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Case Report

Esophageal intramucosal hematoma after peripheral blood stem cell transplantation: case report and review of literature

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Abstract: Esophageal complications occur after hematopoietic stem cell transplantation (HSCT). There are, however, only limited reports on the etiology or management of esophageal complications. Here, we report the occurrence of intramucosal hematoma presenting continuous esophageal hemorrhage in a 34 year-old man following the second peripheral blood stem cell transplantation for acute myeloid leukemia. His hematemesis started 2 months after HSCT and was repeated in supportive care. On day 156, he underwent total esophagectomy as a result of uncontrollable massive hematemesis. Histopathological testings of the resected esophagus confirmed intramucosal hematoma as a cause of hematemesis. This case highlights intramucosal hematoma as one of the important etiologies of esophageal complications following HSCT.

Keywords: Esophageal hemorrhage, intramucosal hematoma, esophagectomy, hematopoietic stem cell transplantation

Introduction

Hematopoietic stem cell transplantation (HSCT) can cause esophageal complications. In the early phase after HSCT, esophagitis due to chemotherapy or total body irradiation (TBI) is common, while chronic graft-versus-host disease (GVHD) or secondary esophageal tumors are occasionally observed in the late phase [1-3]. Although esophageal symptoms are relatively common after HSCT, reports on esophageal complications are limited. We describe a case of esophageal intramucosal hematoma presenting continuous esophageal hemorrhage following the second HSCT and review the previous literature.

Case report

A 34 year-old man received peripheral blood stem cell transplantation (PBSCT) for acute myeloid leukemia (AML) from his HLA B-antigen mismatched mother. He had been in complete remission for three years before the disease recurrence. He received 3 courses of chemotherapies followed by the second PBSCT from the same donor for the refractory disease. Preparative regimen consisted of fludarabine (150 mg/m^2), melphalan (140 mg/m^2) and TBI (4 Gy). Cyclosporin and short-term methotrexate were used for GVHD prophylaxis. Primary neutrophil engraftment was achieved on day 24 and complete donor chimerism was confirmed on day 28. However, he had delayed platelet recovery and required frequent blood transfusions.

His oral mucosal damage due to the conditioning regimen and methotrexate was severe and prolonged after PBSCT. He had hematemesis on day 63, and an emergency endoscopic examination on that day showed diffuse erosions and multiple polyps in the esophagus without apparent findings of infections. A biopsy

