



CASE REPORT

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Elevation of cancer antigen 15-3 owing to oncocytic renal neoplasm in a patient without evidence of breast cancer recurrence on follow-up: a case report

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Abstract

Background Cancer antigen 15-3 is a protein that clinicians commonly measure to monitor outcomes and response to treatment in patients with breast cancer. However, cancer antigen 15-3 can also be elevated in other, benign and malignant conditions.

Case presentation A 73-year-old White woman with history of breast cancer presented to her primary care physician with right hip pain, and laboratory testing revealed elevated cancer antigen 15-3. Further workup with radiographic imaging revealed a large mass in her right kidney. The renal mass was subsequently removed, and the cancer antigen 15-3 level returned to normal.

Conclusions Elevation of cancer antigen 15-3 owing to causes other than breast cancer recurrence can be a potential diagnostic pitfall during a patient's follow-up. It is important for clinicians to be aware of the limitations of cancer markers and to utilize a combination of diagnostic tests for patient evaluation.

Keywords Cancer antigen 15-3, Oncocytic renal neoplasm, Elevated tumor marker, Breast cancer, Case report

Background

Tumor marker 15-3, also known as cancer antigen 15-3, is a protein that is often elevated in the blood of individuals with breast cancer. It is used as a marker to monitor the effectiveness of treatment and to detect recurrence of the disease. However, it has been known to be elevated in benign conditions and can result in false positives.

Case presentation

A 73-year-old White woman with a remote history of stage IA triple-positive breast cancer in her right breast was diagnosed 5 years ago. She underwent lumpectomy and sentinel lymph node biopsy. Her diagnostic pathology was estrogen receptor (ER) 95%, progesterone receptor (PR) 92%, human epidermal growth factor receptor 2 (HER2) positive [immunohistochemistry (IHC) 3+] pT1cN0. She received adjuvant trastuzumab and paclitaxel for 3 months and adjuvant radiation, followed by adjuvant trastuzumab for 9 months.

Four years later, the patient's primary care physician ordered a magnetic resonance imaging (MRI) examination of the right hip due to right hip pain. It was unremarkable except for osteoarthritis. He also ordered CA 15-3 and noted an elevated level of 293.9 U/mL (normal range 0–30 U/mL).

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The patient was referred to a medical oncologist for her abnormal elevated tumor markers. Other than mild joint pain, her medical history was unremarkable. The physical examination was pertinent only for an old healing scar from the right lumpectomy. Mammography with ultrasound and subsequent MRI of the breast revealed only postsurgical changes. Computed tomography (CT) of the abdomen/pelvis and whole-body positron emission tomography (PET) scan revealed a hypermetabolic $11.2 \times 9.9 \times 9.2 \text{ cm}^3$ large enhancing mass within the mid and lower poles of the right kidney, highly suggestive of renal cell carcinoma. Based on this finding, she was referred to a urologic surgeon and subsequently underwent right radical nephrectomy. The surgical pathology revealed complete excision with clear margins. On post-operative histologic examination, the tumor was composed of a uniform population of plump cells with solid and nested growth patterns. The cells had eosinophilic cytoplasm and nuclei with variations in size and shape. Of note, some nucleoli were prominent. These features are characteristic of an oncocytic renal neoplasm with unknown malignant potential. IHC with an antibody to CA 15-3 resulted in diffuse labeling of the tumor cells (Fig. 1). Three months after surgery, the CA 15-3 concentration was within the normal range at 19.8 U/mL (Fig. 2).

Discussion and conclusions

CA 15-3 is a protein that is found on the surface of many normal epithelial cells and that has been linked to changes in metabolism in cancer cells [1]. It is composed of two subunits that remain linked and has a heavily glycosylated outer domain. CA 15-3 may be useful in predicting the outcome and response to treatment in breast cancer [2, 3], but it is not typically used to monitor asymptomatic breast cancer follow-up [4].

Despite the usefulness of CA 15-3 for monitoring breast cancer recurrence, physicians must realize that other conditions can cause high CA 15-3 levels in patients without active breast cancer. Table 1 summarizes case reports of patients with or without history of breast cancer who showed elevated CA 15-3 in the absence of active breast cancer. In patients with history of breast cancer that was resolved, causes for the elevated CA 15-3 included pernicious anemia [5], normal pregnancy [6], and hypothyroidism [7]. Like the patient in the present case report, the patients in the three cited case reports showed normal CA 15-3 levels after receiving treatment for the cause of their CA 15-3 elevation.

