Ascites and constitutional syndrome in a 70-year-old woman

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CASE REPORT

Dr. Carolina Muñoz-Codoceo. A 70-year-old woman born in Ecuador is brought to the Emergency Room at Hospital Universitario “12 de Octubre” because of increased abdominal perimeter, lower extremities edema, and constipation for the last 10 days. She had a constitutional syndrome with 10-kg weight loss in the past three months not associated with abdominal pain, nausea, vomiting, or fever. She also had no gastrointestinal bleeding signs. Her personal history included: type-2 diabetes mellitus, dyslipemia, and acute hepatitis during young adulthood. She had undergone a cesarean delivery at 30 years of age, and had received no blood transfusions. Her family history included a brother who died at 50 years from liver cirrhosis of unknown etiology. She was on chronic metformin, and reported no toxic habits. The patient had travelled from Ecuador to Spain 2 months prior to her admission to our hospital.

Her physical exam revealed: blood pressure 90/50 mmHg, and temperature 36.8 ºC. The patient was conscious and oriented, had a severely ill appearance, and evidence of malnutrition and dehydration was most apparent. Her abdominal semiology was that of ascites (distension, changing dullness, positive wave sign), lower limb edemas, and decreased breath sounds at the right lung base. No chronic liver disease stigmata, abdominal tenderness, masses or visceromegalies were found.

Peripheral blood testing revealed the following: Hb 14.3 g/dl; hematocrit 43%; MCV 90 fl; platelet count 350,000/mm³; WBC count 11,150 (neutrophils 79%, lymphocytes 12%, monocytes 6%, eosinophils 0.6%, basophils 0.2%); ESR 4 mm (1st hour); prothrombin 95%; cephalin time 36”; LDH 454 IU/l; AST 51 IU/l; ALT 19 IU/l; GGT 103 IU/l; alkaline phosphatase 146 IU/l; bilirubin 0.3 mg/dl; albumin 2.9 g/dl; creatinine 1.8 mg/dl; uric acid 14 mg/dl; tumor markers: CA-125 1017 U/ml (N ≤ 35 IU/ml); CEA, CA 19.9, CA 15.3, and α-fetoprotein: all normal. A conventional search for the etiology of her chronic liver disease (viral, metabolic, autoimmune causes) was negative, and thyroid hormone values were within the normal range. The study of her ascitic fluid (AF) revealed the following: WBCs 3700 (10% polymorphonuclear; 90% mononuclear); RBCs 0%; glucose 72 mg/dl; protein 2.6 g/dl; albumin 1.1 g/dl; amylase 2.9 g/dl; protein 6 g/dl; creatinine 1.8 mg/dl; uric acid 14 mg/dl; tumor markers: CA-125 1017 U/ml (N ≤ 35 IU/ml); CEA, CA 19.9, CA 15.3, and α-fetoprotein: all normal. A conventional search for the etiology of her chronic liver disease (viral, metabolic, autoimmune causes) was negative, and thyroid hormone values were within the normal range.

Two AF cytologies were performed –the first one was negative for malignant cells, the second was documented as “suspected malignity”. An abdominal ultrasono-
gram was performed, which showed liver cirrhosis signs with no evidence of portal hypertension, together with grade-2/3 ascites that partly interfered with the exam. Gynecological ultrasounds revealed “conglomerate masses in pelvis consistent with carcinomatosis, and heterogeneous ovarian tissue”, and also confirmed the presence of abundant ascites fluid. A transvaginal sonogram showed a uterus with healthy atrophic endometrium, and a septed free fluid collection in the lesser pelvis, with no apparent axial lesions. An abdomen-pelvic CT scan found evidence of chronic liver disease and massive ascites, with no splenomegaly or portal vein dilation. There were varices in the mesenteric territory with heterogeneously involved mesenteric fat, possibly in association with implants or adenopathies at that level, as well as a nonspecific thickening of the gastric and sigmoidal wall. A colonoscopy was performed to 60 cm away from the anal margin, which revealed a dilated, aperistaltic colon with no other lesions.

