CASE REPORT

A 74-year-old woman with peritoneal carcinomatosis: diagnosis challenges

Vitorino Modesto dos Santos, Cacilda Joyce Ferreira da Silva Garcia, Jânio Wagner Pinheiro Lopes, Herberth Vera Cruz Furtado Marques Junior and Lister Arruda Modesto dos Santos

ABSTRACT

A case of extra ovarian peritoneal carcinomatosis associated with an immunohistochemical pattern similar to that of pancreatic and biliary carcinomas is presented. A 74 year-old patient was admitted to the hospital with nausea, vomiting, abdominal pain, ascites, and loss of body weight. She had serum-ascitis albumin gradient lower than 1.1 g/dL, positive cytology with some cells presenting the characteristic signet ring features, and elevated CA-125 serum level. Echography and computerized tomography of the abdomen and the pelvis did not show images of primary tumors with origin in organs found at these sites. Diagnostic investigations by gastroscopy, colonoscopy, mammography and chest x-rays revealed no abnormalities. Tumor specimens obtained by laparoscopy showed an immunohistochemical panel consisting of CK20 (-), CK7, CK17 and MUC1 (+) consistent with a pancreatic origin. This case study aims at describing a challenging condition for clinicians, highlighting some diagnostic pitfalls.

Key words. Peritoneal carcinomatosis; diagnosis; pathology; old aged; female; immunohistochemistry

Vitorino Modesto dos Santos – physician, PhD, Hospital das Forças Armadas and Universidade Católica de Brasília, Brasília, Distrito Federal, Brazil

Cacilda Joyce Ferreira da Silva Garcia – physician, MSc, pathologist, Hospital das Forças Armadas, Brasília, Distrito Federal, Brazil

Jânio Wagner Pinheiro Lopes – physician, radiologist, Hospital das Forças Armadas, Brasília, Distrito Federal, Brazil

Herberth Vera Cruz Furtado Marques Junior – physician, Internal Medicine, Hospital das Forças Armadas, Brasília, Distrito Federal, Brazil

Lister Arruda Modesto dos Santos – physician, general surgeon, Hospital dos Servidores do Estado, São Paulo-SP, Brazil

Mailing address. Prof. Dr. Vitorino Modesto dos Santos. Hospital das Forças Armadas. Estrada do Contorno do Bosque s/n, Cruzeiro Novo. ZIP code 70658-900, Brasília-DF, Brazil. Phone: 55 61 39662103. Fax: 55 61 32331599.

E-mail address: vitorinomodesto@gmail.com

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RESUMO

Mulher de 74 anos com carcinomatose peritoneal: desafios diagnósticos

Um caso de carcinomatose peritoneal extraovariana é relatado em associação com um padrão imunoistoquímico semelhante ao dos carcinomas pancreáticos e biliares. Uma paciente de 74 anos foi hospitalizada com náuseas, vômitos, dor abdominal e ascite, associados com emagrecimento. Apresentou gradiente de albumina soro-ascite inferior a 1,1 g/dL, e citologia positiva com algumas células de aspecto característico em anel de sinete, e elevação do nível de CA-125 no soro. As ecografias e as tomografias computadorizadas do abdome e da pelve não mostraram imagens de tumores primários originando em órgãos desses sítios. Investigações diagnósticas por gastroscopia, colonoscopia, mamografia e radiografias do tórax não revelaram anormalidades. O painel imunoistoquímico CK20 (-); CK7, CK17 e MUC1 (+) indicou origem pancreática. Este estudo de caso tem o objetivo de descrever essa condição desafiadora para o clínico, enfatizando-se algumas dificuldades diagnósticas.