CA 15-3 levels can also be elevated in patients without history of breast cancer and in the absence of active breast cancer. In our patient, an oncocytic renal neoplasm caused the elevated CA 15-3 levels in a patient with history of breast cancer. A previous case report noted elevated CA 15-3 level owing to a benign renal oncocytoma but in the absence of history of breast cancer [8]. After removing the affected kidney, the CA 15-3 levels returned to normal. Another case report showed elevation of four tumor markers, including CA 15-3, owing to systemic lupus erythematosus [9]. After treatment, this patient's CA 15-3 level reduced but remained above the normal range. Other case reports showed elevated CA 15-3 levels due to ovarian sarcoidosis [10] or idiopathic pulmonary fibrosis [11] but did not report follow-up CA-15-3 values.

CA 15-3 is expressed in healthy kidneys [12], which may contribute to the CA 15-3 expression in the kidney tumor found in our patient. More specifically, researchers observed CA 15-3 expression in the distal tubules and collecting ducts of the nephrons of healthy kidneys but not in the proximal tubules [12]. Renal cell carcinomas also commonly express CA 15-3 [12]. As mentioned

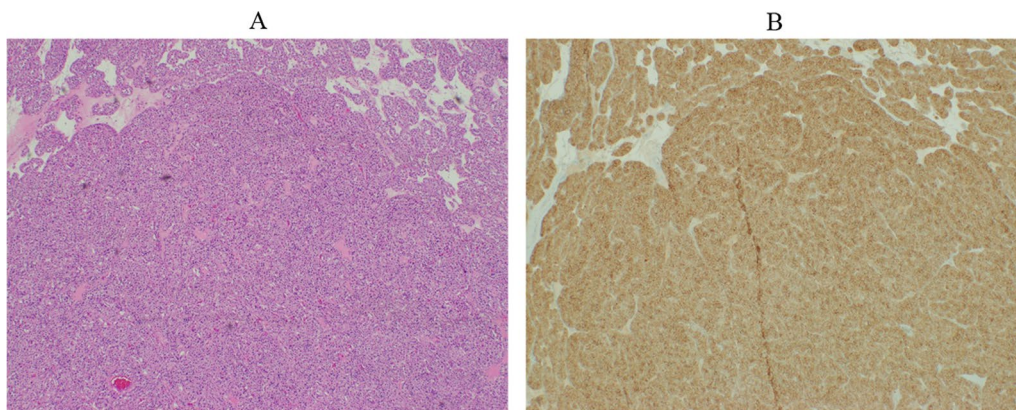


Fig. 1 Oncocytic renal neoplasm pathology. **A** Hematoxylin and eosin stain. **B** Immunohistochemistry showing diffusely positive cancer antigen 15-3 stain on tumor cells

