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CASE REPORT

A case of mantle cell lymphoma presenting with ascites

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Key Clinical Message

Ascites with the finding of peritoneal carcinomatosis is considered an unusual presentation for mantle cell lymphoma (MCL) and has been rarely described in literature. This case reflects the importance of cytological analysis of peritoneal fluid in a patient with intractable ascites not contributing from other comorbidities. In the event a bone marrow (BM) analysis cannot be made, this may serve as an alternative method for diagnosing MCL taking into consideration the good concordance between peritoneal fluid and BM cytological markers.

Keywords

Ascites, B- cell lymphoma, mantle cell lymphoma, non-Hodgkin's lymphoma.

Background

Mantle cell lymphoma (MCL) is a mature neoplasm of the B lymphocytes classified under the category of indolent non-Hodgkin lymphomas (NHL). However, unlike other indolent forms of NHL, MCL behaves more aggressively despite treatment [1]. MCL comprises about 6–7 percent of adult NHLs in the United States and Europe with an incidence rate of 4–8 cases per million per year [1–3]. The median age of diagnosis is 68 years with more frequent occurrence in Caucasian males than females [4–7].

The cell of origin for MCL is a naive B cell in 80% of the cases, but the remaining cases are derived from antigen-stimulated B cells. The translocation t(11,14) (q13; q32) is universally present in MCL and is the primary genetic defect that results in unsuppressed expression of the proto-oncogene CCND1. This in turn leads to the increased production of the protein cyclin D1 [8]. There are a variety of other genetic defects also involved, including loss of tumor suppressor genes and activation of other oncogenes [8].

Around 70% of cases of MCL present for the first time with advanced-stage disease. Around three-quarters of patients have lymph node involvement alone, while one-quarter have extranodal involvement [9]. Most common extranodal sites appear to be that of the bone marrow (BM), spleen, liver, gastrointestinal (GI) tract, and the Waldeyer's ring [9–11]. In terms of GI tract involvement, ascites has been described alongside lesions such as gastric ulcers, lymphomatous intestinal polyposis or peritoneal lymphomatosis. Aside from ascites, serosal lymphomatosis with pleural and pericardial effusions has been described in later stages in the setting of known MCL with positive lymph node status or BM. Development of serosal effusion in the course of malignant lymphomas, either primary or otherwise, is rare and is considered as one of the adverse factors affecting overall survival [12]. However, the presence of peritoneal lymphomatosis with abdominal ascites as the first and primary presentation is rare and only few cases have been reported in the literature [13]. Our patient primarily presents with ascites and BM infiltration without significant lymphadenopathy.

Flow cytometry (FCM) and immunohistochemical staining of the ascitic fluid have helped clinicians identify a diagnosis in such cases. We found the FCM results of samples from different sites could be concordant or discordant within the same patient. As in our case, MCL cell

markers in the peritoneal fluid may be able to serve as surrogate for conventional BM aspirate and biopsy.

Case Report

We are presenting a case of a 46-year-old El Salvadorian male with a past medical history of rheumatoid arthritis, dyslipidemia, and type 2 diabetes mellitus, who presented to the hospital with the complaints of sore throat, shortness of breath, cough, and chills. His symptoms were progressively worsening for 2 weeks. He also mentioned increasing abdominal distension over the last 3 months associated with significant unintentional weight loss of approximately one hundred pounds. He was an ex-smoker and denies any use of alcohol or drugs. His family history was significant for a son that was diagnosed with acute lymphoblastic leukemia at the age of 14, who has since been in remission. On examination, generalized wasting was noted. He was noted to be febrile at 102°F, tachycardic, tachypneic, and hypotensive in the emergency room. There were palpable nontender cervical and submandibular lymphadenopathy present on exam. Chest was clear to auscultation. Abdominal examination revealed nontender distention, and massive nontender hepatosplenomegaly. Initial laboratory workup showed marked leukocytosis of 71.6 K/UL with absolute lymphocytosis of 61.2 K/UI. Laboratory evaluation also revealed a hemoglobin at 4.9 gm/dL and platelet count of 111 K. A peripheral smear showed more than 50% atypical lymphocytes, multiple bands, and multisegmented neutrophils without evidence of blasts.