Two weeks after admission to the Gastroenterology Ward the clinical picture was complicated by severe digestive bleeding. A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Carolina Muñoz-Codoceo. In summary, this is a 70-year-old Latin American woman with abundant ascites, lower limb edema, constipation, and constitutional syndrome for three months. Laboratory tests revealed: leukocytosis with neutrophilia, thrombocytosis, hypoalbuminemia, mild liver panel changes (GOT and GGT), increased LDH, and renal function impairment, together with hyponatremia and hyperuricemia. In AF leukocytes were high with mononuclear cells predominating, LDH levels were also above normal values, and one cytology identified malignant cells. CA-125 levels were high both in peripheral blood and AF, and the serum-ascitic albumin gradient (SAAG: albumin\textsubscript{serum} – albumin\textsubscript{AF}) was greater than 1.1 g/dl. Regarding imaging techniques, signs of chronic liver disease vs. cirrhosis, massive ascites, and pelvic growths of potential carcinomatous etiology with motley ovaries were found, as well as thickened gastric and sigmoid walls, with no disease being identified during left colonoscopy.

The main causes of ascites may be categorized in two major groups based on SAAG. This gradient results from subtracting albumin values in AF from those found in the serum, and is an accurate surrogate marker for portal pressure (1,2). Thus, a high SAAG (≥ 1.1 g/dl) suggests PHT with certainty approaching 97%. In contrast, a low SAAG value (< 1.1 g/dl) will point the etiologic diagnosis of ascites towards the PHT-free group of causes (Table I).

In the present clinical report SAAG was ≥ 1.1 g/dl, a value that suggests a disease with ascites secondary to PHT, among which liver cirrhosis is most frequent. While the patient’s abdominal sonogram and CT scan showed signs of liver disease, no indirect PHT markers such as a dilated splenoportal axis and splenomegaly were associated. Additionally, the patient reported no exposure to hepatotoxic substances such as alcohol and selected drugs; also, the conventional exam for chronic liver disease causes was negative, which makes cirrhosis an unlikely diagnosis. However, with the information available a causal steato-hepatitis cannot be definitely excluded, particularly in a patient with diabetes (3). The absence of liver encephalopathy and coagulopathy, in addition to the patient’s liver profile and subacute clinical course allow to exclude acute liver failure as a possible diagnosis. Ascites vascular causes with PHT (Budd-Chiari syndrome and venoocclusive disease) and potentially malignant liver parenchyma lesions (hepatocarcinoma, metastasis) may be ruled out based on images obtained. Finally, the absence of heart disease and heart failure signs, together with normal thyroid hormones, exclude cardiac and myxedematous ascites in our patient (1,4).

A high SAAG and the presence of malignant cells in the patient’s AF are diagnostic for mixed ascites (1,2). In all, 5% of ascites with SAAG ≥ 1.1 g/dl are designated as “mixed”, and characterized by having two etiologies: typically liver cirrhosis, and then tuberculosis or peritoneal carcinomatosis (4). Our patient’s region of origin, her systemic manifestations, and the predominance of mononuclear WBCs in AF lead to consider a potential underlying peritoneal tuberculosis (5). In addition, tuberculosis may increase CA-125 in a nonspecific manner, as in the present case (Table I). A diagnosis of tuberculous peritonitis is usually difficult, since bacteriological AF or peritoneum results following laparoscopy are usually delayed. Measuring inter-

| Table I. Etiological classification of ascites according to serum-ascites albumin gradient (SAAG) |
|-----------------|-----------------|
| ≥ 1.1 g/dl | < 1.1 g/dl |
| – Liver cirrhosis (80%) | – Peritoneal carcinomatosis (10%) |
| – Portal thrombosis | – Tuberculosis (2%) |
| – Budd-Chiari syndrome | – Infection with bacteria, fungi, parasites |
| – Venoocclusive disease | – Meigs syndrome |
| – Primary liver tumors (hepatocarcinoma) | – Peritoneal mesothelioma |
| – Massive liver metastasis | – Severe hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, malnutrition) |
| – Alcoholic hepatitis | – Granulomatous peritonitis: Crohn, sarcoidosis |
| – Severe acute liver failure | – Serositis in connective tissue disease |
| – Pregnancy-related fatty liver | – Chylous ascites (lymph obstruction from trauma, lymphoma, tuberculosis, filaria, congenital abnormalities) |
| – Cardiac ascites (5%) | – Pancreatic ascites |
| – Myxedema | – Biliary ascites (postsurgical or traumatic) |
| – Mixed ascites (5%) | – Peritoneal dialysis |
feron gamma (IFN-γ) and adenosine-deaminase (ADA) in AF is a fast, non-invasive method that has shown 97% sensitivity and 94-97% specificity in the diagnosis of tuberculosis (6). The fact that it is an uncommon illness, and the absence of tuberculous infection data in our patient’s AF (normal ADA and IFN-γ, negative BAAR and Löwenstein culture), both render a diagnosis with tuberculous ascites unlikely.