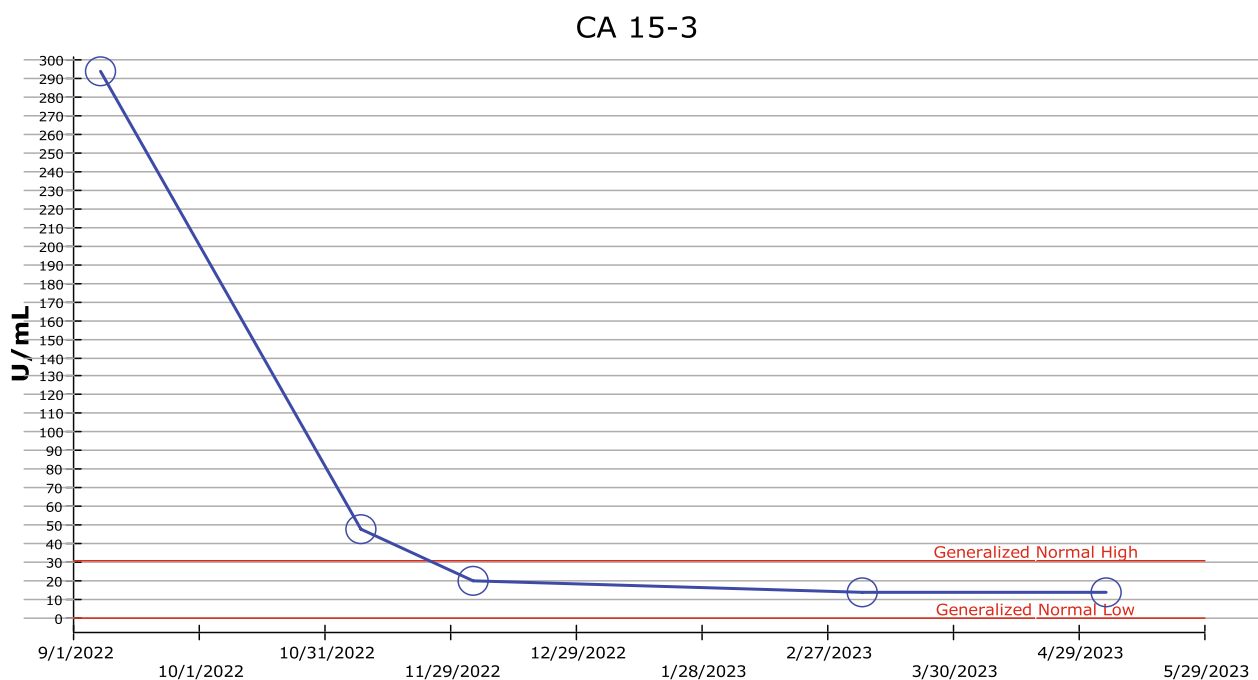


Fig. 2 Graph of the serum cancer antigen 15-3 levels over time. Each circle represents a measurement. The upper and lower horizontal, dashed red lines represent the generalized normal high and low values of cancer antigen 15-3, respectively

Table 1 Previous reports of elevated cancer antigen 15-3 in the absence of active breast cancer

Authors and year	CA 15-3 level (U/mL)	Breast cancer history	Disease context	Ref.
Adachi et al. 2015	80	Yes	Pernicious anemia	[5]
Buonomo et al. 2019	92.6	Yes	Normal pregnancy	[6]
Aguiar-Bujanda et al. 2004	65.50	Yes	Hypothyroidism	[7]
Ghnassia et al. 2001	106	No	Renal oncocytoma	[8]
Bevan et al. 2016	448	No	Systemic lupus erythematosus	[9]
Tsiodras et al. 2018	73.9	No	Ovarian sarcoidosis	[10]
Altube Urrengoetxea et al. 2007	560	No	Idiopathic pulmonary fibrosis (male patient)	[11]

This table includes case reports of patients with or without history of breast cancer who showed elevated CA 15-3 in the absence of active breast cancer

above, a renal oncocytoma in a patient without history of breast cancer also expressed CA 15-3 [8].

The most recent American Society of Clinical Oncology (ASCO) guidelines for the use of biomarkers in breast cancer therapy [13] and a recent retrospective analysis of CA 15-3 use for monitoring breast cancer relapse [14] do not suggest using CA 15-3 alone for therapy decisions or monitoring relapse, respectively. In 2015, the ASCO recommended using CA 15-3 only as an adjuvant assessment with respect to making decisions for therapy for metastatic breast cancer [13]. Similarly, the retrospective analysis concluded that the primary

methods for monitoring breast cancer relapse should include the patient's history, physical examination, and imaging [14]. The study found that patients with elevated CA 15-3 levels and symptoms of nausea, myalgia, or axial bone pain had a higher risk of breast cancer relapse [14]. Thus, this study recommends using CA 15-3 to supplement other parts of the patient's case when monitoring for relapse [14]. However, it does not recommend using CA 15-3 levels alone because the levels can be elevated in the absence of active breast cancer, especially in asymptomatic patients or patients with a body mass index greater than or equal to 25 [14].

This case report includes strengths and limitations. To our knowledge, we are the first to report a patient with elevated CA 15-3 levels due to an oncocytic renal neoplasm in a patient without evidence of breast cancer recurrence on follow-up. While we only report one patient's results, we believe that this case could be generalizable to other patients and can remind physicians that benign conditions can also cause elevated CA 15-3.

In conclusion, the patient's elevated tumor marker CA 15-3 led to the detection of a renal tumor. This case illustrates that elevation of CA 15-3 can be due to causes other than breast cancer recurrence and can be a potential diagnostic pitfall during a patient's follow-up. It is important for clinicians to be aware of the limitations of cancer markers and to utilize a combination of diagnostic tests for patient evaluation.

Abbreviations

ASCO	American Society of Clinical Oncology
CA	Cancer antigen
CT	Computed tomography
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PR	Progesterone receptor

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Not applicable.

