pancreatic ductal epithelium, yet there was no

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Table 1. Summary of pancreatic exocrine insufficiency after allo-HCT

Case	Age/sex	Disease	Transplantation	GVHD	Symptom	Time from allo-HCT to symptom appearance	Pancreatic atrophy	Treatment	Reference
1	59/M	HL	allo-PBSCT	cGVHD of skin and liver	Steatorrhea	3 years	Yes	Pancreatic enzymes	13
2	59/M	AML	–	–	Diarrhea, steatorrhea Weight loss	2 years	Yes	Pancreatic enzymes	14
3	22/F	AML	BMT from an HLA-matched related donor	aGVHD of skin and liver	Diarrhea Weight loss	14 months	Yes	Low-fat diet pancreatic enzymes	15
4	38/F	CML	BMT from an HLA-matched related donor	aGVHD of skin cGVHD of skin and liver	Steatorrhea Weight loss	9 months	No (abdominal ultrasound evaluation)	Enteral feeding Prednisone, cyclosporine Pancreatic enzymes	15
5	65/F	AML	BMT from an HLA-matched unrelated donor	aGVHD of skin and liver	Diarrhea Weight loss	14 months	Yes	Pancreatic enzymes	Present case

GVHD, graft-versus-host disease; allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; CML, chronic myeloid leukemia; allo-PBSCT, allogeneic peripheral blood stem cell transplantation; BMT, bone marrow transplantation; HLA, human leukocyte antigen; aGVHD, acute GVHD; cGVHD, chronic GVHD.

inflammation, endocrine cell damage, or major histocompatibility complex overexpression in the islets. These results suggest that the ductal epithelium is a potential GVHD target, leading to suppressed exocrine function while relatively preserving endocrine function. Consistent with this, our patient presented with diarrhea likely due to exocrine dysfunction, while her pancreatic endocrine function remained intact.

We performed a literature review of pancreatic exocrine insufficiency after allo-HCT and summarized the four published cases, to our knowledge, in Table 1 [13–15]. Diarrhea and weight loss due to pancreatic exocrine insufficiency were present in all cases. The time from transplantation to the onset of symptoms ranged from 9 months to 3 years. Pancreatic atrophy on CT scan was present in all cases except for case 4 where only an abdominal ultrasound was performed. As in our case, pancreatic enzyme replacement was used for all four published cases and was effective except in case 4. These results suggest that pancreatic exocrine insufficiency and atrophy may appear months to years after allo-HCT and that pancreatic enzyme supplementation is an effective treatment.

The published studies discussed above suggest that pancreatic exocrine deficiency and atrophy after allo-HCT may be underappreciated. One reason for this is the broad differential diagnosis of diarrhea after allo-HCT, which includes GVHD, infection, toxicity from the conditioning regimen, as well as pancreatic insufficiency [16]. Pancreatic insufficiency itself also has a lengthy differential diagnosis and is often observed following drug-induced pansteatitis from commonly used medicines in allo-HCT such as cyclosporine or corticosteroids. In cases of refractory diarrhea and/or weight loss, we suggest screening for pancreatitis, pancreatic exocrine insufficiency, and atrophy by obtaining a serum amylase level, assessing fecal fat content, and performing an abdominal CT scan.

In conclusion, we report a rare case of pancreatic atrophy and exocrine insufficiency likely due to atypical chronic GVHD. Persistent steatorrhea and weight loss following allo-HCT should prompt clinicians to evaluate for pancreatic exocrine dysfunction. If present, pancreatic enzyme replacement may be an effective treatment for this rare but perhaps underappreciated manifestation of chronic GVHD. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533381).

Statement of Ethics

Written informed consent for publication of the clinical course and any accompanying images was obtained from the patient. This case report was reviewed and approved by the Ethical Review Committee of Yamagata University Faculty of Medicine, approval number 2023-S-4.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

Yuka Hosokawa and Tomomi Toubai diagnosed and treated the patient and wrote the article. Daniel Peltier and Kenichi Ishizawa provided instructions for writing this article. Koichi Ohya, Yusuke Nagano, Yuki Ishizawa, Masashi Hosokawa, Ryo Sato, Shotaro Watanabe, Akane Yamada, Takuma Suzuki, Keiko Aizawa, Satoshi Ito, and Yusuke Onozato treated the patient.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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