In our case the finding of malignant cells in AF is virtually a definite diagnosis of malignancy, and flow cytometry may increase the probability of a positive diagnosis (7). Malignant tumors are responsible for 10% of ascites, and malignant ascites is present in 15-50% of cancer patients (8). Several mechanisms for tumor-related ascites have been suggested (7,9): a) direct peritoneal infiltration with neoplastic cells (peritoneal carcinomatosis); b) secondary to PHT after tumor compression or invasion of the splenportal axis; c) resulting from neoplastic obstruction of suprapatic veins (Budd-Chiari syndrome); and d) because of extrinsic compression and obstruction of abdominal lymph vessels (chyrous ascites). Also, studies demonstrate that some cytokines, including IL-2, TNF-α, and vascular endothelial growth factor may play a role in the mechanism causing malignant ascites (7). AF cytology identifies malignant ascites provided tumor cells reach this fluid, that is, in peritoneal carcinomatosis but not in liver metastasis, hepatocarcinoma, or malignant lymphoma with lymph obstruction, where a different ascites-forming mechanism operates. On the other hand, cancer-related ascites may be associated with high PMN counts in AF, presumably because tumor cells attract neutrophils towards AF, and this increase may entail confusion regarding SBP. However, lymphocytes usually predominate in malignant ascites, as in our case (7).

Malignant ascites is a manifestation of advanced tumor disease, and has a mean survival of two months whatever its origin; 80% of malignant ascites cases originate in ovarian, breast, endometrial, colon, gastric, pancreatic, or bronchial neoplasms (8,9). Ovarian tumors are the most common cause of malignant ascites, involve 40-60-year-old women in 70% of cases, and usually manifest as fulness and abdominal distension (10,11). In our reported case the image obtained using gynecological sonography, which showed conglomerate pelvic masses with a motley ovary, together with elevated serum CA-125, raise a diagnostic suspicion of ovarian neoplasm and secondary peritoneal carcinomatosis. In addition, these tumors are most commonly associated with ascites and even hydrothorax (Meigs syndrome), as was the case with our patient (5,11,12). However, transvaginal ultrasounds detected no anneximal masses, and TC found no lesions at this level. Also, the main usefulness of tumor markers such as CA-125 is the monitoring rather than the diagnosis of tumors, and this marker may also be elevated in a wide variety of conditions (Table II).

Gastric tumors are the second most common cause of malignant ascites (8). These are more frequent in males, and are usually diagnosed between 65 and 74 years of age, with a higher incidence in Japan, Latin America, and former Soviet Union. Gastric cancer is categorized into two groups: adenocarcinoma and lymphoma (13). Adenocarcinoma represents 90-95% of all gastric tumors, and may be of two different types: “intestinal or expansive”, which is more differentiated, and “diffuse or infiltrating”, which is less differentiated, and endemical in nature, and of poorer prognosis. “Krukenberg’s tumor” is included within the latter group, and refers to gastric adenocarcinoma with usually bilateral ovarian metestases, ascites, and elevated CA-125, while ovarian morphology is preserved (14). In favor of this diagnosis for our reported case are the patient’s age and country of origin, gastric wall thickening defined by CT, malignant ascites, high CA-125 levels, and initially suspected ovarian tumor.

Lymphomas represent 3-6% of gastric tumors, and 95% are non-Hodgkin, B-cell lymphomas (15). In addition, 35-40% of these gastric neoplasms are marginal-zone B-cell lymphomas developing in mucosa-associated lymphoid tissue (MALT lymphoma or primary
low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue). The rest are diffuse large B-cell gastric lymphomas (16,17). Primary gastric lymphomas usually develop in individuals around 60 years of age, with no difference in gender distribution (17,18). These tumors are associated with low socio-financial status, and specifically with *Helicobacter pylori* (*Hp*) infection, present in 98% of cases. They are most commonly located in the antrum, and early stages are usually asymptomatic; tumor progression may result in abdominal pain, nausea, vomiting, anorexia, weight loss, bleeding, fever, nocturnal sweating, and diarrhea (16,19). The sensitivity of endoscopy with biopsy collection for the diagnosis of gastric lymphoma is 95%, as this technique allows the study of the lesion’s morphology and its immunophenotyping using immunohistochemistry and flow cytometry. The endoscopic looks of gastric lymphoma may mimic a polypoid growth, fold thickening, or ulcerative lesions that may be difficult to tell from adenocarcinoma (20). MALT lymphoma may regress after *Hp* eradication, or progress to diffuse large B-cell lymphoma; somatic mutations and genetic factors have been found that may play a role in this progression (21).

