



Esophageal stenosis with sloughing esophagitis: A curious manifestation of graft-*vs*-host disease

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Abstract

We report a case of a 56-year-old woman with a history of allogenic bone marrow transplantation for two years, complaining with dysphagia and weight loss. Upper endoscopy revealed esophageal stenosis and extensive mucosa sloughing. Biopsies confirmed the diagnosis of graft-*vs*-host disease (GVHD). Balloon dilation, corticosteroids and cyclosporin resulted in marked clinical improvement. Gastrointestinal tract is involved in the majority of patients with chronic GVHD. Esophageal manifestations are rare and include vesiculobullous disease, ulceration, esophageal webs, casts or strictures. Sloughing esophagitis along with severe stenosis requiring endoscopic dilation has never been reported in this context.

Key words: Dysphagia; Esophageal stenosis; Sloughing esophagitis; Balloon dilation; Graft-*vs*-host-disease

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Core tip: Esophageal manifestations of graft-*vs*-host

disease (GVHD) are very rare. We report a case of sloughing esophagitis along with severe stenosis requiring endoscopic dilation, as a manifestation of chronic GVHD, after allogenic bone marrow transplantation. This manifestation has never been reported in this context. Endoscopy may play a significant role in early diagnosis and treatment of esophageal GVHD. Histological examination of gastrointestinal biopsies is needed to confirm the diagnosis.

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INTRODUCTION

Graft-vs-host disease (GVHD) is a serious complication of allogenic hematopoietic stem cell transplantation (HSCT). It is a multisystem disorder that can involve the skin, gastrointestinal (GI) tract and liver^[1]. Nausea, vomiting, anorexia and diarrhea are common manifestations of GI-GVHD, but they may also be attributable to chemoradiation toxicity, medication side effects or infections^[1,2]. Thus, it is difficult to establish the diagnosis based only on clinical grounds.

Sometimes, GI-GVHD can cause life-threatening complications such as massive diarrhea, hemorrhage, paralytic ileus and perforation^[3,4]. Therefore, recognition of GI-GVHD is essential for directing specific therapy. Although endoscopy with biopsy is accurate in the identification of GI-GVHD, several mucosal patterns can be observed, ranging from normal to mild edema or severe erythema, exudates, erosions and ulceration^[2,5].

In particular, involvement of the esophagus in chronic-GVHD (initially defined as a disorder occurring 100 d after HSCT)^[1] is not common, with only a few reports found in the literature^[5-8]. It can be manifested as a vesicubullous disease, ulceration, web, desquamative esophagitis, esophageal cast or stricture^[1,2,5-9].

We report a rare case of chronic-GVHD with esophageal involvement, presenting with dysphagia and weight loss, due to severe esophageal stenosis and mucosal sloughing.

CASE REPORT

A 56-year-old woman with acute myeloid leukemia M5b (monocytic) underwent allogenic bone marrow transplantation (BMT). After 3 mo, she developed a full-body skin rash and abnormal liver function tests with increased bilirubin. She was diagnosed with acute GVHD and was treated with prednisolone (1 mg/kg per day)



Figure 1 Skin lesions of the lower limbs, with erythematous papules and induration areas.

and cyclosporine. The patient improved clinically and after 10 mo of therapy, prednisolone was discontinued.

Two years after transplantation, the patient complained with dysphagia for solids with progressive worsening in the last 2 wk and was referred to Gastroenterology Department. She reported xerostomia, anorexia and weight loss of 18 kg in 2 mo (> 20% of total body weight). Physical exam revealed aphthous stomatitis and skin lesions of the lower limbs, with pruriginous and erythematous papules, desquamation and induration areas (Figure 1). Her blood pressure, pulse rate, and body temperature were normal. Neurological examination was normal. Laboratory studies revealed hemoglobin 11.5 g/dL, leucocytes 11000, albumin 2.7 g/dL, AST 82 IU/L, ALT 87 IU/L, alkaline phosphatase 514 IU/L, GGT 282 IU/L, total bilirubin 1.3 mg/dL, C-reactive protein 1.17 mg/dL, international normalized ratio (INR) 1.1, antinuclear antibody (ANA) 1:160. Hepatitis A, B and C, HIV, cytomegalovirus, herpes and Epstein-Barr virus infections were ruled out by serology. Based on these observations, we considered as more probable the diagnostic hypothesis of chronic GVHD with GI, cutaneous and liver involvement. We also considered systemic-cutaneous auto-immune diseases (pemphigus, pemphigoid), infectious esophagitis, central cause dysphagia or a paraneoplastic syndrome/LMA recurrence.