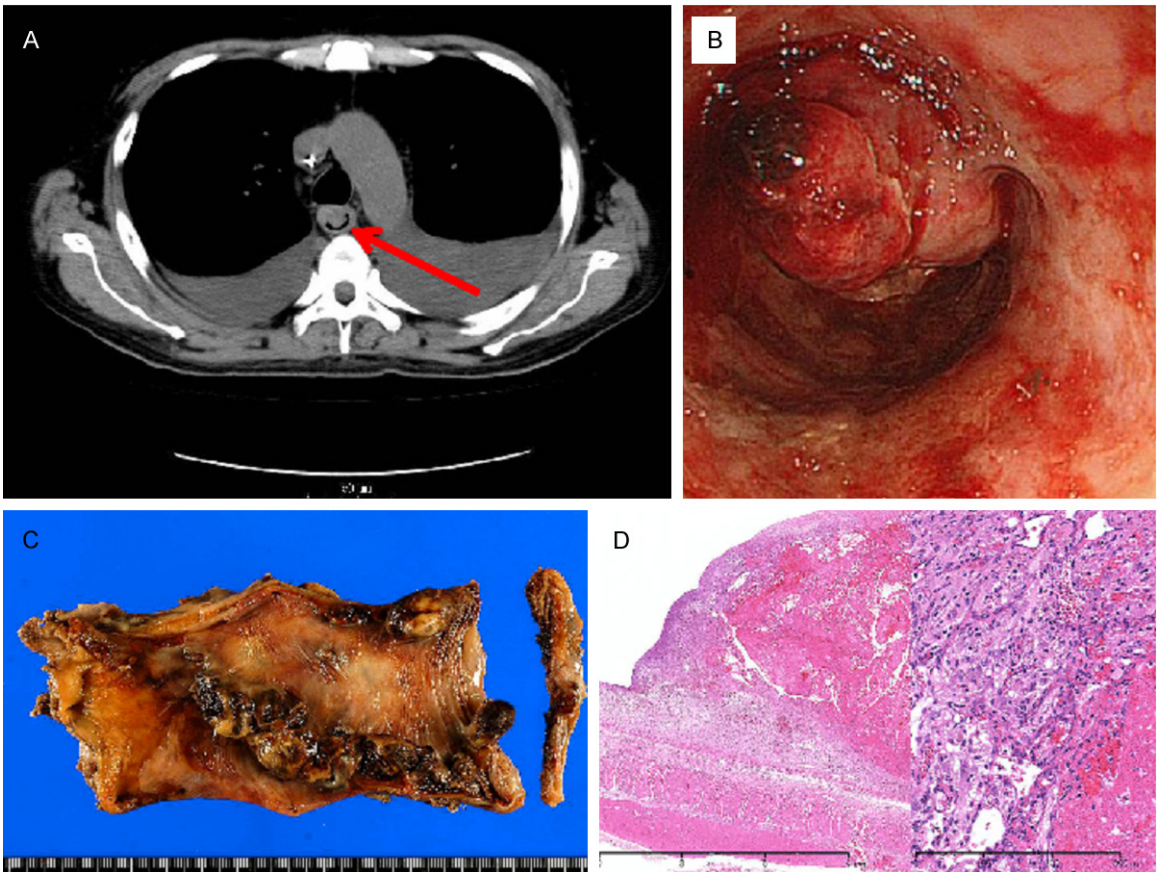

Figure 1. A: CT of the esophagus on day 118. The arrow indicates the thickened wall of esophagus. B: Endoscopic view of the middle intrathoracic esophagus with a protruded lesion on day 153. C: A macroscopic view of the resected esophagus on day 156. The right is the oral side. D: The microscopic view of the esophageal specimen. The protrusion mainly consisted of intramucosal hematoma (left) with the proliferation of capillary blood vessels and reactive myofibroblasts with prominent nucleoli (right).

was not performed because of a risk of massive hemorrhage and we continued supportive care. On day 85, 2 mg/kg of methylprednisolone was initiated since an increase of total bilirubin levels (2.9 mg/dL) as well as pericardial and pleural effusion, indicated the presence of acute GVHD. He repeated massive hematemesis on day 108 and 115, and computed tomography (CT) on day 118 revealed the intramucosal mass and thickened wall of esophagus resulting in narrowed esophageal lumen (**Figure 1A**). The endoscopic finding on day 153 showed gradual progression of hematoma (**Figure 1B**) and a small biopsy sample indicated only erosions.

On day 156, he had massive hematemesis again and fell into a hypovolemic hemorrhagic shock after a total volume of hematemesis reached 4.5 L. At that time, he had normal coagulation tests, but still required platelet transfusions. As a life-saving measure, we performed the total esophagectomy on the same day. Macroscopic findings of the resected esophagus were characterized by three large pedunculated reddish-brown protrusions (size: 1.5 cm to 7.0 cm), multiple small protrusions, and erosions of esophageal mucosa (**Figure 1C**). The protrusions mainly consisted of a hematoma with the proliferation of capillary blood vessels and reactive fibroblasts with atypia involving hemorrhage (**Figure 1D**). Both GVHD and malignancy such as leukemia, squamous cell carcinoma, Kaposi's sarcoma or angiosarcoma were denied. Bacterial, fungal and viral (cytomegalovirus (CMV), Epstein-Barr virus, herpes simplex virus, and human herpes virus (HHV)-8) pathogens were not detected. A thorough pathological study of the resected esophagus was as follows:

Table 1. Complications in esophagus after hematopoietic stem cell transplantation from the literature

Disease		Time period	Symptoms		Treatment	References
			Bleeding	Mass formation		
Regimen related toxicity		Early	± ~ +	-	Supportive care	[1]
Infections	Fungus (Candida)	Early ~ anytime	± ~ +	-	Anti-fungal agent	[4]
	Virus (CMV, VZV)		± ~ +	-	Anti-viral agent	[5, 6]
GVHD	Acute	Early	± ~ +	-	Corticosteroid	[7]
	Chronic	Late	± ~ +	±	Immunosuppressive drugs	[2]
Solid tumor		Very late	±	+ ~ +++	Excision	[3, 8-12]
Varix due to VOD		Early	± ~ +++	+ ~ ++	Supportive care	[13]
Intramural hematoma		Early ~ anytime	+ ~ +++	± ~ ++	Supportive care, esophagectomy	

Superscripts correspond to the indexed numbers of the articles in the References. CMV: cytomegalovirus. VZV: varicella-zoster virus. VOD: veno-occlusive disease. GVHD: graft-versus-host disease.

