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LETTERS TO THE EDITOR

Multiple myeloma with serous membrane involvement and increased CA-125 and CA 15-3

Dear Editor,

Multiple myeloma (MM) is a disease characterized by overproduction of monoclonal immunoglobulins or light chains (LC) due to neoplastic plasma cell (PC) infiltration of the bone marrow [1]. Osteolytic bone lesions, anemia, hyperviscosity, predisposition to infections, renal dysfunction, hypercalcemia and Bence-Jones proteinuria (BJP) are common findings in patients with MM. The albumin-globulin ratio is often reversed and M protein is detected in the sera and/or urine [2].

A 43-year-old female presented with ascites and pretibial edema. All laboratory analyses were normal except increased erythrocyte sedimentation rate (110 mm/h). Pleural and pericardial fluid were detected by x-rays and echocardiography. No monoclonal paraprotein was detected on serum electrophoresis. Ascites and pleurisy had exudate characteristics. Serum CA-125 and CA 15-3 levels were very high (825 IU/L, normal up to 35) and 564 IU/L, normal up to 29, respectively). Search for malignancies and tuberculosis was negative. Peritoneal biopsy and pleural fluid cytology revealed large atypical PCs. BJP wasn't found and cranium radiography was normal. Serum β2-microglobulin level was 6.6 mg/L (normal range 0-2.5). Serum and urine immunoelectrophoresis showed kappa LC 1352 mg/dl (normal range 170-370), and 1081 mg/dl (normal< 1.5), respectively. Bone marrow aspiration (BMA) showed 38% PCs. The patient was diagnosed with kappa LC MM and 6 cycles of VAD (vincristine, adriamycin, dexamethasone) were administered. Following treatment, the patient's effusions disappeared, LC levels returned to normal and PC count regressed to 1% in BMA. In addition, CA-125 and CA 15-3 levels decreased (20 ad 25 IU/L, respectively). Entering remission with VAD, the patient underwent high-dose chemotherapy with melphalan 200 mg/m^2 and autologous stem cell transplantation (ASCT). After ASCT, she is still in complete remission for 2 years.

Serous fluid involvement and increased levels of tumor markers are rare findings in MM. Although there are reports of rare cases of MM presenting with fluid accumulation at different localizations, no cases describing involvement of all serous membranes together with increased CA-125 and CA 15-3 levels at the time of diagnosis have been reported in the literature [1,3].

The mechanism of ascites development could be attributed to serosal reaction due to peritoneal infiltration by PCs, portal hypertension resulting from PC liver infiltration or PC infiltration of membranes [4]. Furthermore, pleurisy was reported to be a finding of terminal phase and poor prognosis in MM [1].

Although some authors have reported that an average of 25% of patients with MM and more than 50% of patients with MM with serous involvement are of IgA type myeloma, our case, interestingly, was kappa LC MM [1].

CA-125 and CA 15-3 are glycoproteins with high molecular weight. CA-125 is released from the coelomic epithelium during the embryonic development [2]. CA 15-3 is released from malignant epithelial cells. They are often released from some solid tumors and are considered as indicators of poor prognosis [5].

PC dyscrasias (PCD) with increased level of CA-125 and ascites have been reported [2]. The authors argued that CA-125 was produced by PCs and proved in an *in vitro* study that PCs indeed produced CA-125. Similarly, Cloosen et al. reported that glycoforms of CA 15-3 were released from the PCs in MM [5].

There is no specific chemotherapy regimen for MM with serous membrane involvement. Treatment options include melphalan-prednisolone, VAD and high dose chemotherapy with ASCT [4].

This case shows that PCD should also be considered besides malignancies of other systems in the differential diagnosis of patients with fluid accumulation in serous membranes and/or increased tumor marker levels. However, we do not yet know the answers to "May these findings be of prognostic value?" and "Should chemotherapy protocols be modified based on the presence or absence of these findings?".

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Docetaxel-induced enterocolitis: a serious and potentially fatal adverse event

Dear Editor,

Taxanes are mitotic inhibitors and work by disrupting microtubule polymerization. Gastrointestinal toxicity and mainly bowel toxicity are not commonly seen [1-4].

We report the case of a 64-year-old, ex-smoker male who presented in 2008 with cough and thoracic discomfort. Chest x-ray showed a mass in the right inferior pulmonary lobe, while chest CT confirmed a 3.6 cm mass in the area and a 1.8 cm mass in the left superior lobe with multiple right hilar nodules. After repeated failures

of guided fine needle aspiration, he underwent a thoracotomy with wedge excision of the right lung tumor. The biopsy showed a pulmonary adenocarcinoma, moderately-well differentiated with infiltration of the perivisceral pleura. Further staging revealed the presence of CNS metastases, managed with brain radiotherapy.

