

Hypoproteinaemia, ascites and a tumour marker rise in a patient with a history of cancer

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Summary

Ascites and lower limb edema in a patient with a history of intra-hepatic cholangiocarcinoma and breast cancer raised suspicion of cancer recurrence. Although CA 125 and CA 19.9 were elevated

and initial cytologic findings for the ascitic fluid were consistent with this diagnosis, further tests revealed that the patient suffered from protein-losing enteropathy, a benign, unusual condition.

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Introduction

Cancer patients in complete remission usually undergo a follow-up phase. Unfortunately, follow-up guidelines are often lacking or based on empirical evidence. Furthermore, for the majority of solid malignancies, there is no clear evidence that intensive follow-up improves cancer outcomes,¹ but discharge from follow-up or excessively liberal follow-up policies are often perceived as insufficient by patients as well as some physicians.² A more intensive follow-up schedule seems to be appropriate if there are treatments available that change patient survival in case of early diagnosis of relapse.

In addition to issues such as optimal follow-up intensity and duration, the choice of appropriate tests may also be problematic. In most cases, physicians will opt for some form of radiological assessment. Tumour markers are simple, but relatively costly tests that are used for many purposes in the oncology practice. However, apart from a handful of malignancies such as prostate cancer, ovarian cancer and germ cell tumours, in which the performance of tumour markers is known to be high, their role as follow-up tests in other solid tumours such as breast³ cancer and colorectal⁴ cancer is currently unclear. Nevertheless, cancer recurrence is such a burden for these patients and their physicians that when no clear national or institutional policies have been established, they tend to be performed. If radiological tests and serum tumour markers do not provide sufficient information to confirm or rule out recurrence, histologic confirmation is

occasionally required. Patients with easily accessible lesions or fluid collections, single lesions, no tumour marker elevation and with a history of cancer at low risk of recurrence are more likely to undergo histologic or cytologic confirmation.

Occasionally, the diagnosis of recurrence may be challenging and errors will inevitably occur. This may be devastating for patients and also leads to inappropriate treatment. Except perhaps for ovarian cancer,⁵ prostate cancer⁶ and germ cell tumours,⁷ the diagnosis of recurrence based solely on tumour marker elevation is particularly risky, because of the low sensitivity and specificity of these tests in most solid tumours. Because of the lack of tissue morphology, cytology-based diagnoses appear to result in higher rates of incorrect diagnosis as compared to histologic examination.

Patient history

A 66-year-old woman was seen on a routine follow-up visit and complained of abdominal swelling and lower limb edema. She had a history of intra-hepatic cholangiocarcinoma and breast cancer.

She had been in complete remission of her intra-hepatic cholangiocarcinoma, treated 9 years earlier by enlarged left hepatectomy. Her past surgical history included a radical total hysterectomy for a carcinoma in situ of the cervix. Three years earlier she had undergone conservative surgery of the left breast. The tumour was an invasive ductal carcinoma, and histoprognotic factors were as follows: size of 24 mm, gra-

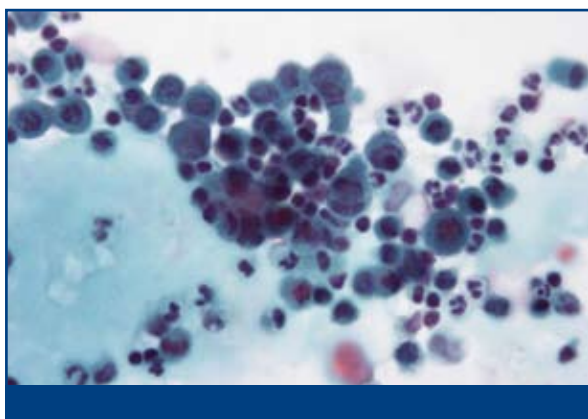


Figure 1. Cytology of the ascites.

de 3, node-negative, ER(-), PR(-), Her-2(-) and Ki67 expressed in up to 80% of the cells. The disease was considered at high risk of recurrence and the patient received adjuvant chemotherapy consisting of 6 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) and radiotherapy.

