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Case Report
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Treatment of Relapsed Multiple Myeloma with Myelomatous Ascites Using Bispecific T-cell Engager (BiTE) Therapy

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Abstract

Myelomatous ascites is seen in less than 1% of multiple myeloma cases and associated with poor prognosis. This case report presents a 62-year-old male with relapsed MM who developed severe myelomatous ascites after autologous Hematopoietic Stem Cell Transplantation (HSCT). Upon initiation of Bispecific T-cell Engager (BiTE) therapy with talquetamab, the patient showed a rapid clinical improvement, including reduced ascites and a significant decrease in serum free lambda light chain levels within the first month. To our knowledge, this is the first report documenting the successful use of BiTE therapy for this rare complication.

Introduction

Multiple Myeloma (MM) is a malignant plasma cell disorder characterized by the clonal proliferation of plasma cells in the bone marrow, leading to a variety of clinical manifestations including bone lesions, renal dysfunction, anemia, and hypercalcemia [1]. Isolated myelomatous ascites preceding overt myeloma is rare and is seen in less than 1% of myeloma cases, but occasionally can present as the first sign of the disease [2-5]. The etiologies of myelomatous ascites can be direct peritoneal infiltration by MM, or secondary to liver involvement, heart failure, or kidney failure [6]. The prognosis is very poor and often can be fatal.

Bispecific T-cell Engager (BiTE) antibodies represent a novel class of immunotherapeutic agents designed to redirect cytotoxic T cells against tumor cells, by simultaneously binding to CD3 on T cells and a tumor-associated antigen. Several agents have been shown to induce deep and durable responses in heavily pre-treated relapsed/refractory MM, with ORR ranging from 61% to 73% [7-9].

Here we report a case of massive ascites as initial presenting symptom of relapse in a patient with high-risk MM despite having undergone autologous Hematopoietic Stem Cell Transplantation (HSCT). A rapid clinical and serum Free Light Chain (FLC) response was achieved following urgent initiation of BiTE therapy.

Case Presentation

A 62-year-old male patient with an initial presentation of bilateral leg swelling, anemia and acute renal failure requiring hemodialysis was diagnosed with lambda free light chain multiple myeloma, Revised International Staging System stage III, in February 2023. High-risk cytogenetic features included tetraploidy, copy gain of 1q21 (CKS1B gene), and relative deletion of the p53 gene. He was treated with 1 cycle of Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD), followed by 7 additional cycles of daratumumab plus CyBorD. He remained on dialysis 3 times weekly but achieved a good partial response. The patient then received preparative regimen of melphalan 140 mg/m^2 followed by autologous stem cell transplant. Unfortunately, he developed progression of disease within 2 months following transplant and was started on Pomalidomide, Carfilzomib and Dexamethasone (KPD) in February 2024. He achieved a very good partial response after 2 cycles of KPD, but shortly afterwards he presented with worsening abdominal distension, tightness and early satiety over 2 weeks. An examination revealed ECOG PS of 3, cutaneous pallor without jaundice, tense ascites and minimal leg edema. Investigations revealed WBC 2.8 bil/L, hemoglobin 10.2 g/dL, RBC 3.05 tril/L, platelet 113 bil/L, normal sodium, potassium, ALP, AST, ALT, bilirubin, creatinine

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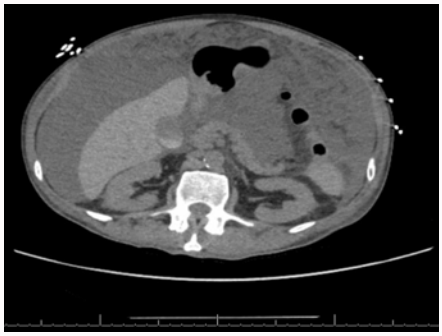

Figure 1: Computed tomography scan of the abdomen and pelvis showing a large amount of ascites with infiltration of the omental fat.

7.34 mg/dL, BUN 18 mg/dL, albumin 3.3 g/dL, normal magnesium and phosphorus, beta-2-microglobulin 42 mg/L. Rare plasma cells were noted in the peripheral smear. Serum protein electrophoresis during the same admission revealed persistent free lambda light chain, too small to quantitate. Serum free light chain study showed abruptly increased free lambda of 1904 mg/dL, compared to 155.7 mg/dL just 3 weeks prior. Free kappa was 0.36 mg/dL. CT abdomen/pelvis showed development of a large amount of ascites, with infiltration of the omental fat (Figure 1). Doppler ultrasound of abdomen revealed patent hepatic vasculature with appropriate directional flow.

Diagnostic and therapeutic paracentesis was performed. 5 L of clear yellow fluid was obtained. Fluid studies showed albumin 1.8 g/dL, calculated Serum Ascites Albumin Gradient (SAAG) 1.5, LDH 240 U/L, total protein 2.8 g/dL, RBC 3000/mcl, total nucleated cells 2742/mcl, 15% lymphocytes and 82% atypical cells with morphological features of plasmablasts. Immunohistochemistry revealed atypical cells were positive for CD138 and MUM-1, and Ki-67 was >60% (Figure 2). Flow cytometry of a separate paracentesis sample showed aberrant plasma cells that expressed CD38 (moderate), CD45, CD138 (bright) and lambda monotypic light chain. CD19, CD20, CD56 and CD117 were negative.