Two months after an initial response to 6 cycles of carboplatin and pemetrexed chemotherapy disease progression was documented in the thorax and docetaxel chemotherapy was initiated. After 2 cycles the patient was admitted to the hospital with abdominal pain, nausea and severe watery diarrhea (up to 20 loose stools per day), followed by febrile neutropenia and mucositis. Physical examination revealed hypotension, tachycardia and abdominal distention. Full blood count revealed WBC 1730 with an absolute number of 480 neutrophils, normal hemoglobin and platelets. Colonoscopy revealed edema of the mucosa and congestion with diffuse ulcerations. Antibiotic therapy with intravenous metronidazole and oral vancomycin as well as granulocyte colony-stimulating factor (GCSF) was initiated with complete resolution of symptoms. He later received 3 more cycles of reduced dose of docetaxel but was readmitted 10 days after the last cycle with recurrence of colitis, abdominal pain, bloody diarrhea and grade 4 febrile neutropenia. A flexible sigmoidoscopy revealed moderate to severe mucosal sigmoid inflammation with diffuse subepithelial hemorrhages. Biopsy revealed mucosal ulceration and inflammation, crypt abscesses and dilatation. The patient received supportive care with fluids and steroid administration. Seven days later he was discharged free of symptoms.

From 2000 to 2010, 22 cases of severe colitis have been reported in the literature (20 with metastatic breast cancer, 1 prostate, 1 pancreatic cancer). Docetaxel-based chemotherapy regimens have been associated with a wide spectrum of colitis, with a 1.9% incidence of grade 3-4 severity. The most frequent types of colitis is the ischemic, as well as the hemorrhagic colitis. Severe complications include bowel necrosis, colonic perforation and typhlitis. Ischemic colitis presents with acute abdominal pain and tenderness with neutropenia, fever and/or bloody diarrhea. Suggestive computed tomography (CT) scan of the abdomen and pelvis and a negative *Clostridium difficile* test support the diagnosis of colitis. Septicemia frequently occurs and the most common causative organisms are aerobic gram-negative bacteria. Neutropenia, fever and positive blood cultures are occasionally absent. Colonoscopy is associated with an increased risk of perforation and, therefore should be discouraged. The histopathological analysis is compatible with inflammatory changes, including mucosal and submucosal edema, hemorrhage, acute inflammatory infiltrates, mucosal ulceration and serositis [1-3]. Potential predisposing factors include age, abdominal surgery, hypertension, coronary artery disease, peripheral vascular disease, diabetes mellitus, localization in ascending colon, poor nutrition [1-3]. The pathophysiology is complex and still under investigation. The rapidly dividing crypt cells throughout the intestinal epithelium are damaged by chemotherapy which affects the absorptive capacity and results in an increase of solutes in the intestinal lumen, osmotic shift of water into the lumen and diarrhea [4]. The majority of cases can be controlled with anti-peristaltic agents, aggressive fluid resuscitation, bowel rest and broad antibiotic coverage. In contrast to other cases, ours hints that adequate reduction in docetaxel dose does not always prevent the relapse. Docetaxel-induced enterocolitis should be taken into account during daily practice.

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A case of hepatic flexure carcinoid with extended brain metastases

Dear Editor,

A 56-year-old Caucasian male was subjected urgently to right hemicolectomy due to a mass of the hepatic flexure, causing complete obstruction of the lumen. Pathology revealed a goblet cell carcinoid tumor. Chest and abdominal CT scan demonstrated hepatic, mediastinal and abdominal lymph node metastases, while bone scintigraphy yielded a "super-scan" image. The patient received 8 cycles of chemotherapy with paclitaxel, gemcitabine, bevacizumab, oxaliplatin and zoledronic acid. Six months after the operation, the patient was admitted to our department for surgical debulking of the liver disease due to symptomatology of carcinoid syndrome (diarrhea and hot flushes). Besides the standard preoperative studies, the patient was subjected to somatostatin-receptor whole-body scintigraphy which confirmed the liver, nodal metastases and bone metastases. He underwent excision of the segments II, III, IV, left half of the hepatic segment I, wedge excision of a lesion in the hepatic segment VI and microwave ablation of 3 smaller foci. Hepatoduodenal ligament lymph node dissection was also performed as well as cholecystectomy. The patient was discharged in good condition on the 7th postoperative day. He was re-admitted 4 days later due to fever. Chest and abdominal CT scans were performed without significant findings, the fever was attributed to wound infection, the wound was drained, antibiotic treatment was initiated and the patient was discharged afebrile 9 days later. He was admitted once again one month after the liver operation due to weakness and stupor and a brain MRI scan demonstrated diffuse brain lesions compatible with metastases, extending to both cerebral and cerebellar lobes, and causing obstructive hydrocephalus. The patient's mental status deteriorated and he passed away 5 days later.

Carcinoid tumors are distinct malignancies included in the family of neuroendocrine tumors with variable clinical manifestations, most of them (60%) arising from the gastrointestinal tract, 3.8% from the colon and rectum, while the hepatic flexure is one of the rarest sites accounting for less than 0.15% [1]. Tumors originating from the colon have the worse prognosis with a 5-year survival rate < 45% [2]. Brain metastases are very rare, occurring in about 2% of the