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Graft-versus-host diseases characterized by effusion: A case of steroid-refractory graft-versus-host disease

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ABSTRACT

Background: Although the biology of steroid-refractory acute GVHD is still unknown, the pathogenesis of steroid-refractory acute GVHD is recognized to be associated with aberrant cytokine milieu.

Case presentation: We treated a 41-year-old Japanese male representing a characteristic clinical manifestation among unspecific cases of heterogeneous steroid-refractory acute GVHD. The patient underwent allogeneic bone marrow transplantation due to relapsed neurolymphomatosis. He achieved neutrophil engraftment on day 21 with mild engraftment fever. Acute GVHD occurred on day 56 after transplantation with systemic skin eruptions and precedent body weight gain. Corneal ulceration and gut GVHD symptoms followed the skin lesions sequentially. A biopsy of skin and gut mucosa revealed pathological GVHD. We recognized that the patient presented anasarca symptoms due to acute GVHD. We treated the patient with 1.0 mg/kg corticosteroids (prednisolone) starting on day 68, but his edema worsened. He did not respond to 2.0 mg/kg prednisolone from day 80. He required artificial ventilation on day 80 due to the bilateral massive pleural effusion and died of respiratory failure on day 99 after transplantation. A measurement of serum cytokines before corticosteroid therapy, IL-6 (61.5 pg/mL; normal range: <4.0), VEGF (51 pg/mL; <38.3), IFNγ (0.2 IU/mL; <0.1), and TNF-α (10.5 pg/mL; 0.6–2.8) were elevated. Th2 cytokines, IL-4 (7.2 pg/mL; <6.0) and IL-10 (6.0 pg/mL; <5.0) were also elevated.

Conclusions: Our case was prominently characterized by anasarca manifested as follows: systemic edema, massive ascites and pleural effusion. We speculated that acute/chronic GVHD with anasarca has an immunological propensity for proinflammatory and the Th2 cytokine milieu. We advocate that immunological modification by biologic agents such as tocilizumab would be promising theoretically for the treatment of such type of GVHD.

1. Introduction

Munneke et al. [1] systematically reviewed the survival benefit of using mesenchymal stromal cells (MSCs) in steroid-refractory acute graft-versus-host disease (GVHD). Salvage therapy with MSCs is currently the most promising cell therapy for steroid-refractory acute GVHD. Steroid-refractory acute GVHD is a major concern and of interest in stem cell transplantation (SCT). The biology of steroid-refractory acute GVHD is still unknown. The pathogenesis of steroid-refractory GVHD is recognized to be associated with cytokine dysregulation [2,3]. We treated a stem cell transplant recipient with anasarca after the development of steroid-refractory acute GVHD.

2. Case presentation

A 41-year-old Japanese male was diagnosed with primary diffuse large B-cell lymphoma of the peripheral nerves, representing neurolymphomatosis. He received first-line rituximab plus CHOP (R-CHOP) chemotherapy and achieved complete remission. His initial presentation at the onset was looking like neurolymphomatosis. International prognosis index (IPI) and revise IPI were low and good risks, respectively. However, his disease relapsed 12 months after completion of R-CHOP. He underwent SCT from an HLA DRB1 (HLA class II molecule) locus-mismatched, unrelated bone marrow donor with standard cyclophosphamide total body irradiation (CY 120 mg/kg and TBI 12 Gy). He achieved neutrophil engraftment on day 21 without any severe adverse events. Engraftment syndrome occurred before engraftment, but no organ toxicity was observed. His engraftment syndrome became in

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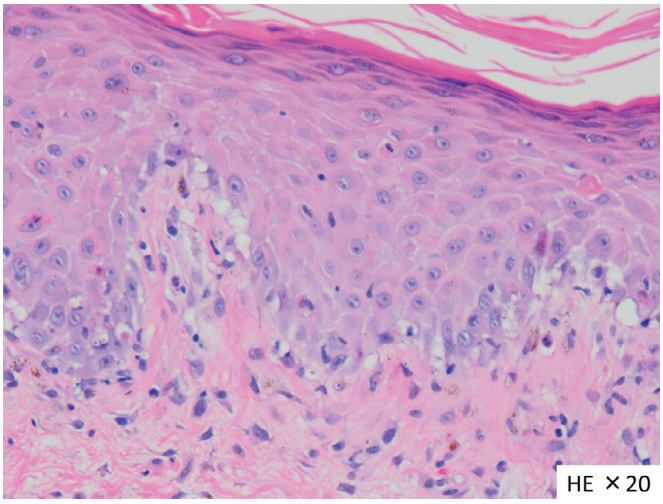

Fig. 1. Pathological findings of the skin Patient's biopsy revealed GVHD. Apoptosis and vacuolization were seen in the basal layer of epidermis cells with the lymphocyte infiltration.