The next diagnosis deserving consideration among the causes of malignant ascites—in order of frequency—includes colon neoplasms (1,2,7). Patient age, presence of intestinal habit changes with tendency toward constipation, and constitutional syndrome, together with sigmoid-wall thickening as seen in CT scans, justify such diagnostic suspicion. However, the absence of anemia and/or gastrointestinal bleeding, normal levels of tumor markers, and primarily colonoscopy, where no masses, polyps or suspect growths may be seen, most probably exclude this diagnosis. On the other hand, colonic dilation and aperistalsis as revealed by CT may be accounted for by a tumor-related extrinsic compression and/or adhesions secondary to peritoneal tumor spread.

Finally we must consider the possibility that the patient’s condition results from blood cancer. The study of AF using flow cytometry introduces this diagnostic possibility, as it allows an appropriate classification of blood disease in 90% of cases upon the study of selected physical features, presence of cell antigens, and even the expression of cell cycle suppressor genes (22). The expansion of B-cells with predominant light kappa or lambda chains detected by this technique is characteristic of B-cell lymphoproliferative syndromes, including multiple myeloma. This type of tumor has an incidence peak at 50-70 years of age, and usually manifests as a constitutional syndrome, commonly associated with renal failure (22,23). However, cytometry established no specific diagnosis in our reported case. In addition, the absence of typical symptoms such as bone pain or anemic syndrome, normocytic-normochromic anemia, hypergammaglobulinemia, and/or increased ESR make this diagnosis less likely. On the other hand gastrointestinal involvement and ascites are manifestations that rarely occur in this type of tumors, and no radiographic evidence, serum or urine electrophoretic data, or bone biopsy is available to raise stronger suspicion of this etiology.

Dr. Martínez-González (Pathology). Dr. Ulloa, can you describe the patient’s outcome, and the procedure that ultimately led to her diagnosis?

Dr. Ulloa (Gastroenterology). The development of gastrointestinal bleeding prompted an emergency gastroscopy. During this exam the gastric body mucosa was seen to have scarce compliance and markedly thickened folds with edema and multiple ulcerations, and hence biopsy samples were taken. The patient subsequently developed hypovolemic shock complicated with acute renal failure, and severe hypotenremia and hyperkalemia—she finally died from multiple organ failure.

Dr. Carolina Muñoz-Codoceo. As previously discussed, once the ovarian origin of ascites was excluded a gastric tumor was the most likely cause to consider. In addition to the patient’s age and country of origin, the image described by gastroscopy is consistent with diffuse gastric wall infiltration or plastic linitis, associated with edematous folds and ulcerations. These findings may correspond to gastric adenocarcinoma or lymphoma. The absence of signet-ring cells in the cytology of AF, and the presence of plasmatic lineage cells in said fluid would support a lymphoma diagnosis. The pathological study of gastric biopsies collected during gastroscopy will likely provide a definitive diagnosis.

**CLINICAL DIAGNOSIS**

Dr. Pérez-Carreras (Gastroenterology). We thought the patient had an ovarian tumor with carcinomatous spread and malignant ascites. However, when the discordant information obtained from the various imaging techniques, clinical severity, and the possibility of positive response to chemotherapy were considered a gynecological laparoscopy was suggested, and assessment by medical oncologists was requested. While the patient was on the wait list for elective gastroscopy, the development of digestive bleeding led us to perform this exploration in an urgent setting.

