Nonmyelomatous Ascites Resulting from the Increased Secretion of Vascular Endothelial Growth Factor in Multiple Myeloma

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Abstract:
Ascites is a rare complication of multiple myeloma (MM); in most cases, the direct invasion of myeloma cells to the peritoneal cavity has been assumed to be the etiology because the effusion is usually exudative and contains a high proportion of myeloma cells. We herein report a case of MM with massive ascites containing only a small amount of myeloma cells. Instead, high levels of serum and ascitic vascular endothelial growth factor were detected. This was suggested to be a potential mechanism underlying the development of ascites.

Key words: multiple myeloma (MM), vascular endothelial growth factor (VEGF), pleural effusion, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome

(Intern Med 57: 725-727, 2018)
(DOI: 10.2169/internalmedicine.8886-17)

Introduction
Ascites is a rare complication of multiple myeloma (MM), and in most cases, is assumed to be caused by direct invasion of myeloma cells into the peritoneal cavity, as suggested by exudative effusion and a high proportion of myeloma cells (1-3). This is in contrast to pleural effusion, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome, another type of plasma cell dyscrasia, in which ascites is more common and which may be caused by the aberrant secretion of vascular endothelial growth factor (VEGF). Although VEGF is also secreted by MM cells, its relationship with the symptoms of MM is poorly elucidated. In the present case, the serum and ascitic levels of VEGF were significantly elevated and decreased after chemotherapy for MM. The decrease in the levels occurred alongside a reduction in the amount of ascites, suggesting that the elevation VEGF may be associated with the formation of ascites.

A 43-year-old man presented to our hospital for anemia in 2009 and was diagnosed with MM [immunoglobulin (Ig) G kappa type, Durie Salmon stage I]. Although a bone marrow examination showed 6% plasma cells, we diagnosed the patient with symptomatic myeloma due to the presence of monoclonal gammopathy and associated symptoms (i.e., anemia). Pathological immunostaining showed kappa-deviated restriction. A surface marker analysis showed that the myeloma cells were positive for CD56 and IgG and negative for CD20, CD79a, IgA, IgM, and cycline-D1. A chromosomal examination revealed a normal karyotype. A few months after the diagnosis, the patient developed massive ascites. Abdominal paracentesis revealed clear, non-bloody fluids. A laboratory analysis of the ascites fluid revealed the following: white blood cell (WBC) count, 500/mL; total protein (TP), 6.5 g/dL; lactate dehydrogenase (LDH), 66 IU/L; and glucose, 95 mg/dL, which corresponded to transudates. Wright's staining of a centrifuged
ascites sample revealed that the cells were mainly composed of neutrophils and only 2% plasma cells. Bacterial cultures were all negative, and empiric antibiotic therapy did not reduce the volume of ascites. No organ dysfunction that could account for transudative ascites was detected (including hepatic, renal, or cardiac failure). The IgG level, blood counts, and bone marrow findings did not suggest the progression of MM. Thus, we focused on VEGF as a causative agent, as it is related to ascites in POEMS syndrome (4).

There were no characteristic symptoms (i.e., polyneuropathy, organomegaly, endocrinopathy, monoclonal gammapathy, skin changes) in our case, with the exception of monoclonal gammapathy. We therefore hypothesized that that patients with MM may develop pathophysiological conditions that are similar to those associated with VEGF.

Both the serum and ascites showed increased VEGF levels [553 pg/mL in serum (normal range <38.3 pg/mL); 988.0 pg/mL in ascites (normal range not set)]. We considered the elevated VEGF level and ascites to be signs of the progression of myeloma, and decided to start chemotherapy. After the administration of high-dose dexamethasone therapy (40 mg/body/day on days 1-4, 9-12, and 17-20), there was a marked decrease in the volume of ascites, the serum VEGF levels decreased to 223 pg/mL, and the patient’s MM showed a partial response (the IgG level decreased from 3,644 mg/dL to 1,593 mg/dL) (Figure). Bone marrow aspiration (BMA) showed almost normocellular bone marrow with a marked decrease in the proportion of plasma cells (proportion of myeloma cells reduced to <1%). After discharge, the patient’s IgG levels declined continuously during 4 courses of high-dose dexamethasone therapy; this was accompanied by a recovery of the patient’s Hb and albumin levels (Hb: from 8.0 g/dL to 14.0 g/dL; albumin: from 2.5 g/dL to 3.5 g/dL). At 6 months after discharge (with follow-up), the patient was transferred to another hospital for autologous peripheral blood stem cell transplantation (auto-PBSCT).

### Table. Previous Reports of VEGF Levels in MM and POEMS Syndrome Patients.

| Reference | Patients number | Serum VEGF levels (normal range <38.3, pg/mL mean±SD) |
|-----------|----------------|---------------------------------------------------|
| 10 (POEMS) | 21             | 403±245                                           |
| 11 (MM)   | 57             | 273.5±179.1                                       |
| 12 (MM)   | 14             | 239                                               |

VEGF: vascular endothelial growth factor, MM: multiple myeloma, POEMS: pleural effusion, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammapathy, skin changes, SD: standard deviation

### Discussion

VEGF induces vessel hyperpermeability and leads to the retention of pleural effusion. In certain solid tumors, reports suggest an association between malignant ascites and elevated VEGF levels (5). Elevated ascitic VEGF levels are useful to distinguish between malignant and nonmalignant ascites, as such ascites associated with liver cirrhosis (6). Although the secretion and production of VEGF have been documented in myeloma cells (7, 8) (Table), the elevation is
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