CASE REPORT

Ascites as a Manifestation of GVHD: a Rare Phenomenon

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Abstract Graft versus host disease (GVHD) usually have involvement of classical target organs. Manifestations of Chronic GVHD (cGVHD) are much more protean than acute GVHD. NIH consensus criterion for cGVHD proposes different diagnostic and distinctive features of cGVHD. It acknowledges certain uncommon manifestations that can be attributed to cGVHD only when they are associated with more specific features. Patients rarely may develop such manifestations which are not diagnostic of cGVHD themselves. In the absence of more specific features of cGVHD, they may pose diagnostic challenge. Amongst the rare reported manifestations of cGVHD is serositis manifesting as pleural effusion, pericardial effusion or ascites. We report two patients developing ascites as an isolated manifestation of cGVHD.

Keywords Ascites · Serositis · Graft versus Host Disease · Allogeneic Transplantation

Majority of patients with graft versus host disease (GVHD) will have involvement of classical target organs. Manifestations of Chronic GVHD (cGVHD) are much more protean than acute GVHD. NIH consensus criterion for

cGVHD proposes different diagnostic and distinctive features of cGVHD [1]. It acknowledges certain uncommon manifestations that can be attributed to cGVHD only when they are associated with more specific features. Patients rarely may develop such manifestations which are not diagnostic of cGVHD themselves. In the absence of more specific features of cGVHD, they may pose diagnostic challenge. Amongst the rare reported manifestations of cGVHD is serositis manifesting as pleural effusion, pericardial effusion or ascites. We report two patients developing ascites as an isolated manifestation of cGVHD.

Case 1: A 42 year male underwent allogeneic stem cell transplant from 6/6 HLA matched sister for myelofibrosis. His renal function was compromised (GFR of 32 ml/min) and he received Fludarabine-cyclophosphamide-2 Gy TBI as conditioning regimen and cyclosporine (CsA) with mycophenolate mofetil as GVHD prophylaxis. On day +18 he developed grade 2 skin GVHD, which responded to topical steroid application. He was discharged from the unit on day +26 on voriconazole prophylaxis. Owing to worsening of renal function, his CsA tapering was started early from day +60 and it was stopped completely by day +90. On day +65 he presented with fever, decreased appetite and abdominal discomfort. He received empirical antibiotics for fever but there was no response. Gradually his abdominal distension increased and ultrasound of abdomen revealed gross ascites. CT scan of abdomen did not show any abnormality besides the presence of gross ascites. Serum creatinine, bilirubin and liver enzymes were normal. Ascitic tap revealed straw colored fluid with protein of 3.2 g/dl, albumin of 2.2/dl and LDH 270 U/l. Corresponding values in blood were 5.4 g/dl, 3.1 g/dl and 432 U/l respectively, suggestive of exudative fluid (serum ascites albumin gradient, SAAG of 0.9). Cytology analysis showed 170 cells per mm³ with 88 % lymphocytes and no

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abnormal cells. Bacterial, fungal and mycobacterial stains and cultures were negative and adenosine deaminase was normal. Portal venous doppler ruled out portal hypertension or portal venous thrombosis. He also received empirical intravenous antifungal (Caspofungin) without any benefit. A repeat ascitic fluid tap revealed similar finding without any evidence of infection. He was given a trial of 4 drugs anti tuberculous treatment for one month without any improvement. In view of lack of response to these measures and absence of documented infection on repeated testing, he was given a trial of oral prednisolone at 1 mg/Kg. Patient improved symptomatically and repeat imaging USG revealed complete resolution of ascites by second week. His steroids were gradually tapered and stopped by day +189. However ascites reappeared on day +240 requiring retreatment with steroids. Later he also developed GVHD of lung on day +318, musculoskeletal system on D + 465 and keratoconjunctivitis sicca on day +634. However during these episodes of cGVHD he did not develop ascites. Currently he is two and half year post transplant without any evidence of disease or cGVHD.