**CLINICAL DIAGNOSIS BY DR. MUÑOZ-CODOCEO**

Disseminated gastric adenocarcinoma with both pelvic and peritoneal implants (Krukenberg’s tumor) vs. gastric lymphoma.
PATHOLOGICAL DISCUSSION

Dr. Garrido-Ruiz. Endoscopic biopsy samples from various gastric body sites (4 tissue fragments measuring 0.8 x 0.8 x 0.3 cm) were received. From a microscopic perspective a gastric mucosal fragment showed standard histological characteristics, and various specimens showed extensive infiltration with mid- or large-sized lymphoid-looking round cells with vesiculous nuclei, prominent nucleoli, and discreetly visible cytoplasms that were diffusely distributed with focal mucosal ulcerations (Fig. 1). Similarly, gastric mucosa sites with focal though extensive infiltration with small lymphocytes with moderate atypias were seen in aggregates and with lymphoepithelial lesion images (Fig. 2). These histopathological findings prompted a histological diagnosis of “large B-cell gastric lymphoma with adjacent areas suggestive of MALT lymphoma”. Immunohistochemistry revealed lymphoid infiltration that was positive to CD79α, CD43, and CD38, and negative to CD20, CD3, CD10, BCL-6, and CD30, with a high proliferative index (80%), in high-grade lymphoma foci, in association with low-grade lymphoma areas where infiltrates were positive to CD20, CD79α, and CD43, and negative to the remaining markers in the panel (Figs. 3 and 4). Thus, this study confirmed the diagnosis with diffuse large B-cell lymphoma, “activated variant”, probably derived from the adjacent MALT lymphoma.

To explain the etiopathogenesis of gastrointestinal tract lymphomas Isaacson and Wright defined the concept of mucosa-associated lymphoid tissue (MALT) lymphoma in 1983. This is a kind of extranodal non-Hodgkin lymphoma resulting from malignant transfor-
mation of B-cells in the marginal area. The stomach is most commonly involved, and the condition represents around 24% of all extranodal primary lymphomas (17). According to criteria by Dawson et al., a gastric lymphoma is considered primary when the stomach is the predominantly involved organ, and intraabdominal adenopathies, if any, are located in the gastric lymph drainage routes. Therefore, patients with peripheral and/or mediastinal adenopathies, and peripheral blood, hepatosplenic, or bone-marrow involvement must be excluded from this diagnosis (7,17). Primary gastric lymphoma is uncommon, but its incidence is on the rise (24). It is a low-grade tumor at diagnosis in 45-85% of cases; the rest represent high-grade lymphomas. It is most often located in the gastric antrum, but may have multiple foci in 33% of cases (19,20).

Multiple studies have shown a close relationship between Hp infection and gastric MALT lymphoma development (21,25). Normal gastric tissue has no organized lymphoid tissue, and infection with this bacterium prompts a subset of patients to develop mucosa-associated lymphoid tissue (MALT tissue), lymphoid hyperplasia, and clonal B-cell expansion, which may result in lymphoma. Hp infection is believed to induce acute inflammation, which evolves to chronic inflammation with increased lymphocytes, plasma cells, and eosinophils. During the progression of this chronic gastritis lymphoid follicles and lymphatic aggregates may develop, the histological substrate for MALT lymphoma development. B-cell tumoral proliferation is secondary to specific reactive T-cell activation, with these cells being specifically activated by Hp and host cytokines (25). The most obvious association between this germ and MALT lymphoma is determined by tumor regression following Hp eradication, as initially described by Stolte in 1993, and then confirmed by a number of studies (21).

The classification of lymphomas into “low-grade” and “high-grade” varieties is accomplished according to the percentage of blast cells in the lesion (17). This differentiation is important, since a high-grade lesion entails more aggressive manifestations and poorer prognosis. Histological grading may be difficult in selected patients, as both types may coexist in the same lesion or in different foci. In addition, progression from low to high grade has been reported in a number of MALT lymphomas (18,19). Thus, the presence of islets with more than 20 transformed cells, or a percentage of high-grade cells greater than 15-20% in a low-grade lesion is considered clinically significant. In contrast, no evidence of low-grade lesion may be seen in some high-grade lymphomas, and such tumors may hence be considered “de novo” high-grade neoplasms. Nevertheless, this finding has no prognostic relevance, as no clinical differences have been reported between such lymphomas and those originating from low-grade lesions.

PATHOLOGICAL DIAGNOSIS

Gastric diffuse large B-cell lymphoma, “activated variant”; probably derived from adjacent MALT lymphoma.

REFERENCES


