

Story from the frontlines:

A woman in her fifties presented to clinic with nonspecific abdominal pain. As part of her workup she had a CA-125 level drawn which came back elevated at 210 (normal 35 U/mL or less). The patient was subsequently referred to a gynecologist due to concern for ovarian malignancy. Pelvic ultrasound and abdominal CT were pursued which came back negative. She had a subsequent CA-125 level drawn a few months later which was elevated at 188. Oncology was informally consulted by the primary physician, who stated that given the down-trending value, a non-malignant etiology is more likely, and to repeat the value a third time and not pursue further testing if downward trend continues. Three months later, the patient had a repeat CA-125 level which came back at 66, thus negating the need for further testing.

Teachable moments:

Ovarian cancer is the fifth leading cause of cancer-related deaths in the United States. In three-fourths of cases, it is diagnosed in advanced stages, necessitating the need for a reliable, sensitive, and specific biomarker. CA-125, a macromolecular glycoprotein, emerged as a potential biomarker for ovarian cancer in the 1980s. However, we are now aware of its low sensitivity and specificity, especially in early disease. Additionally, CA-125 can be elevated in a variety of other conditions, including pregnancy, endometriosis, menstruation, inflammatory diseases in the peritoneum or GI tract, and 1% of healthy women.¹ In addition, pertinent to our case, CA-125 can be elevated in patients with severe heart failure, and the degree of elevation has been shown to correlate with disease severity and BNP.²

In 2004, a retrospective study of 751 females in the UK looked at every patient who had a CA-125 measurement from 2000-2002 in one hospital system. A CA-125 level was obtained due to suspicion for ovarian cancer in only 34% of patients. The most common reason to obtain a CA-125 was suspicion for general malignancy (44%), of which 36% of these patients presented with abdominal pain (15% of total cases). Of the patients that did have a positive CA-125, the most common subsequent testing included abdominal/pelvic ultrasound or CT. The study concluded that CA-125 is widely used for reasons other than its purpose.³

Another interesting review of the literature was a case report by Klopicka et al. This was a case of a 32 year old woman with Crohn's disease and ascites concerning for ovarian malignancy. A CA-125 level was obtained which was elevated, and imaging was pursued to rule out ovarian malignancy. CA-125 elevation was ultimately attributed to ascites and gut inflammation secondary to Crohn's disease.⁴ This case parallels my patient's case. It is highly likely that GI edema and inflammation secondary to both lymphocytic colitis and HFrEF contributed to an elevated CA-125.

Per the USPSTF, the most recent evidence recommends against using CA-125 as a screening tool for ovarian cancer in asymptomatic women, as it does not significantly change morbidity or mortality.⁵ In addition, screening can lead to significant harm, including surgical intervention in women with a false positive, unnecessary radiation exposure, costs to the health care system, and social distress about a questionable cancer diagnosis.

The best uses of this marker currently include helping to predict prognosis, as well as monitoring response to therapy in ovarian cancer patients. Consistently elevated levels despite

chemotherapy typically suggests worse outcomes.⁶ In addition, CA-125 elevation after remission strongly suggests recurrence of malignancy, and has been shown to preclude radiological or symptomatic findings by 2-4 months. Thus, CA-125 is FDA approved for monitoring of epithelial ovarian cancer. It is also approved for screening together with a transvaginal ultrasound in BRCA1 positive patients.⁷

References:

Dasgupta A Wahed A. (2014). Chapter 14 – Tumor Markers. In *Clinical Chemistry, Immunology and Laboratory Quality Control*.

Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res.* 2019;12(1):28. Published 2019 Mar 27. doi:10.1186/s13048-019-0503-7

Henderson JT, Webber EM, Sawaya GF. Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA.* 2018;319(6):595–606. doi:10.1001/jama.2017.21421

Ibraheemi A, Dasgupta A, Wahed A. (2013). Chapter 12 – Pitfalls in Tumor Marker Testing. In *Accurate Results in the Clinical Laboratory*.

Kłopocka M, Liebert A, Bielińska J, Manerowski M. Diagnostic Difficulties in Woman with Crohn's Disease, Ascites, and Elevated Value of Serum CA125 Antigen. *Case Rep Med.* 2014;981726. doi:10.1155/2014/981726

Moss EL, Hollingworth J, Reynolds TM. The role of CA125 in clinical practice. *Journal of Clinical Pathology.* 2005;58:308-312. doi:10.1136/jcp.2004.018077

Nolen, BM, Lokshin AE. (2014). Chapter 45 - Pancreatic and ovarian cancer biomarkers. In *Biomarkers in Toxicology*. Retrieved from <https://www.sciencedirect.com/science/article/pii/B9780124046306000452#bib42>.

USPSTF Final Recommendation Statement. (2018). Retrieved from <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/ovarian-cancer-screening>.

¹ Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res.* 2019;12(1):28. Published 2019 Mar 27. doi:10.1186/s13048-019-0503-7

² Dasgupta A Wahed A. (2014). Chapter 14 – Tumor Markers. In *Clinical Chemistry, Immunology and Laboratory Quality Control*.

³ Moss EL, Hollingworth J, Reynolds TM. The role of CA125 in clinical practice. *Journal of Clinical Pathology*. 2005;58:308-312. doi:10.1136/jcp.2004.018077

⁴ Kłopocka M, Liebert A, Bielińska J, Manerowski M. Diagnostic Difficulties in Woman with Crohn's Disease, Ascites, and Elevated Value of Serum CA125 Antigen. *Case Rep Med*. 2014;981726. doi:10.1155/2014/981726

⁵ USPSTF Final Recommendation Statement. (2018). Retrieved from <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/ovarian-cancer-screening>.

⁶ Dasgupta A Wahed A. (2014). Chapter 14 – Tumor Markers. In *Clinical Chemistry, Immunology and Laboratory Quality Control*.

⁷ Nolen, BM, Lokshin AE. (2014). Chapter 45 - Pancreatic and ovarian cancer biomarkers. In *Biomarkers in Toxicology*. Retrieved from <https://www.sciencedirect.com/science/article/pii/B9780124046306000452#bib42>.