Case 2: A 38 year man with CML-chronic phase underwent allogeneic stem cell transplant with 6/6 HLA matched brother as the donor. He received busulfan (16 mg/kg)-cyclophosphamide (60 mg/kg day-3 and day-2) as conditioning and CsA-methotrexate as GVHD prophylaxis. His neutrophil and platelet engraftment occurred on day +9 and day +10 respectively. He developed grade 3 skin GVHD on day +24 and was treated with topical steroid application and oral prednisolone 1 mg/kg which were stopped by day +95. While his cyclosporine was being tapered, he developed GVHD of the oral cavity, upper gut and eyes. His further CsA tapering was withheld and he was started on systemic steroids with voriconazole as anti-fungal prophylaxis from day +144. His steroids were tapered and stopped by day +217. Two weeks later, he presented with abdominal distension and vomiting. Ultrasound showed presence of gross ascites. CT scan of abdomen revealed gross ascites with thickening of jejunal mucosa. Diagnostic ascitic tap revealed chylous fluid with triglyceride of 200 mg/dl, 40 cells per mm³ with 60 % lymphocytes and 40 % neutrophils and no abnormal cells were seen. Protein and albumin in ascitic fluid were 0.8 g/dl and 0.4 g/dl while serum protein and albumin measured 5.6 and 3.6 gm g/dl respectively. SAAG was 3.2 suggestive of transudative ascites. The fluid was sterile. An upper esophago-duodenoscopy was done which revealed normal gastric duodenal and jejunal mucosa. Biopsy from proximal jejunal mucosa revealed mild increase in the chronic inflammatory cell infiltrate in lamina propria with focal loss of glands resulting in focal atrophy and fibrosis. Lymphangiectasia was also noted. There was no evidence of any infection including CMV or mycobacteria (Fig. 1; 2).

Fig. 1 Biopsy shows a fragment of small intestinal mucosa with marked dilatation of lymphatic channels within the lamina propria. One of the glands also shows partial destruction in the form of single cell apoptosis; one of the features of GVHD. (Haematoxylin and eosin staining, 40× magnification)

Fig. 2 Fragment of small intestinal mucosa showing partial atrophy of villi, probably attributable to chronic GVHD. Dilated lymphatics are seen within the lamina propria. (Haematoxylin and eosin staining, 40× magnification)

Serum creatinine and liver function tests were normal. Since there was no obvious cause for these manifestations, he was given steroids (prednisolone 1 mg/kg) with prompt relief. There was no evidence of concurrent GVHD of any other organ. Unfortunately he succumbed to severe lung GVHD later.

In both the cases, ascites without any evidence of infection or disease in ascitic fluid, propensity for development of cGVHD of other organs at different time points, response to steroids and recurrence of ascites after steroid taper in first case supports GVHD as cause for ascites. While it is not clear what was the exact mechanism responsible for ascites in the first case, in the second patient

it was possibly due to lymphatic ooze from the intestine as biopsy had shown presence of lymphangiectasia on intestinal biopsy and ascitic fluid was chylous.

Serositis manifesting as sterile effusion has been reported as a manifestation of GVHD [2–4]. Ivanov et al. reported a case of ascites of donor lymphocyte origin in a patient with CLL post reduced intensity conditioning allogeneic stem cell transplant [5]. A series of seven patients with peritoneal, pleural and/or pericardial effusion as manifestation of GVHD has been reported by Seber et al. [6]. In that series except for one, all patients had developed extensive cGVHD while five had acute GVHD as well. None of the reported cases mentions ascites as an isolated manifestation of GVHD. Unless massive, ascites can be missed on examination and it is usually not specifically looked for. Hence it may be more common than reported in literature. At times it may not be of much clinical significance but can be a diagnostic dilemma. Also it probably signifies significant alloreactivity with chance of development of severe multiorgan GVHD as seen in both of our patients and in cases reported earlier.

In summary, we report an unusual manifestation of cGVHD in form of ascites necessitating the use of immunosuppressive therapy.

Conflict of Interest The authors declare no conflict of interest.

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