Commentary

Elevation of tumour marker CA-125 in serum & body fluids: interpret with caution

The cancer antigen (CA) -125 is a high molecular mass glycoprotein produced both by ovarian cancer cells as also by normal cells of tissues derived from coelomic epithelium. Serum CA-125 levels are used as a marker of tumour activity in patients known to have ovarian carcinoma and commercial tests for serum CA-125 have been available since 1983. In women with histologically proven ovarian carcinoma, levels of serum CA-125 are elevated >35 U/ml in more than 80 per cent of cases. Levels are also measured after debulking surgery and during chemotherapy.

Response to chemotherapy is quite usefully assessed in ovarian carcinoma patients who have a high persisting level of serum CA-125 after surgery. It provides the oncologist with a marker of disease activity that should drop progressively with each successive dose of treatment. Ease of access to the glycoprotein marker in the blood is crucial to its practical use in the clinic. Relapse after completion of treatment for ovarian carcinoma may also be monitored using serum CA-125 levels, especially in those patients who had a high tumour marker level prior to their initial treatment. A relatively small proportion, nearly 20 per cent, of ovarian carcinoma patients will not produce elevated serum CA-125 levels and is termed “marker negative”. Repeated measurement of this marker will not usually provide useful information and can be omitted.

However, elevation of CA-125 levels may occur in malignant conditions other than ovarian cancer, in benign diseases and in 1-2 per cent of normal healthy individuals. Some of the malignant conditions associated with elevated tumour marker include lung, bladder, gastric, hepatic and pancreatic cancers, leukaemia, non-Hodgkin’s lymphoma and mediastinal teratoma. This tumour marker is also elevated in pleural effusion associated with Meigs’ syndrome secondary to ovarian fibroma and pseudo-Meigs’ syndrome related to other benign pelvic tumours.

Benign conditions associated with elevated CA-125 levels are diverse and include cardiac failure, pleuropulmonary diseases, chronic liver disease, connective tissue disease, peritoneal dialysis and recent surgery. In a Spanish study of 380 randomly selected patients attending a general hospital clinic, 16 per cent had CA-125 levels greater than 35 U/ml. The most frequent diagnoses in women were pulmonary diseases and heart failure, and the most frequent diagnosis in men was hepatic cirrhosis. These benign conditions generally represent injury or proliferation of mesothelial cells leading to serosal effusions (pleural effusion or ascites). Given the similar embryonic developmental origins of peritoneal and pleural lining cells, it is hardly surprising that irritation or inflammation of either tissue results in an elevated secretion of CA-125 into the fluid.

Serum CA-125 levels are generally found to be higher in malignant conditions compared to benign conditions. Any cut-off value should be interpreted with caution. Levels exceeding 1000 U/ml have been described in benign conditions associated with
massive pleural effusion and ascites. Kalantri et al. in this issue have studied CA-125 levels in pleural effusion and ascitic fluid. In this study, all patients with ascites and 70 per cent with pleural effusion had elevation of tumour marker in body fluid when the aetiology was tuberculous or pyogenic. Levels of tumour marker were significantly higher in ascitic fluid compared with pleural effusion leading to suggestion that peritoneal epithelium had a greater capacity to secrete CA-125 than pleural epithelium. Their findings are in contrast with another recent study from India where elevated CA-125 in peritoneal fluid was found in only one out of 36 patients with TB peritonitis. Measurement of ascitic fluid levels of tumour markers like CA-125 has never been a routine part of ovarian cancer management in the clinic, for various reasons. Likewise, CA-125 levels in pleural fluid are not routinely measured for ovarian or other cancers. Simultaneous measurement of CA-125 in serum and body fluids and/or simultaneous assay of CA-125 with a panel of other tumour markers may improve diagnostic accuracy in malignant and non-malignant diseases.