With the presumptive diagnosis of septic shock from pneumonia, he was admitted to intensive care unit. Broad spectrum intravenous antibiotics and oseltamivir were initiated. Hemodynamic support was provided in the form of vasopressors, mechanical ventilation, and transfusion of blood products. Further workup revealed elevated uric acid of 10 mg/dl and lactate dehydrogenase (LDH) of 278 U/L. Initial blood cultures were positive for hemophilus influenza. Serum protein electrophoresis, histoplasma antigen, aspergillus antigen, HIV, and hepatitis panel, Epstein–Barr virus antibodies and CMV antibodies were all negative. CT scan of head, neck, chest, abdomen, and pelvis was performed and showed significant pelvic, retroperitoneal, and axillary lymphadenopathy. Peritoneal carcinomatosis with marked hepatosplenomegaly, ascites and opacification of maxillary and ethmoid sinuses were also noted. Peripheral blood FCM and cytogenetics were subsequently performed showing t(11:14)+, cyclin D1+, CD5+, CD10−, CD23−. With this data, the diagnosis of MCL was made (Fig. 1). Serum beta-2 microglobulin was also elevated at 18.2 mg/L. As mentioned before, blood smear showed atypical lymphocytes which, in the settings of leukocytosis, could not be explained merely by infection but also secondary to a neoplastic process. Hydroxyurea and allopurinol were initiated.

Following stabilization from septic shock, he underwent a BM biopsy which showed extensive involvement by the MCL (Figs. 2 and 3). He presented with Ann Arbor stage 4 disease, hemoglobin less than 12, an elevated LDH, and an ECOG performance status of 2. With this data, he was stratified as a high-risk stage 4 MCL. An abdominal paracentesis performed as he developed worsening abdominal distention. Cytological analysis of which was consistent with MCL by FCM (Figs. 1 and 4).

Thereafter, he was started on chemotherapy with cyclophosphamide, doxorubicin, vincristine, and

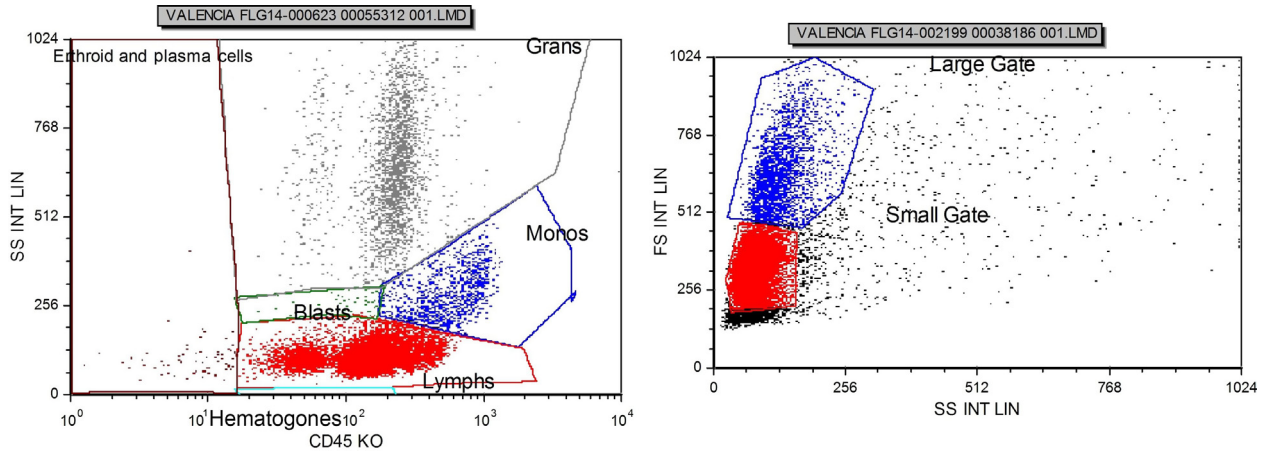

Figure 1. Flow cytometry graphs of the peripheral blood [Left] and peritoneal fluid [Right].