Proliferated blood vessels: CD31(+), CD34(+), the fraction of MIB-1 positive endothelia varies from less than 10% to 30%, CMV(-), EBER-ISH(-), HSV-1(-), HSV-2(-), HHV-8(-).

Fusiform cells in pars tuberalis: AE1/AE3(-), CD34(-), Vimentin(+), S100(+) (focal), S68(+) (focal), CMV(-), EBER-ISH(-), HSV-1(-), HSV-2(-), HHV-8(-).

Cells with large nuclei in pars tuberalis: AE1/AE3(-), CD34(-), Vimentin(+), HMB45(-), MART-1(-), Melan-A(-), 1A-4(+) (focal), MPO(-), CMV(-), EBER-ISH(-), HSV-1(-), HSV-2(-), HHV-8(-).

The patient was thus rescued by the total esophagectomy, but on day 236, he died of pneumonia and sepsis by *Pseudomonas aeruginosa* spread from the surgical site. Throughout the entire course after the second PBSCT, he was in complete hematological remission.

Discussion

Although esophageal complications are occasionally observed in HSCT recipients, most patients recover from the complications by supportive care alone. To our knowledge, esophageal intramucosal hematoma characterized by multiple protrusions with continuous hemorrhage has not been reported and discussed as one of the complications following HSCT.

The previously reported esophageal complications after HSCT are summarized in **Table 1**. The complications are categorized into five groups based on their etiologies: regimen related toxicity (RRT), infection, GVHD, malignancy, and veno-occlusive disease (VOD). RRT after HSCT includes esophagitis caused by radiation or several drugs such as melphalan and methotrexate, and reflux esophagitis by continued vomiting [1]. Fungal or viral infection in the esophagus is an important etiology. Candida infection can cause esophageal perforation [4], and CMV or varicella zoster virus induces esophagitis and hemorrhagic ulcer [5, 6]. GVHD is also important as esophageal complications following HSCT. The diagnosis of esophageal chronic GVHD has been established [2], while the diagnosis of esophageal acute GVHD is still uncertain. Some cases with esophageal acute GVHD have been reported and the diagnoses were performed on the basis of the diffuse involvement of GVHD in the gastrointestinal tract [7]. Squamous cell carcinoma is the most common secondary malignancy following HSCT [3, 8-10] and other tumors such as Kaposi's sarcoma by HHV-8 have also been reported [11, 12]. Esophageal varix is well-known as a complication of liver cirrhosis, but in several cases after HSCT, esophageal varix has been reported as a complication of VOD [13, 14].

In our case, the pathological study of the esophagus proved that the cause of the hemorrhage was intramucosal hematoma, which is one type of intramural hematoma. This is similar to the case of the intraepithelial hemorrhage of esophagus in the hematological disorder reported by Shimizu *et al* [15]. Intramural hematoma is considered to be caused by trauma or abnormal hemostasis [16]. The symptoms of intramural hematoma are chest pain, hematemesis, and odynophagia. The risk factors for development or progression of intramural hematoma are repeated vomiting and prolonged thrombocytopenia [16, 17]. Although intramural hematoma can be diagnosed with

CT or endoscopy, the diagnosis would be more complicated in HSCT recipients who have diffuse epithelial erosions in the esophagus. Treatment of intramural hematoma is generally supportive care such as total parenteral nutrition and H_2 blocker, and rarely surgical removal or therapeutic angiography [18].

The experience of our case will serve as a caveat against the oversight of intramural hematoma following HSCT. Endoscopy and biopsy are recommended in HSCT recipients who have continuous complaints about the esophagus. Although the treatment for intramural hematoma in most cases is similar to that for esophagitis due to radiation or medication, the control of nausea or maintenance of sufficient platelet counts may have an effect on protection of progression or early cure. Moreover, in some severe cases, aggressive interventional approach such as therapeutic angiography or esophagectomy may be required.

Disclosure of conflict of interest

The authors have no potential conflicts of interest.

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