Palavras-chave. *Carcinomatose peritoneal; diagnóstico; neoplasias peritoneais; patologia; mulher; idosa; imunoistoquímica.*

INTRODUCTION

Ascites is the first evidence of peritoneal carcinomatosis in up to 54% of affected patients, and it is characterized by low serum-ascites albumin gradient and positive oncotic cytology.[1] Clinical history, physical examination, peritoneal fluid analysis, biochemical and tumor markers, histopathology and immunohistochemical staining are other routine procedures.[1] Peritoneal carcinomatosis causes approximately 10 % of ascites of a well-known origin and it frequently indicates a far advanced malignancy out of the possibilities of curative treatment. Management is very often palliative, with a focus on abdominal pain and discomfort.[1,2] Ovarian and gastrointestinal carcinomas are the main causes of this condition;[1,2] therefore, laparoscopy or laparotomy must be done if routine methods do not find the tumor of origin.[1] Primary extra ovarian peritoneal carcinoma is a very rare condition, which was first described by Swerdlow in 1959, and diagnosis is often a challenging task.[2,3] Clinical suspicion is based on the absence of an identified primary site of origin; elevated serum levels of CA-125 marker; and computed tomography (CT) images of a diffuse irregular mass involving the omentum (omental cake).[2-4] Ovarian carcinoma is the most common malignant cause of this radiological change, which has been described since the early 1900s, but various other malignancies and benign conditions are associated with omental caking.[2,4] Laparoscopy or laparotomy are necessary procedures to establish a conclusive diagnosis.[3]

Peritoneal carcinomatosis and omental cake are reported in an old woman with a primary tumor of unknown cause, focusing on diagnosis challenges in spite of cytological and histopathological data. The role of a necropsy study when etiology cannot be established during life is commented.

CASE REPORT

A 74-year-old woman was hospitalized for investigation of a progressive loss of weight and increasing abdominal volume. She complained of asthenia, loss of appetite and early satiety, nausea, vomiting and constipation. She hadn't undergone peritoneal dialysis or any other kind of intraperitoneal procedure. There was no alcohol or drug abuse, tobacco smoking or contact with asbestos. She was pregnant 13, para 12, and her last gestational event was an abortion. Her father had died of gastric cancer, and one of her sons had been diagnosed with lung cancer. Physical examination showed BMI: 23.4 Kg/m^2, temperature: 36° C, dyspnea, grade 3 ascites, and a hard irregular mass palpated between the epigastrium and right hypochondrium regions. Liver, spleen, and lymph nodes were not palpable and nails were normal.

Her initial blood parameters were not remarkable (Table 1). Except for CA-125: 465 (normal: ≤ 35) IU/mL, tumor markers were normal – beta HCG: 2.78 (normal: ≤ 5) mIU/mL, CEA: 1.0 (normal: ≤ 4.0) ng/mL, CA 15-3: 191.6 (normal: ≤ 35) IU/mL, CA 19-9: 0.3 (normal: ≤ 37) IU/mL, alpha-fetoprotein: 2.4 (normal: ≤ 5.5) IU/mL.

Abdominal and pelvic ultrasound confirmed an extensive ascites. A CT scan with contrast of total abdomen showed an enhanced image of "omental cake" in the epigastric and splenic areas, measuring 140 x 56 x 52 mm, enlarged periaortic and mesenteric lymph nodes, bilateral pleural effusion, and absence of adnexal and pancreatic masses. Mamography, upper digestive endoscopy and colonoscopy were unremarkable, including the histopathological studies of biopsied specimens. Electrocardiogram and radiography of the thorax showed no abnormalities.