Upper GI endoscopy was performed and at 17 cm from the dental arch, we identified a regular ring, with 5 mm in diameter, causing unsurpassable obstructive stenosis (Figure 2). After barium instillation, we concluded that the stenosis was 1 cm length and proceeded to progressive dilation with Hercules[®] 3 stage wire guided balloon (Cook Medical) to 13.5 mm. After dilation, we were easily able to overcome the stenosis and observed friability and severe extensive detachment of the esophageal mucosa (Figure 3). In bulbar apex and second portion of duodenum, the mucosa was irregular with hyperemia and pearly areas (Figure 4). Esophageal, gastric and duodenal biopsies were obtained.

Esophageal biopsies showed increased intrae-

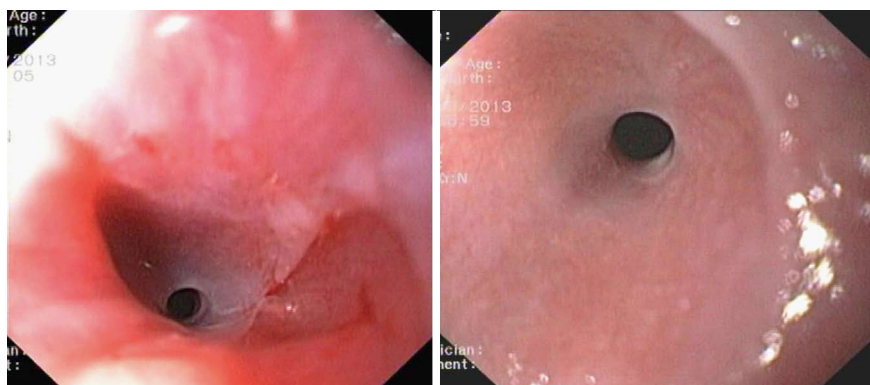


Figure 2 Regular stenosis with 5 mm in diameter at the upper third of the esophagus (17 cm from the dental arch).

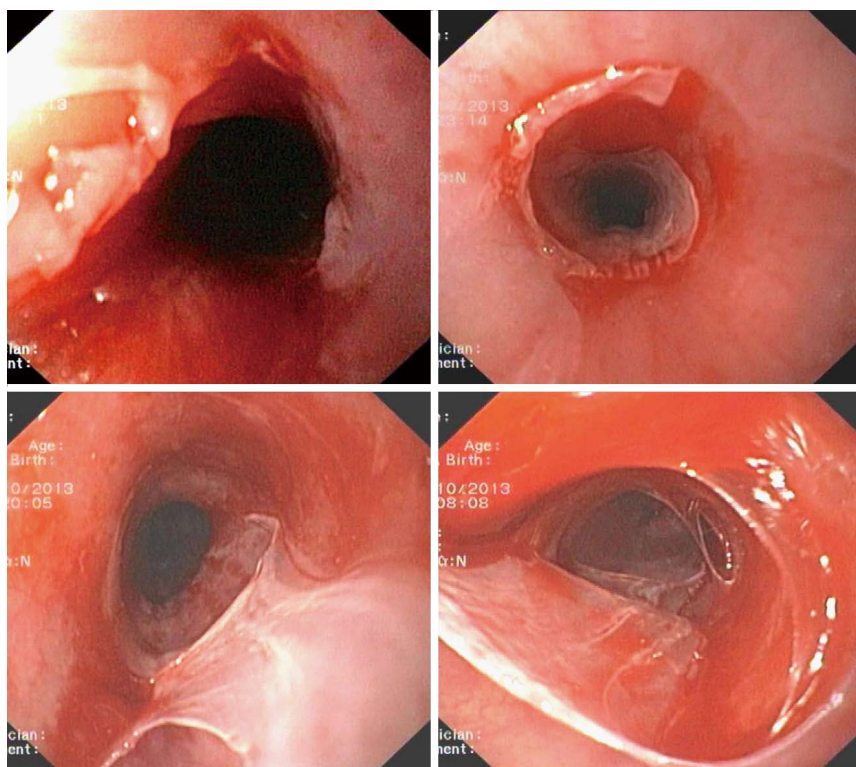


Figure 3 Friability and extensive detachment of the esophageal mucosa (esophageal mucosa sloughing) after balloon dilation.

pithelial lymphocytes, dyskeratotic squamous cells and apoptosis of individual squamous cells, with acanthosis and spongiosis. Congestion of the subepithelial vessels and increased submucosal fibrosis were also observed (Figure 5). These findings suggested the diagnosis of GVHD. Duodenal and gastric biopsies supported the diagnosis. Special stains for fungi and CMV were negative. Skin biopsies also confirmed the diagnosis of chronic GVHD.