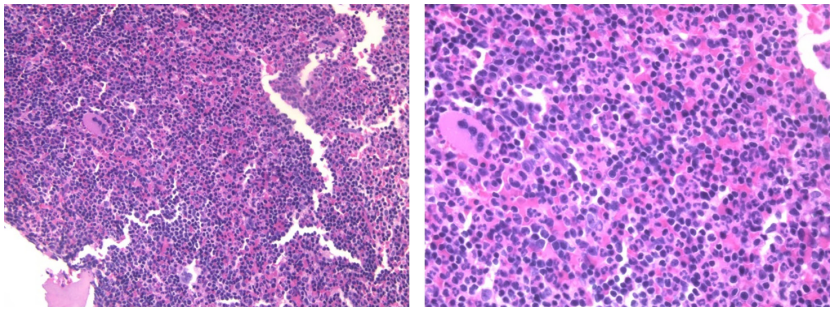

Figure 2. H/E stain of the bone marrow showing predominant lymphocytes infiltration.

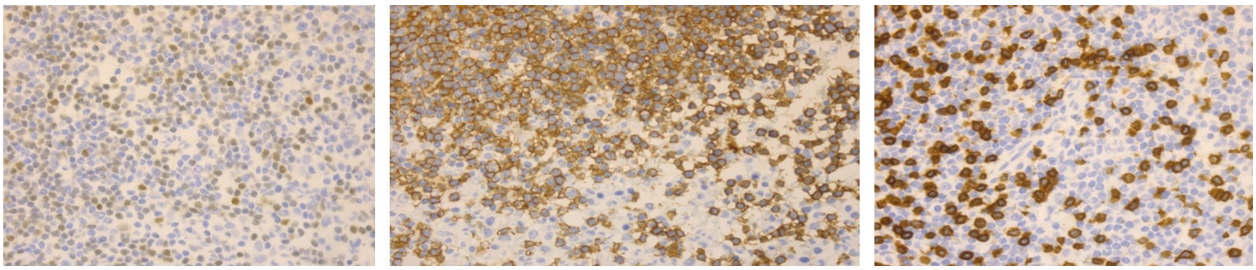

Figure 3. From left to right showing the IHC stains of bone marrow cells positive for cyclin D1, CD 20, and CD 3 markers.

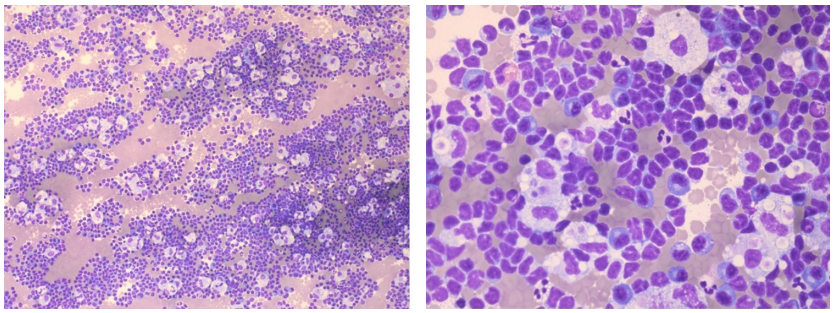

Figure 4. Ascitic fluid cytology showing lymphocytic predominant cells with foamy macrophages.

dexamethasone and received two cycles of therapy. Despite discharge after further stabilization, he had multiple admissions from progression of his symptoms and recurrence of ascites that required multiple paracentesis. Due to inadequate response to the therapy, he was then switched to palliative chemotherapy with the use of bortezomib for seven cycles. He continued to have disease progression and subsequently passed away.

Ascites, as described in our patient, with the finding of peritoneal carcinomatosis is considered an unusual presentation for MCL and has been rarely described in literature. This case reflects the importance of cytological analysis of peritoneal fluid in a patient with intractable ascites not contributing from other comorbidities. In the event a BM analysis cannot be made, this may serve as an alternative method of diagnosis.

Discussion

Throughout history, MCL has carried different names such as intermediate lymphocytic lymphoma, centrocytic lymphoma, mantle zone lymphoma, and lymphocytic lymphoma of intermediate differentiation [2, 3]. Since the 1990s, all these names were categorized under MCL after finding that all described cases carried the t(11, 14) (q13; q32) [8].

The malignant cells resemble the lymphocytes in the mantle zone of the lymphoid follicle. Being a tumor rising from B cells, the surface markers that are detected by immunohistochemistry include pan-B cell antigens CD19, CD20, CD5, sIgM, and FMC7. They lack CD23 and CD11c. Cyclin D1 is present in most of the cases of MCL as mentioned earlier. SOX11 could be a useful marker in

cyclin D1-negative MCL [12–14]. Though the translocation t(11, 14) (q13;q32) is the primary genetic defect, other genetic defects include loss of tumor suppressor genes like ATM, CDKN2A, and TP53 with the concurrent activation of some oncogenes like MYC, SYK, BCL2 [8, 14].

