

Postmenopausal bleeding and vaginal nodules as the first presenting sign of adenocarcinoma of the gallbladder

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Summary

Vaginal submucosal nodules were observed in a 67-year-old woman, with ultrasonographic features of an advanced uterine neoplasm. On biopsy, light microscopy suggested that the lesions might be metastatic foci from an extragenital cancer, with a prevalent tubular growth pattern. Parallel immunohistochemical reactions revealed a diffuse, strong CA 19-9 positivity in both the cell membrane and cytoplasm. Subsequently, high serum levels of such tumor marker were also found, and an extragenital cancer was suspected of pancreatic or biliary origin. A mass in the gallbladder fossa was then detected by computed tomography and a primary gallbladder adenocarcinoma was confirmed on ultrasound-guided biopsy.

Key words: Vaginal metastatic cancer; Gallbladder adenocarcinoma; Gallbladder genital metastases; CA 19-9-expressing neoplasm.

Introduction

Primary gallbladder adenocarcinoma (PGA), most often affecting women over 50 years old, early on spreads to the liver, stomach and first duodenal portion. Recurrences in the female genital tract seldom arise in the ovary, but uterine or vaginal metastases have exceptionally been reported [1, 2]. Gallbladder cancer cells, especially in tubular-type adenocarcinomas, are said to express the carbohydrate antigen 19-9 (CA 19-9) [3, 4], which has been perspected as an unfavorable predictor of metastatic potential, relating to both the tumor grade and microvessel invasion [4, 5].

The present study was aimed at assaying CA 19-9 expression in vaginal metastases of PGA on both the serum and tissue levels to assess the diagnostic significance of such tumor marker.

The results were finally compared to the conventional features of tumor malignancy, despite an asymptomatic clinical course.

Case Report

A 67-year-old woman was hospitalized because of recurrent spotting. At gynecological examination, an enlarged uterine body was found, with a stiffening of the right parametrium and several hard nodes in the posterior vaginal fornix, which were excisionally biopsied for both histologic and immunohistochemical purposes. Hysteroscopy disclosed a content of thick, greyish mucinous material and atrophic endometrium. Light microscopy of the vaginal nodes showed the presence of newly formed glandular structures, consisting of irregular tubules, lined by malignant low-cuboidal cells and surrounded by desmoplastic stroma, below an ulcerated mucosal layer. The lesion deeply infiltrated the submucosal stroma, invading some blood and lymphatic vessels. A metastatic, moderately differentiated adenocarcinoma was diagnosed, with a prevalently

tubular pattern. Immunohistology was carried out, without antigen retrieval, using a CA 19-9 monoclonal antibody, diluted 1:100 (Clone 116-NS- 19-9, DAKO, A/S Copenhagen, Denmark). It showed a strong staining for malignant cells at both the cell membrane and cytoplasm (Figure 1) which suspicious was of a metastatic malignancy deriving from an extragenital tumor lesion of the pancreatic-duodenal region. Abdominal and chest X-rays and rectosigmoidoscopy failed to demonstrate pathological findings. Pelvic-abdominal computed tomography showed an enlarged uterus with a misshapen uterine cervix adhering to the right parametrium, pelvic ureter and sigmoid colon, associated with an ipsilateral high-grade hydronephrosis. The gallbladder was found to be enlarged with a diffuse parietal thickening, endoluminal stones and a back-sited exophytic formation that infiltrated the sixth hepatic segment, omentum and descending portion of the duodenum (9 cm distal to the pylorus). Several nodular lesions also occurred elsewhere, in the liver and peritoneum. On a percutaneous echoguided needle biopsy, the gallbladder mass was identified as a primary gallbladder adenocarcinoma, recapitulating histologic and immunohistologic features of the above-described vaginal nodules. Tumoral marker investigations displayed normal serum levels of alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125) moderately elevated (118 U/ml, exceeding the normal value of 35 U/ml), while serum CA 19-9 was highly increased up to 21,856 U/ml (normal values from 0 to 40 U/ml).

Due to the patient's condition worsening, on her own request she was discharged from our department and died five weeks later. No autopsy was performed.