The patient was treated with intravenous prednisolone 1 mg/kg per day, cyclosporine 1.5 mg/kg, 12 h/12 h and antifungal prophylaxis with posaconazole 300 mg/d. After 20 d of follow-up, she reported marked improvement of the dysphagia, with tolerance for solids and weight gain of 8 kg. Cutaneous lesions and laboratory studies also improved significantly.

Prednisolone was maintained for 3 mo and then tapered for a total duration of 9 mo. Immunosuppressive therapy was maintained for 2 years.

DISCUSSION

Acute and chronic GVHD are multisystem disorders that are common complications of allogenic HSCT^[1]. They occur when immune cells transplanted from a non-identical donor recognize the transplant recipient as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient^[9].

GVHD, the leading cause of morbidity and mortality after HSCT^[2], has been classically divided into acute and chronic variants based upon the time of onset using a cutoff of 100 d^[1]. However, this conventional

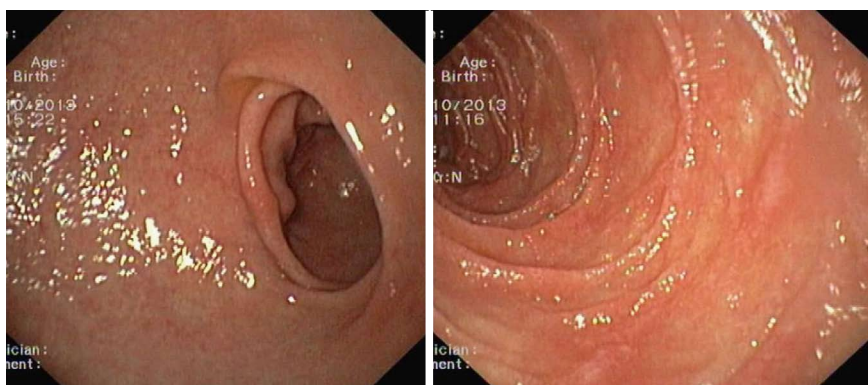


Figure 4 Irregularity of the bulboduodenal mucosa, with hyperemia and pearly areas.

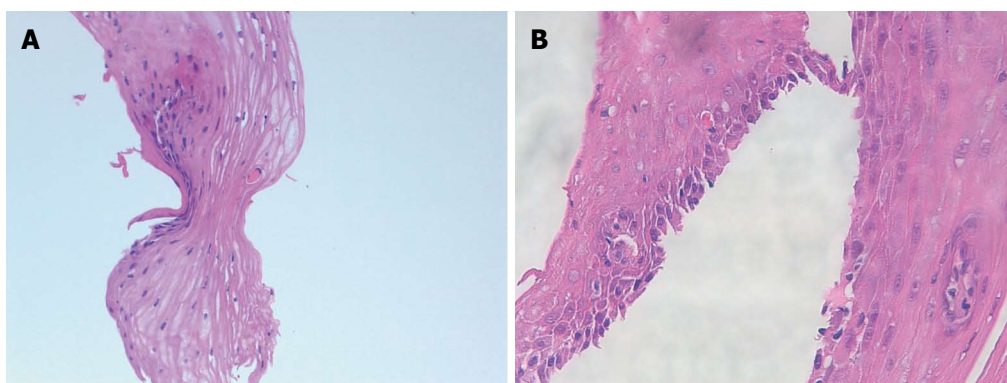


Figure 5 Microscopy. Esophageal mucosa with dyskeratotic squamous cells, apoptosis of individual squamous cells, acanthosis and spongiosis. Hematoxylin-eosin staining, magnification $\times 100$ (A), $\times 200$ (B), respectively.

division has been challenged by the recognition that signs of acute and chronic GVHD may occur outside these designated periods. This has led to the increased use of clinical findings, rather than a set time period, to differentiate between acute and chronic GVHD. The National Institute of Health consensus criteria for the diagnosis of GVHD include an overlap syndrome in which diagnostic or distinctive features of acute and chronic GVHD appear together^[1].

Clinical manifestations of acute GVHD include a classic maculopapular rash (70%), nausea, vomiting (and) abdominal cramps with high-volume diarrhea (74%) and liver involvement (44%) with a rising serum bilirubin^[10]. Patients with chronic GVHD commonly demonstrate skin involvement (67%) resembling lichen planus or cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations (60%); dysphagia, weight loss, chronic diarrhea and malabsorption (30%); liver involvement (52%) suggested by elevations in serum alkaline phosphatase and bilirubin concentrations; and pulmonary involvement (50%) resulting in bronchiolitis obliterans^[1,11]. Chronic GVHD can also result in exocrine pancreatic insufficiency^[1,11].