The presentation of the MCL can vary from chronic/indolent form to a more fulminant course resulting in shortened overall survival [1]. Ascites or serous effusions are considered uncommon presentations of hematological malignancies [13]. Diffuse large B-cell lymphoma being the most common of all NHL has been associated with ascites. In a case series of 101 cytology-positive cases of malignant ascites, only 8% were shown to be lymphoma [15]. In another case series, the rate was even lower as 2% [16]. We find that GI tract involvement with or without ascites have been seen in indolent lymphoma to aggressive MCL [12, 13, 17–20]. Infiltration due to tumor mass or vascular leakage due to stimulation by the vascular endothelial growth factor contributes to the pathogenesis of the ascites. Ascites, usually described as bloody in nature, can be present concurrently with GI tract involvement, peritoneal lymphomatosis, or multiple lymphomatous polyposis of the intestine. Gastric MCL is more likely to occur with other GI diseases such as Crohn's disease and adenocarcinoma. The involvement of peritoneum with MCL as initial presentation is quite rare.

Here, we illustrate five other cases of MCL described in the literature presenting with ascites. (Table 1) [12, 13, 17–19].

Diagnostic evaluation of the peritoneal fluid can be assessed by flow cytometric analysis. Flow cytometric analysis was performed in four of the five cases and the expression of cytological markers in both ascitic fluid and BM or peripheral blood. It was concordant in two cases. One of the cases presented as postsurgical seeding following splenectomy resulting in peritoneal involvement [19]. In the cases without BM involvement, cytological markers were consistent with MCL and patients were treated as such [12, 13, 17, 18]. Two previous studies showed that different specimens from different sites in the same patient with NHL carry the same set of cytological markers most of the time [21–23]. Huh Yo et al. mentioned in his study of 29 patients with NHL that if there is discordance in results, then it is either secondary to two different primary lymphomas in the same patient or a result of modulation of antigen expression of the tumor, in relation to the host environment [22]. In one study, it was observed that discordant antigen expression was associated with a more aggressive course of disease [23]. So far, the data are very limited as there are few cases that are able to be studied.

Treatment for this particular disease is quite complex as very few treatment options provided a complete and long-lasting response. Depending on the performance status, comorbidities, and age of the patient, current guidelines suggest that those with an improved performance status are more likely to be treated with combination treatment regimens such as R-hyperCVAD/R-HD-MTX-Ara-C regimen. Those with a poorer performance status are suggested to be treated with R-CHOP or R-CVP based regimens [8]. Intraperitoneal application of rituximab was shown by Martina Chrysandt et al. to be effective in local control of the disease process in one of the case reports involving stage IV MCL [17].

Though we remain unsure if we could use MCL cytological markers in the peritoneal fluid as a surrogate to conventional BM biopsy and testing, the data are promising in terms of concordance. If BM testing is not able to be performed or testing has shown a lack of involvement

Table 1. Illustrating five cases of mantle cell lymphoma with ascites on presentation.

Age (years)	Concordance of cytological markers between bone marrow (BM) & ascitic fluid	Associated LAP, hepatomegaly, or splenomegaly	BM involvement	Outcome
74	NA	None	Not involved	Partial response to treatment with disappearance of ascites and 30% decrease in the thickening of the colonic wall
64	Concordant	Retroperitoneal, mesenteric, pelvic LAP, Splenomegaly	Involved	Patient had complete response to treatment
75	Concordant	Cervical and Axillary LAP, Hepatomegaly and splenomegaly	Involved	Poor response, course was complicated by sepsis
55	NA	Peritoneal mass seen with diffuse peritoneal thickening and pleural involvement	Not involved	Patient did not respond to treatment
47	Concordant	Hepatomegaly and splenomegaly	Not involved	Patient had complete response to treatment

LAP, Lymphadenopathy.

of the BM by MCL, peritoneal sampling may be able to confirm a diagnosis. This will need further investigation in larger clinical trials, however.

Conflict of Interest

The authors declare no competing financial interests.
Off-label drug use: None disclosed.

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