Section A -Research paper

Role of Carcinoembryonic antigen (CEA) in Diagnosis of Pleural Effusion

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Abstract:

Conventional tests are not always helpful in making a diagnosis of pleural effusion (PE). Many studies have investigated the utility of pleural carcinoembryonic antigen (CEA) in the early diagnosis of PE.

Keywords: CEA, PE, Pleural Effusion.

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Introduction

Carcinoembryonic antigen (CEA) is a non-specific serum biomarker that is elevated in various malignancies such as colorectal cancer, medullary thyroid cancer, breast cancer, mucinous ovarian cancer, etc. It was first detected in colon cancer cells by Freedman and Gold and eventually was found in various other epithelial cells in the stomach**,** tongue, esophagus, cervix, and prostate. It is a glycoprotein with a molecular weight of 200 kDa and is normally derived from embryonic endodermal epithelium in the fetus, controlled by fetal oncogenes. It usually disappears from serum after birth; however, small quantities of CEA may remain in colon tissue. CEA and related genes (29 of which 18 are normally expressed) constitute the CEA family in human beings and are clustered on chromosome 19q13.2 **(1).**

Since it is associated with various types of malignant and nonmalignant medical conditions, elevated serum CEA is not a definitive marker of a particular site of cancer origin **(2)**. Therefore, it is not recommended for routine screening or diagnosis of cancers by itself. CEA is currently being studied as a target for various cancer-directed therapies **(3)**.

Pathophysiology

CEA belongs to the immunoglobulin family called CEA-related cell adhesion molecules (CEACaMs). CEA is closely associated with various functions of

endothelial cells, including adhesion, proliferation, and migration of cells both in vivo and in vitro. It is present on the endoluminal side of the cell membrane of normal cells and is thought to inhibit apoptosis and hence is involved in tumor pathogenesis. Although CEA is predominantly associated with gastrointestinal tumors, literature shows its close correlation with breast, lung, ovarian, mucinous adenocarcinomas of the cervix and thyroid cancers **(4).**

Specimen Requirements and Procedure

The test for CEA measurement is usually conducted on a blood sample collected by the health care personnel/phlebotomist. A small quantity of the blood (3 to 5 cc) is collected in a vial and sent to the laboratory to estimate the CEA Level. The risks associated with such a procedure are minimal, including needle site pain/stinging, bruising, bleeding, or infections. The procedure takes less than five minutes and does not need specific requirements, such as fasting. Occasionally, a CEA test is performed on other bodily fluids such as pleural fluid, peritoneal fluid, or rarely cerebrospinal fluid **(1)**.

Testing Procedures

A large number of commercially available products utilize different technologies such as sandwiched enzyme-linked immunosorbent assay (ELISA), immunonephelometry, chemiluminometric immunoassay (CLIA), immunomagnetic reduction (IMR), etc. CEA levels can fluctuate based on the type of testing procedure utilized. Therefore, discordant serial CEA levels need to be carefully correlated with differences in testing procedures. Using monoclonal antibodies directed against the six reactive isotopes of CEA in specific assays could result in erroneous findings amongst those patients who have been previously treated with monoclonal antibodies **(1).**

Interfering Factors

CEA is predominantly metabolized in the liver. Therefore, hepatic and biliary dysfunction can be associated with elevated levels causing false positives. Because of high first-pass hepatic metabolism, significantly elevated levels correspond to either CEA-producing tumors or metastases outside portal venous drainage territory. Tumor differentiation can also affect the CEA levels, with higher CEA levels seen in well-differentiated cancers **(5)**. The CEA level is an important tumor marker that may be increased depending on the intensity of exposure to tobacco smoke **(6)**.

Results, Reporting, and Critical Findings

Ranges

In healthy, non-smoking adults, CEA is considered within normal limits at a level of <=3.0 µg/L. Smokers may have elevated CEA, and therefore it is considered within normal limits at a level of <5 µg/L. Pre-treatment serum CEA levels of greater than five µg/L but less than ten µg/L suggests localized disease and a low likelihood of recurrence, hence a favorable prognosis. A serum level of >10 µg/L indicates a higher likelihood of recurrence and poor prognosis. Serum titers of >20 µg/L are usually associated with metastatic disease in breast

and colon cancers. However, given the variability in CEA expression or secretion, values <2.5 µg/L do not necessarily rule out primary, recurrent or metastatic cancers, either. For colorectal cancers, a CEA threshold of 2.5 µg/L carries a sensitivity of 82% and a specificity of 80%, while a threshold of 10 µg/L carries a sensitivity of 68% and specificity of 97% **(7).**

Advantages

Serum-based CEA testing is a cost-effective surveillance method in various cancers and is part of various national and international surveillance guidelines. It is also an equally important tool to assess ongoing response to palliative treatments in metastatic cancers, along with imaging studies. It is a very easy and widely available tool, even in a community setting**(1)**.