Approximately 3,500 mL of a turbid fluid were drained during the laparoscopic procedure; a voluminous mass with some necrotic areas was observed on the serous surface of the gastric

Table 1. Laboratory data of a 74-year-old woman with peritoneal carcinomatosis

PARAMETERS/ DATE (2012)*	APRIL 9	APRIL 19	APRIL 24	MAY 7	MAY 11	MAY 19
Red cells (4.5-6.1 x 10^{12}/L)	4.67	4.79	5.05	4.77	4.32	4.18
Hemoglobin (11.1-16.1 g/L)	13.5	13.8	14,2	13.0	12.1	11.7
Hematocrit (42-52 %)	**41.4**	**41.8**	44.0	42.0	**37.8**	**37.5**
WBC* (4.0-10.0 x 10^9/L)	7.7	8.6	**10.5**	8.2	6.8	6.1
Neutrophils (1.8-7.0 x 10^9/L)	6.2	**7.1**	**8.6**	6.5	**8.3**	5.0
Platelets (140-450 x 10^9/L)	445	**454**	397	**495**	429	429
Urea (16.6-48.5 mg/dL)	32	**54**	**56**	36.7	23.0	28.9
Creatinine (0.7-1.2 mg/dL)	1.0	0.8	1.1	0.8	0.9	1.0
Sodium (136-145 mmol/L)	**134**	**132**	**135**	136	136	**135**
Potassium (3.5-5.1 mmol/L)	3.9	3.5	3.8	3.6	**2.7**	**3.2**
Calcium (1.12-1.32 mmol/L)	1.32	**1.37**	1.26	1.26	1.16	1.16
Magnesium (1.6-2.5 mg/dL)	2.0	1.8	**1.4**	**1.4**	**2.7**	2.2
AST† (< 40 U/L)	**45**	39	**44.3**	**44.3**	**48**	**51.4**
ALT‡ (< 41 U/L)	21	20	24.4	24.4	24	20.7
Albumin (3.5-5.2 g/dL)	**3.3**	**2.6**	**2.7**	**2.3**	**2.4**	**2.4**
Globulin (2.9-3.1 g/dL)	**3.4**	**2.2**	**2.3**	**1.9**	**2.0**	**2.0**
ESR# (< 20mm/1st hour)	**42**	**34**	Nd §	Nd	Nd	**61**

* Acronym: *WBC = white blood cells; †AST = aspartate aminotransferase; ‡ALT = alanine aminotransferase; #ESR = erythrocyte sedimentation rate; § Nd = not done. Abnormal data are shown in bold.

greater curvature; appendix, diaphragm, liver, gallbladder, spleen, small intestine, colon, kidneys, uterus, tubes and ovaries appeared to be disease-free. Therefore, no primary site of the peritoneal carcinomatosis was located.

Laboratory results showed amylase: 64 mg/dL, glucose: 64 mg/dL, LDH: 689 IU/L, total protein: 4.2 g/dL, and a serum-ascites albumin concentration gradient (SAAG) < 1.1 g/dL; 1,365 leukocytes/ mm^3 (mononuclear cells: 88%, and neutrophils: 12%), numerous histiocytes and mesothelial cells. Oncotic cytology revealed numerous epithelial malignant cells with pleocytosis, karyomegaly, granulous chromatin, enlarged nucleoli, and some nuclei were displaced by cytoplasmic vacuoles resembling signet ring cells.

Histopathology study of specimens of the peritoneal mass, obtained by laparoscopy, showed a poorly differentiated adenocarcinoma with psammoma bodies and a conspicuous desmoplastic reaction (Figure 1). In addition to the omentum, the tumor had only infiltrated the serous surface of the stomach. Furthermore, immunohistochemical staining of tumor samples was strongly indicative of a tumor of pancreatic origin: negative CK20 and positive CK7, CK17 and MUC1.

Despite intense clinical care and nutritional support, she evolved with severe immediate postoperative complications and had a relentless evolution to death in a short period of time. Necropsy was required, but her relatives did not authorize this procedure.