The patient was quickly accumulating ascites with more than 1 L per day. Given his frequent need of paracentesis, cachexia, high Ki-67 of plasma cells in the ascites sample, and rapidly increasing free lambda light chain, decision was made to initiate inpatient salvage therapy. He was assessed by the cellular therapy service and started on Talquetamab in May 2024. He tolerated the treatment well without any adverse effects including cytokine release syndrome and neurotoxicity. His free lambda improved to 38.3 mg/dL within three weeks of BiTE therapy. The patient completed inpatient rehabilitation during the same time and was subsequently discharged home. He remained paracentesis-free for two months.

Discussion

Myelomatous ascites is an extremely rare extramedullary manifestation of MM and is associated with a poor prognosis with limited treatment options. Harbhajanka et al. reported a single institution experience over 20 years where out of 797 patients treated for multiple myeloma, 13 developed myelomatous serous cavity effusions, and only 1 patient had involvement of peritoneal cavity. Median survival among this population was 32 days despite aggressive treatment [10]. A separate review of 56 patients with serous cavity involvement by MM showed that 90% died within 1 year of diagnosis [11].

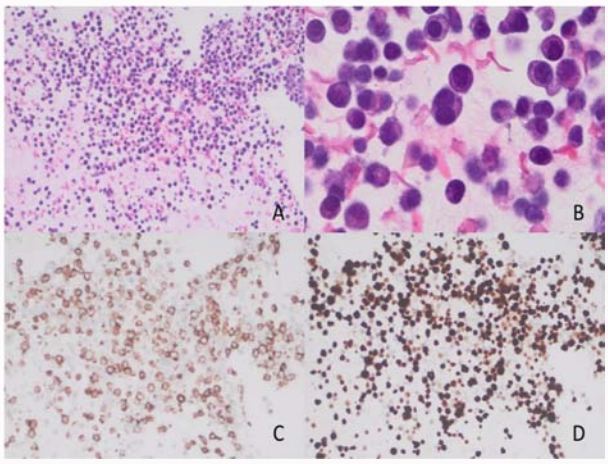

Figure 2: The sections of cell block of the peritoneal fluid showing atypical plasma cells: A) HE stain (200x); B) HE stain (1000x); C) Plasma cells are positive for CD138 (200x); D) Plasma cells are mostly positive for Ki-67 (200x).

The etiology for myelomatous ascites is peritoneal infiltration by plasma cells and accumulation of globulins in the peritoneal cavity. Other differential diagnosis for ascites in MM include ascites secondary to heart or renal failure, portal venous hypertension due to hepatic infiltration by plasma cells or development of hepatic amyloidosis [12]. Although typical ascitic fluid analysis with SAAG, total protein and cell count can aid the initial differential diagnosis, specificity may be limited [13]. In our case, SAAG (1.5) was above 1.1, which would suggest portal venous hypertension and heart failure as more common etiology, and peritoneal infiltration and malignant effusions as less common. Indeed, this led to initial clinical suspicion of ascites because of portal venous hypertension secondary to portal venous thrombosis which was ruled out by doppler ultrasound. At the same time, his elevated total nucleated cells (2742) greater than 500/mcl provided clue for possible malignant ascites, which was confirmed by cytology, immunohistochemistry, and flow cytometry with identification of CD38 positive, CD138 positive and lambda monotypic light chain positive plasma cells. This case highlights the importance of histopathological examination of peritoneal fluid whenever there is clinical suspicion of myelomatous ascites.

Most of the available literature on management of myelomatous ascites are based on recent case reports, a significant majority of which reported death shortly after starting next line of therapy including bendamustine based regimen or DT-PACE or CyBorD [14-16]. One patient was successfully salvaged with VAD (vincristine, Adriamycin and dexamethasone) followed by autologous HSCT [17]. Talquetamab is a novel GPRC5D-targeted BiTE that has shown promising efficacy in a phase 1 clinical trial in patients with relapsed/refractory MM, including those with extramedullary disease [18]. At the recommended phase 2 doses, talquetamab induced an overall response rate of 74% (weekly dosing) and 73% (biweekly dosing) and a median duration of response of 10.2 and 7.8 months respectively [9,18]. While clinical data on the use of GPRC5D-targeted BiTEs like talquetamab in myelomatous ascites is limited, ongoing clinical trials are evaluating their safety and efficacy in patients with relapsed/refractory MM, including those with extramedullary disease. Our patient achieved marked clinical response with diminishing ascites re-accumulation, as well as >90% reduction in free light chain, merely 3 weeks after 1st dose of talquetamab. To our knowledge there has

been no previous report of the successful use of BiTE to treat this rare complication.

Conclusion

The present case shows that myelomatous ascites may respond favorably to BiTE salvage.

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