remission without aggressive or intensive therapy. The onset of GVHD occurred on day 56 after transplantation with systemic skin eruptions (stage 3, grade 2). Corneal ulceration and gut GVHD symptoms (diarrhea) followed the skin lesions sequentially. A skin biopsy revealed GVHD (Fig. 1). We performed gastrointestinal screening by endoscopy. Both stomach and colon mucosa pathologically revealed GVHD (Fig. 2). Atypical findings were few cytomegalovirus (CMV)-positive cells seen in the gastric mucosa and remarkable interstitial edema in the terminal ileum. Altogether, clinical evaluation led to the diagnosis of GVHD as the main pathogenesis in the patient. From day 50, his body weight gradually increased from 77.8 kg to 118.8 kg within 30 days. Leg edema initially manifested and subsequent ascites, pleural effusion, and pericardial effusion increased (Fig. 3). Those anasarca symptoms did not respond to any supportive treatments, including diuretics and albumin supplements. Pleurocentesis was performed on the right side of the chest. Pleural effusion was transudative (by Lights criteria) and sterile. Cytological diagnosis was class 2 pleural effusion with infiltration of macrophages. Infection markers, including β-D glucan, aspergillus antigen, CMV antigenemia, and procalcitonin, were all negative. Antinuclear antibodies were not detected. We recognized that the patient had cytokine syndrome presenting as anasarca due to GVHD. He received 1.0 mg/kg corticosteroids (prednisolone) starting on day 68. Concomitantly, he was treated with ganciclovir (10 mg/kg/day) and CMV antigenemia remained negative throughout his treatment course. Even after standard corticosteroid therapy, his edema worsened and his body weight continued to increase. The gut symptoms did not improve even after 14 days of corticosteroid treatment. We increased the dose of corticosteroids from 1.0 mg/kg to 2.0 mg/kg on day 80 and added treatment with albumin, continuous furosemide, dopamine, and hANP. However, the patient's effusions did not improve. He required artificial ventilation on day 80 due to the bilateral massive pleural effusion and died of respiratory failure on day 99 after transplantation. Serum cytokines were measured in the sample taken before corticosteroid therapy. Serum IL-6 level had elevated to 61.5 pg/mL (normal range: $<$4.0 pg/mL) before steroid treatment, VEGF level was 51 pg/mL (normal range: $<$38.3 pg/mL), and IFNγ level was slightly elevated at 0.2 IU/mL (normal range: $<$0.1 IU/mL). TNF-α level was moderately elevated at 10.5 pg/mL (normal range: 0.6–2.8 pg/mL). IL-4 and IL-10 levels were 7.2 pg/mL (normal range: $<$6.0 pg/mL) and 6.0 pg/mL (normal range: $<$5.0 pg/mL), respectively.

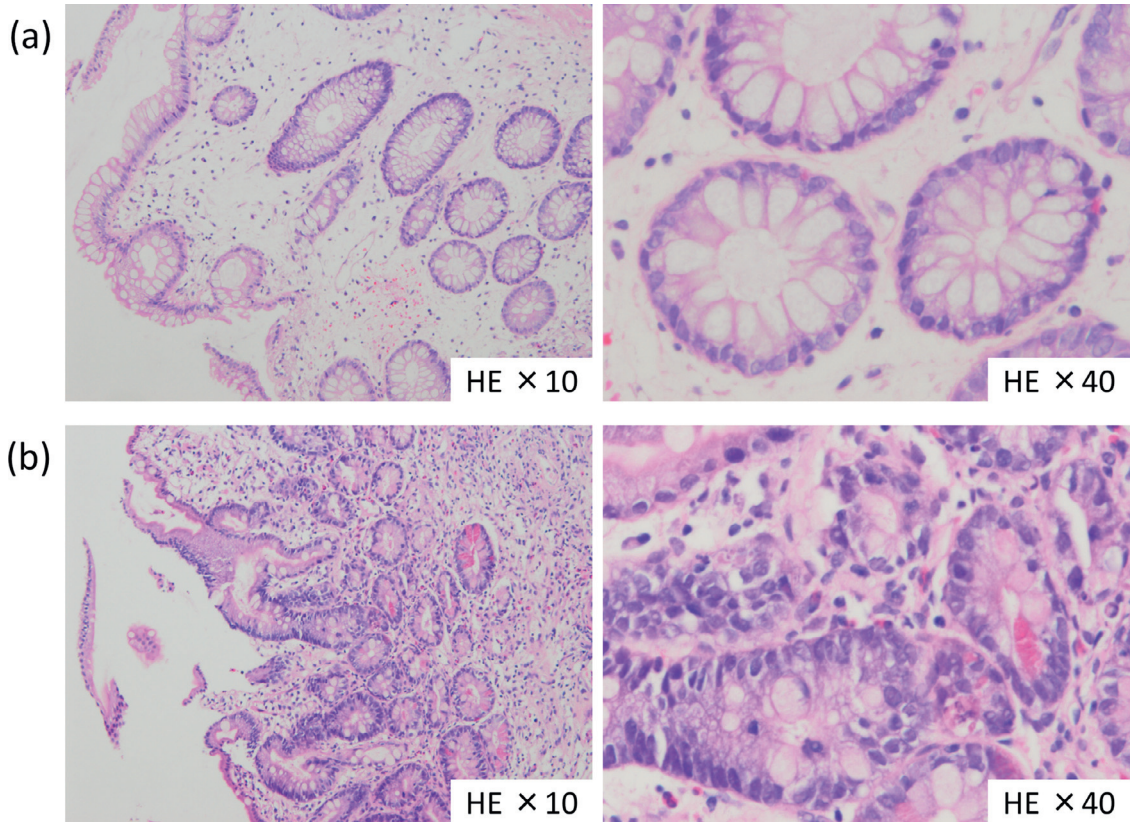

Fig. 2. Pathological findings of the gastric and colon mucosa We performed gastrointestinal and colon endoscopy. (a) Gastric mucosa indicated apoptotic epithelial cells with submucosal edema and lymphocytes infiltration. (b) The colon mucosa showed crypt mucosal apoptosis with submucosal lymphocytes infiltration.