The GI tract is involved in the majority of patients with chronic GVHD^[1,11]. Oral lesions are seen in 60% of patients and other areas of GI tract involvement

are present in 30%^[11]. The diagnosis is often difficult because of the nonspecific GI symptoms. In fact, they may also be attributable to chemoradiation toxicity, medication side effects or a variety of bacterial, fungal and viral infections^[2].

Risk factors for the development of chronic GVHD include higher degree of HLA mismatching, older age of donor/receptor, donor and receptor gender disparity, source of stem cells (peripheral blood rather than bone marrow), cytomegalovirus seropositivity and prior acute GVHD^[1,11]. In fact, our patient developed acute GVHD, 3 mo after BMT.

Endoscopy with biopsies remains the gold standard for the diagnosis of GI-GVHD^[2]. The endoscopic appearance can range from normal to edema, erythema, erosion, ulceration and active bleeding. Histological criteria are the presence of epithelial single-cell apoptosis and crypt cell dropout^[12]. There is a discrepancy between endoscopic and histologic assessment of the severity of GI-GVHD^[2].

Esophageal involvement in GVHD occurs in less than 15% of BMT patients^[13]. This can be manifested as vesiculobullous disease, esophageal cast, desquamative or sloughing esophagitis (*esophageal dissecans superficialis*), or severe ulceration which leads to web and stricture formation^[1,2,5-9,13]. In patients with chronic

GVHD, the production of autoantibodies may alter intercellular adhesions and cell matrix adhesion leading to desquamative esophagitis and stenosis^[7-12].

We report a case of severe chronic GVHD two years after BMT. In fact, the patient presented involvement of the skin (erythematous papules, desquamation and induration areas in the lower limbs), liver (altered liver function tests) and esophagus (esophageal stricture and mucosal sloughing). Only a few cases of esophageal manifestations of GVHD were reported in literature^[5-9]. Moreover, a wide area of sloughing mucosa along with severe stenosis requiring endoscopic dilation, as observed in the present case, has never been reported. Therefore, we point out that this is a rare complication of chronic GVHD, which is associated to the patient's background disease and its treatment - bone marrow transplantation for acute myeloid leukemia two years ago.

In conclusion, esophageal stenosis and sloughing esophagitis are rare but typical manifestations of chronic-GVHD. This diagnosis should be considered when assessing patients with history of BMT.

COMMENTS

Case characteristics

A 56-year-old woman with a history of allogenic bone marrow transplantation for two years, presented with dysphagia, xerostomia, anorexia, and weight loss.

Clinical diagnosis

Physical exam revealed aphthous stomatitis and skin lesions of the lower limbs, with pruriginous and erythematous papules, desquamation and induration areas.

Differential diagnosis

The authors considered the diagnosis of chronic graft-vs-host disease (GVHD) with gastrointestinal (GI) and cutaneous involvement; systemic-cutaneous autoimmune diseases (pemphigus, pemphigoid); infectious esophagitis; central cause dysphagia; paraneoplastic syndrome or LMA recurrence.

Laboratory diagnosis

Laboratory studies revealed hemoglobin 11.5 g/dL, leucocytes 11000, albumin 2.7 g/dL, AST 82 IU/L, ALT 87 IU/L, alkaline phosphatase 514 IU/L, GGT 282 IU/L, total bilirubin 1.3 mg/dL.

Imaging diagnosis

Upper GI endoscopy identified a regular ring in cervical esophagus, causing unsurpassable obstructive stenosis, as well as friability and severe extensive detachment of the esophageal mucosa.

Pathological diagnosis

Esophageal biopsies showed increased intraepithelial lymphocytes, dyskeratotic squamous cells and apoptosis of individual squamous cells, with acanthosis and spongiosis, congestion of the subepithelial vessels and increased submucosal fibrosis.

Treatment

Endoscopic dilation of the esophageal stenosis; prednisolone 1 mg/kg per day, cyclosporine 1.5 mg/kg, 12 h/12 h and posaconazole 300 mg/d.

Related reports

Very few cases of esophageal manifestations of GVHD are reported in literature. Sloughing esophagitis along with severe stenosis requiring endoscopic dilation has never been reported in this context.

Experiences and lessons

This case report presents the clinical and endoscopic characteristics of an extremely rare and curious manifestation of esophageal GVHD, which required endoscopic intervention. Therefore, endoscopy may play a significant role in the early diagnosis and treatment of GVHD.

Peer-review

The case report written by Trabulo *et al* describes a case of graft-vs-host disease complicating a rare esophageal lesion. The case report is a unique and interesting one, and well-described. This severe form of complication is related to the treatment (bone marrow transplantation) of acute leukemia and subsequent development of graft vs host disease.

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