Drawbacks

Due to low sensitivity and specificity, it cannot be used as a screening test to detect malignancies. Although used for detecting recurrence of cancer after primary surgical and adjuvant treatments, a single value (one-time measurement) is inadequate due to low sensitivity (high false-positive rate), and serial measurements (trend) are essential. Raising CEA cut-off (>10 µg/L) and combining it with other modalities such as CT scans of chest, abdomen, and pelvis at 12 months intervals is recommended instead of using it as a sole test for monitoring recurrence of colorectal cancer. People exposed to certain animal antigens may develop antibodies to CEA that might affect CEA levels and lead to unreliable results. Smokers are highly likely to get false-positive results; therefore, the test is unreliable in active smokers. It is not recommended to use CEA for follow-up in active smokers with colon cancer after primary treatment **(1)**.

Clinical Significance

CEA in Colorectal Cancer Diagnosis and Post-Treatment Surveillance to Monitor Recurrence/Residual Tumor

CEA is a strong prognostic biomarker in patients with colorectal cancer who underwent surgical resection and adjuvant chemotherapy **(8).** Elevated CEA level of >5 µg/L at the time of new diagnosis of colorectal cancer is associated with poor prognosis. However, normalization of elevated CEA levels after surgery is not associated with a poor prognosis. Hence routine assessment of CEA before surgical treatment is not indicated, and usually, post-operative detection is more useful in detecting recurrence within the first year of surgery and prognostication **(9).** Follow-up with CEA level in patients with colorectal cancers after primary treatment was found effective in detecting cancer recurrences that can be treated with curative intent in the follow-up after colorectal surgery (FACS) trial **(10).**

CEA in Medullary Carcinoma of the Thyroid

According to the revised guidelines of the American Thyroid Association for the management of medullary thyroid carcinoma, CEA is not a specific biomarker for medullary carcinoma. However,

measuring CEA levels is very helpful in assessing the disease progression and post thyroidectomy monitoring. According to Chen et al., the North America Society for Neuroendocrine Tumors (NANETS) guidelines, preoperative levels above 30 µg/L indicate the extra-thyroid spread of the disease. In contrast, levels greater than 100 µg/L are associated with invasive disease, including lymph node involvement and distant metastasis **(1)**.

CEA in Ascitic Fluid

CEA levels are proven to be of some value in cases where ascitic fluid cytology is inconclusive. Serum levels greater than 5 µg/L are suggestive of carcinoma. However, higher values were common in cancers with peritoneal involvement with a sensitivity of 51 % and specificity of 97% for carcinomatosis ($p < 0.01$) **(1)**.

CEA in Pleural Fluid

An elevated CEA level in a patient with pleural fluid and negative cytology precludes more invasive modalities such as VATS guided biopsy to rule out malignant etiology. In contrast, lower CEA levels may support a close follow-up **(11)**.

Among all tumour markers, the carcinoembryonic antigen (CEA) is the most examined and frequently used marker for pleural fluid. Although there have been numerous scientific evaluations, its significance remains controversial due to varying results. The high-quality papers among those published have shown high specificity, however sensitivity largely varies.

In lung adenocarcinoma, CEA elevation can be found in both serum and malignant pleural effusion. However, CEA elevation in cytologically negative pleural effusion in the presence of adenocarcinoma without pleural infiltration has not been described **(12)**.

CEA in Non-Small-Cell Lung Cancer (NSCLC)

Due to limited preoperative imaging sensitivity, 30% of patients with stage I NSCLC have positive N2-N3 nodes at the time of diagnosis. Preoperative CEA levels help identify patients with advanced disease that might be missed on imaging. Higher CEA levels correlate with advanced stage, nodal metastasis, and poor survival. It potentially identifies the patient population who would benefit from invasive mediastinal lymph node staging by mediastinoscopy or endoscopic ultrasound and benefit from neoadjuvant chemotherapy or chemoradiotherapy than upfront surgery**(13).**

CEA in Breast Cancer

Currently, routine use of CEA in screening for breast cancer is not recommended as per ASCO due to limited sensitivity and specificity. However, in addition to CA 15-3 and CA 27.29, CEA and diagnostic imaging can be used to monitor patients with metastatic disease receiving active therapy **(14).**

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