An MRI of the upper abdomen, performed as part of her routine follow-up schedule, showed the presence of ascites but no evidence of liver recurrence. The FDG-18 PET-CT was completely normal. Tumour markers were elevated, with a CA 19.9 at 136 U/mL (N<37) and a CA 125 at 345 U/mL (N<25). CA 15.3 levels were normal at 14.6 U/mL (N<25). A CT-scan of the abdomen performed 3 weeks after the initial MRI showed bilateral pleural effusions as well as persistent widespread ascites. Ascites drainage had to be performed daily and yielded up to 5 litres a day. Cytology of the ascites was consistent with an adenocarcinoma (*Figure 1*). The possibility of chemotherapy was discussed with the patient, but at this point it was still unclear whether the patient had breast cancer or cholangiocarcinoma recurrence, or a new primary cancer.

Serum albumin levels were strikingly low (1.6 g/dL) and, strangely enough, ascites and widespread edema progressively improved with spironolactone treatment and appropriate feeding. Based on these findings, pathologists were urged to re-analyse the original ascitic fluid cytology. Immunohistochemistry (IHC) was negative for EMA, CA 19.9, ER, PR and CK20. There was a mild staining for CK, highlighting reactive mesothelial cells. Based on the IHC profile and careful review of the histologic and IHC characteristics of the previous cancers (cholangiocarcinoma and breast), the pathologists could no longer confirm the presence of malignant cells in the ascitic fluid. The atypical cells described initially correspond to reactive

mesothelial cells which can be very challenging to identify through cytology alone. Suspected neoplasia in effusions should always be confirmed by IHC to avoid false positive cases.

The patient was finally diagnosed with small bowel protein-losing enteropathy (In-111). The ascites slowly disappeared and tumour markers gradually returned to normal levels.

Interestingly, the patient had presented at the emergency room 6 months earlier with clinical symptoms of acute viral hepatitis (severe jaundice, increased liver enzymes), immediately after returning from a long trip to Morocco. At that time, serologies for ordinary causes of infectious hepatitis were negative.

Discussion and conclusions

This case report highlights the importance of an accurate diagnosis of cancer recurrence and in particular the fact that tumour marker rise and cytology results should always be interpreted with caution and in light of clinical findings. In the case of this patient, physicians were attentive to the fact that malignant ascites is not expected to resolve with diuretics. In addition, either recurrence of an intrahepatic cholangiocarcinoma 9 years after initial treatment or of a 'triple-negative' breast cancer with ascites only would be uncommon.

Clinicians should constantly be on the lookout for inconsistencies and never hesitate to request pathology review or re-biopsy when appropriate. The sensitivity of cytologic detection of malignancy in ascites is only 58 to 75 percent,⁸ and reactive mesothelial cells in ascites can be mistaken for malignant cells in a wide variety of conditions such as hepatic cirrhosis, chronic uraemia, chemotherapy administration and peritoneal dialysis.⁹

Though not always easy in daily practice, clinicians should try to work closely with pathologists, who are often unaware of the presenting and/or new clinical findings and who may add complementary tests (i.e. IHC). When appropriate, not simply rushing to start treatment may also be a wise decision, as illustrated in this case. The natural course of the disease will eventually lead to the correct diagnosis, though this requires a high level of patient-clinician communication and trust, as under such circumstances physicians are often under pressure to make decisions and start treatment.

Finally, there are numerous potential causes of tumour marker elevation, many of which are benign.¹⁰ CA 125, for instance, is increased in case of ovarian, endometrial, breast, lung, and pancreatic

Key messages for clinical practice

1. Cytologic findings must always be interpreted in light of clinical findings.
2. A tumour marker elevation can have a benign cause, even in a patient with a history of cancer.
3. Clinicians and pathologists must interact more closely.

cancer. It is also elevated in numerous benign conditions, such as endometriosis, uterine leiomyoma, cirrhosis, peritonitis, pancreatitis and pelvic inflammatory disease. Furthermore, CA 125 levels are increased in the presence of pleural or peritoneal fluid or disease involvement. Approximately 1% of healthy women have increased levels of CA 125. Menstruation and pregnancy can also cause an increase in CA 125. CA 19.9 can be elevated in benign pancreaticobiliary disorders like acute cholangitis as well as in cirrhosis.

An extensive discussion of the pathogenesis and clinical course of small bowel protein-losing enteropathy, which was the final diagnosis in this case, lies beyond the scope of this report. Briefly, it is a highly heterogeneous condition characterized by an excessive loss of serum proteins into the gastrointestinal tract, resulting in hypoproteinemia, edema, and, in some cases, pleural and pericardial effusions.

It was hypothesized that it could be related to the previous episode of hepatitis, thus of infectious origin, but this could not be established with certainty retrospectively.

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