Discussion

Metastases in the female genital tract from extragenital neoplasms are not frequent and when they spread to the genital tract they mostly involve the ovary. Such lesions may be mistaken for primary malignancies in 20% of the cases, but really arise in the gastrointestinal tract, namely stomach, pancreas and colon, and also in the breast, lung and skin [2]. PGA is infrequent and, lacking in specific

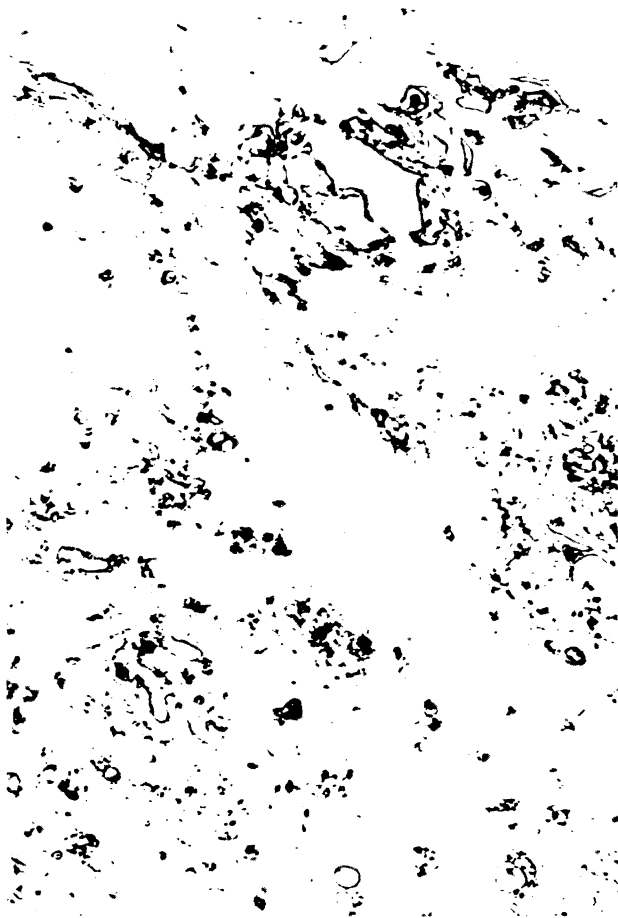


Figure 1. — Ca 19-9 immunolabelling underlines vaginal metastatic adenocarcinomatous cells below the squamous cell mucosal layer (original magnification 375x).

signs and symptoms, the diagnosis is late and prognosis extremely poor. The spread of neoplasia is characterized by local invasion of the liver, stomach, duodenum, hepatic flexure of the colon and omentum [4, 5], while distant metastases occur late in disease progression, most often via hematogenous spread. Six cases of ovarian involvement from carcinoma of the gallbladder or bile ducts have been discovered during the life of the patient [2]: in one case the ovarian neoplasia was detected five weeks before the gallbladder cancer, while in three cases ovarian and gallbladder neoplasias were detected simultaneously. Finally, in two cases ovarian metastases were discovered one and two years after the biliary neoplasias. Two gallbladder adenocarcinomas have also been reported, with postmenopausal vaginal bleeding and atypical cervical cytology, respectively [1]. In our case as well, the first sign of the disease was postmenopausal vaginal bleeding. Gynecologic ultrasonography revealed

a series of findings evoking an advanced uterine cancer. Light microscopy and immunohistology on vaginal biopsy suggested metastatic extragenital adenocarcinoma of possible pancreatic origin, but the highly increased serum and tissue levels of CA 19-9 were also consistent with a metastatic lesion from an advanced gallbladder carcinoma. In this study, we examined sialyl Le(a) expression in human gallbladder adenocarcinoma and its clinicopathological significance. The presence of a gallbladder malignancy was indicated by the marked pathologic findings detected at computed tomography and by very high serum levels of tumoral markers, namely CA 19-9, which typically increase in patients with gallbladder pathologies (calculosis, polyposis). CA19-9, a sialyl Le(a) antigen, was first described as a pancreatic and gastrointestinal tumor marker. It is a ligand for E-selectin and plays an important role in lymphatic tumor invasion and metastasis [4]. The definitive diagnosis of primary gallbladder malignancy was confirmed by percutaneous needle biopsy which demonstrated histologic feature analogues to those detected in the vaginal biopsies. Unfortunately, the late incidental diagnosis and the advanced stage of the neoplasia did not allow appropriate management. Consequently, the prognosis for our patient was extremely poor with rapid worsening and death a few weeks later.

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