Elevation of CA-125 in serum, and less commonly in other body fluids, will continue to challenge the diagnostic acumen of physicians. The challenges are likely to be greater for physicians managing patients of South Asian ethnicity. The first scenario can be of a female patient with large pleural effusion, negative tuberculin skin test, negative TB smears, negative cytology and markedly elevated CA-125 level. While in a 20 yr old the diagnosis of malignant effusion may be difficult to accept but in a 70 yr old such a diagnosis can be easily proposed by the physician and a terminal prognosis accepted by the family. Systemic symptoms of anorexia, weight loss and cachexia are common to TB, cancer and other systemic diseases. In tuberculous pleural effusion smear examinations for acid fast bacilli are rarely positive. TB culture takes several weeks to report and the yield of positive culture result is low. In such a case needle pleural biopsy would be the investigation of choice as it is minimally invasive and is likely to be positive showing chronic granulomatous inflammation in majority of patients with TB effusion.

Differentiation between abdominal TB and malignancy may be even more difficult. Abdominal distension, abdominal pain, abdominal mass and weight loss are common symptoms. Abdominal TB is associated with omental thickening, mesenteric lymphadenopathy, pelvis or tubo-ovarian mass, ascites and elevation of CA-125 levels in serum and ascitic fluid. Ascitic fluid examination reveals an exudate with lymphocyte predominance. Yield of TB smear and culture remains very low. Tuberculin skin test has limited usefulness in high prevalence area and a negative skin test may be seen in many patients with histologically confirmed abdominal TB. While detection of Mycobacterium by polymerase chain reaction has high sensitivity but availability, cost and quality control are important limiting factors in developing countries. Peritoneal biopsy (e.g., laparoscopic) would clinch the diagnosis in such cases. Response to anti-TB therapy is apparent within few weeks, with symptoms improving first but resolution of inflammatory masses may take several months.

Chronic liver disease, secondary to viral or toxic cause, is another common medical condition that is prevalent in South Asian developing countries. In advanced disease stages, rapidly declining general health is associated with abdominal distension and pleural effusion. Pleural effusion is a transudate that is often large (hepatic hydrothorax). This may be recurrent mimicking malignancy and may become a source of considerable discomfort. Very high levels of CA-125 may suggest an underlying ovarian cancer but raised tumour marker may also occur with hepatocellular carcinoma or simply due to presence of large amount of ascites and pleural effusion. Decisions based on elevated tumour marker may lead to inappropriate management and suboptimal symptom palliation.
From an oncologist’s point of view, it would seem that there will be limited general application of a test on ascitic or pleural fluid that does not reliably distinguish between different malignant tumours or indeed between benign and malignant causes. The lack of specificity of this glycoprotein makes its measurement unhelpful as a screening tool. Serum CA-125 should, therefore, not be used as a screening tool for picking up asymptomatic cases of ovarian cancer. The American College of Physicians (ACP), The European Group on Tumour Markers (EGTM), The European Society of Medical Oncology (ESMO), The National Institute for Health (NIH) and The National Academy for Clinical Biochemistry all agree on this point. Research is ongoing on algorithms that calculate risk of ovarian cancer based on serial CA-125 values and referral of patients at highest risk for transvaginal sonography. Use of the algorithm is currently being evaluated in a trial with 200,000 women in the UK that will test critically the ability of a two-stage screening strategy to improve survival in ovarian cancer 8.

A general physician may remember that some common medical conditions can be associated with elevated tumour marker in serum and in body fluids. Cardiac failure and chronic liver disease can be picked up by a careful bedside clinical examination. Tuberculosis may be less easy to confirm and indeed facilities for further confirmatory tests, in many under resourced areas, may either be not readily available or beyond the financial means. A therapeutic trial of anti-TB medications for 4-6 wk would be justified if doubt persists about the final diagnosis.

Finally from a researcher’s perspective, CA-125 is an ovarian tumour marker and the challenge is to detect early stage ovarian cancer that can be cured with currently available therapy. CA-125 is also a marker of mesothelial proliferation and there is still much to learn about the mechanisms of CA-125 production at various sites in the body and its utilization in medical conditions other than ovarian carcinoma.

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References