DISCUSSION

This 74-year-old woman had a hard abdominal mass; high levels of CA-125, and CT scan images of omental cake. Histopathology analyses of biopsies of the mass showed features indicative of adenocarcinoma, some signet ring cells, psammoma bodies, and a desmoplastic reaction. Computed tomographic features of omental cake are variable and diverse causes are involved. This change usually occurs if the omental fat is replaced by tumor infiltration and fibrosis.[2] Peritoneal carcinomatosis is the most frequent malignant etiology, which also includes ovarian, gastrointestinal, pancreatic, hepatobiliary, genitourinary, breast, and lung cancers; melanoma, and lymphomas.[2,4] More rarely, images of omental caking may be caused by primary malignancies and benign conditions of the peritoneum and omentum, such as mesothelioma, hemangiopericytoma, leiomyoma, leiomyosarcoma, gastrointestinal stromal tumor, lipoma, liposarcoma, fibrosarcoma, round cell tumor; tuberculosis, mycobacteriosis, actinomycosis, coccidioidomycosis, histoplasmosis, amyloidosis, paragonimiasis, and endometriosis.[2,4] Peritoneal invasion may appear encasing viscera and mimicking an abdominal cocoon.[2,5]

Diagnosis suspicion was based on CT scan images of omental cake, elevated titers of CA-125, and unremarkable levels of other tumor markers. Peritoneal carcinomatosis is a condition that involves the search for primary sites of tumor, which can be disseminated by peritoneal seeding, direct invasion, and lymphatic or hematogenous routes.[2] Cancer of unknown primary site is a malignancy with metastasis for which the site of origin cannot be established after accurate clinical and complementary evaluation.[6] This condition occurs in nearly 3-10% of malignant tumors,[5] and approximately 50% are adenocarcinomas.[6]

Women with peritoneal carcinomatosis of unknown primary site who undergo treatment schedules for metastases of ovarian carcinoma may have good outcomes.[6,7] They can present with clinical and anatomopathological features similar to those of ovarian carcinomas, and some may have multifocal serous extra ovarian carcinomas or serous papillary peritoneal carcinomas.[3,7] CA-125 is a high-molecular weight mucinous glycoprotein that was first described by Bast *et al.* (1981). This celomic epithelial antigen is derived from mesothelial cells of the abdominal, pleural and pericardial cavities; it is elevated in endometriosis, liver cirrhosis, congestive heart failure, premenopausal phase, and menses.[8] Increased levels of CA-125 occur in up to 80% of all epithelial ovarian cancers,[8] and in malignancies of the fallopian tubes, endometrium, lung, breast, pancreas, and gastrointestinal tract, as well as in peritoneal lymphomatosis.[9] It is noteworthy that CA-125 can be expressed by inflamed peritoneum,[8] a phenomenon that might explain the high blood levels of this tumor marker in the patient of the present case study.

This tumor marker is also found in primary peritoneal serous psammocarcinoma, which is either characterized by infiltration of abdominal viscera or a peritoneal invasive growth.[10,11] Psammoma body is a round-to-oval concentrically laminated and calcified microstructure.[12] Mechanisms of these pathologic calcifications involve local relative alkalinity due to ischemic necrosis; mucin-derived glycoproteic nidus of tissue calcification; mucin-related odontogenetic calcification process, mineralization of whorled collagen bodies; degenerated cells with hydroxyapatite within matrix vesicles; and macrophage osteopontin protein.[12] Differing from invasive peritoneal serous adenocarcinomas, psammoma bodies of primary peritoneal psammocarcinomas are present in more than 75% of tumor papillae.[11]

Characterization of a malignant peritoneal tumor was established by laparoscopy, and the irregular mass in gastric topography in combination with typical "signet ring cells" were strongly indicative of a primary mucin-producing tumor. This histopathological finding is more often reported in association with gastric adenocarcinoma, but it has been described in various other tumors.[2] Psammoma bodies may be found in female patients presenting with benign conditions such as intrauterine devices, use of oral contraceptives, salpingitis, endometritis, and endometriosis.[13]

However, they can be detected in various malignancies such as cervical and tubal carcinoma, central nervous system meningioma, duodenal carcinoid, endometrial adenocarcinoma, gastric adenocarcinoma, pancreatic somatostatinoma, prolactinoma, ovarian adenocarcinoma, breast, renal cell and thyroid carcinoma, and pleural as well as peritoneal mesotheliomas.[12,13] Diffuse malignant peritoneal mesothelioma may show elevated levels of CA-125, psammomatous bodies and desmoplastic reaction,[14] which might have increased the diagnosis challenges in this case. Psammoma bodies were also reported in 123 cases (3.7%) out of 3,335 samples of body cavity fluids; 112 of these (91%) were in peritoneal fluid and 63.4% had a malignant origin.[13]

Cytokeratins CK7 and CK17 and MUC1 are useful markers to distinguish pancreatobiliary from the extra-pancreatobiliary malignancies with primary site on the adrenal gland, breast, colon, gynecological organs, kidney, lung, stomach, thyroid, and malignant mesothelioma.[15,16]

Before laparoscopic evaluation, pseudomyxoma peritonei was included among the possible causes of ascites in this female patient. This rare tumor was first described by Werth in 1884; it often affects patients who are 24-76 years of age and is associated with appendiceal or ovarian masses. Immunohistochemistry often shows CK20+, and negative CK7, MUC1 and CA-125.[17] Extra-gastrointestinal stromal tumor from omentum peritoneum or mesentery are rare – less than 5% of cases – and for this reason were ruled out. These tumors usually occur in people over the age of 50, but they typically have no connection with the gastric walls.[18] Another initial concern in this case study was the possibility of a malignant peritoneal mesothelioma, which affects women between 40 and 70 years. The epithelioid variant can mimic ovarian cancer or primary peritoneal carcinoma, and increases diagnosis pitfalls.[16] In fact, clinical features, elevation of CA-125 levels, and the immunohistochemical profile CK7+/CK20- may be indistinct from the data described in the aforementioned malignancies.[16] In most patients, results of peritoneal fluid cytology are reported as adenocarcinomas,[16] a fact that results in additional misdiagnosis with peritoneal metastases of adenocarcinomas of pancreatic, biliary, gastric, colorectal, breast, pulmonary, and female genital tract.[16]

Although scarcely reported, extra ovarian primary peritoneal adenocarcinoma was included in the roll of hypotheses, after initial lack of data to elucidate the origin of this omental cake. This tumor was first described by Swerdlow in 1959. It almost exclusively affects the omentum, very rarely involves abdominal or pelvic organs, and diagnosis depends on histopathology.[3] Microscopically, clusters of the neoplasm are surrounded by desmoplastic tissue, and few lymphocytes and psammoma bodies appear scattered,[2] similarly to the tumor reported in this work. Most cases are of the serous type, but Brenner tumor, clear cell, endometrioid, mixed müllerian tumors, and mucinous are scarcely described variants of this malignancy.[3] Primary peritoneal serous carcinoma is an uncommon entity, predominantly affecting women between 45 and 75 years, and with no antecedent or evidence of other primary site of tumor.[19] The origin of this peritoneal serous carcinoma is not well established, and might be from peritoneal mesothelium, celomic epithelial lining of abdominal cavity, or tubal epithelium.[19]

Histopathology, CK7 expression, and CA-125 levels can mimic epithelial ovarian cancer.[19,20] Differential diagnosis between this group of tumors and ovarian serous adenocarcinomas include predominant serous features at extra ovarian site of involvement, and normal ovaries.[3] Similarly to this report, there is high CA-125, lymphocyte infiltration, and psammoma bodies.[3] Enlarged abdominal lymph nodes and lymphatic metastases occurred in this 74-year-old woman, similarly to what was found in 71 and 87-year-old women with primary peritoneal carcinoma.[20,21] Immunohistochemical studies of samples of pancreatic ductal carcinoma, pancreatobiliary type of ampullary carcinoma, and cholangiocarcinoma may show CK7+/CK17+/MUC1+.[15] Autopsy is a main tool to solve

antemortem diagnostic dilemmas; however, difficulties to get authorization from relatives occur in industrialized and developing countries.[22]

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