Author contributions

SGC conducted the literature review and contributed to writing the manuscript. HX examined the renal pathology and contributed to the literature review. MAJ initiated and oversaw the research and contributed to writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study did not require Institutional Review Board approval because it does not meet the United States Department of Health and Human Services' definition of research. This work follows the principles of the Declaration of Helsinki. The patient provided consent to participate in this case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

We have no conflicts of interest with respect to this article.

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References

- Mehla K, Singh PK. MUC1: a novel metabolic master regulator. *Biochim Biophys Acta*. 2014;1845(2):126–35. <https://doi.org/10.1016/j.bbcan.2014.01.001>.
- Li X, Dai D, Chen B, Tang H, Xie X, Wei W. Clinicopathological and prognostic significance of cancer antigen 15-3 and carcinoembryonic antigen in breast cancer: a meta-analysis including 12,993 patients. *Dis Mark*. 2018;2018:9863092. <https://doi.org/10.1155/2018/9863092>.
- Perrier A, Boelle PY, Chretien Y, et al. An updated evaluation of serum sHER2, CA15.3, and CEA levels as biomarkers for the response of patients with metastatic breast cancer to trastuzumab-based therapies. *PLoS ONE*. 2020;15(1): e0227356. <https://doi.org/10.1371/journal.pone.0227356>.
- Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31(7):961–5. <https://doi.org/10.1200/JCO.2012.45.9859>.
- Adachi Y, Kikumori T, Miyajima N, et al. Postoperative elevation of CA15-3 due to pernicious anemia in a patient without evidence of breast cancer recurrence. *Surg Case Rep*. 2015;1(1):126. <https://doi.org/10.1186/s40792-015-0128-z>.
- Buonomo B, Noli SA, Santini A, Alviggi C, Peccatori FA. Can we trust tumour markers in pregnancy after breast cancer? A case of elevated CA 15-3 in the third trimester of pregnancy normalising after delivery. *Eccancermedicallscience*. 2019;13:979. <https://doi.org/10.3332/ecancer.2019.979>.
- Aguiar-Bujanda D, Bohn-Sarmiento U, Aguiar-Morales J. False elevation of serum CA 15-3 levels in patients under follow-up for breast cancer. *Breast J*. 2004;10(4):375–6. <https://doi.org/10.1111/j.1075-122X.2004.21369.x>.
- Ghnassia JP, Rodier JF, Eber M. Elevation of CA15-3 caused by a benign tumour. *Lancet Oncol*. 2001;2(2):102. [https://doi.org/10.1016/S1470-2045\(00\)00227-8](https://doi.org/10.1016/S1470-2045(00)00227-8).
- Bevan J, Richardson M. Diminution of falsely elevated tumour markers following immunosuppression for systemic lupus erythematosus with neurological involvement. *BMJ Case Rep*. 2016. <https://doi.org/10.1136/bcr-2016-214549>.
- Tsiodras S, Gouloumi AR, Tsakiraki Z, et al. Falsely elevated CA 15-3 levels in ovarian sarcoidosis with peritoneal involvement and ascites. *Case Rep Obstet Gynecol*. 2018;2018:2039730. <https://doi.org/10.1155/2018/2039730>.
- AltubeUrrangoetxea L, Salinas Solano C, AburtoBarrenetxea M, Moraza Cortes FJ, Ballaz Quincoces A, Capelastegui SA. Accelerated phase of idiopathic pulmonary fibrosis [Fase acelerada de la fibrosis pulmonar idiopatica]. *Arch Bronconeumol*. 2007;43(9):516–8. [https://doi.org/10.1016/s1579-2129\(07\)60117-7](https://doi.org/10.1016/s1579-2129(07)60117-7).
- Cao Y, Karsten U, Zerban H, Bannasch P. Expression of MUC1, Thomsen-Friedenreich-related antigens, and cytokeratin 19 in human renal cell carcinomas and tubular clear cell lesions. *Virchows Arch*. 2000;436(2):119–26. <https://doi.org/10.1007/pl00008210>.
- Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2015;33(24):2695–704. <https://doi.org/10.1200/JCO.2015.61.1459>.
- Shaikh ME, Hall S, Wen S, Liu H, Miah A, Salkeni MA. Retrospective analysis of the role of CA 15-3 as a biomarker for breast cancer relapse. *J Clin Oncol*. 2017;35(15_suppl): e23051. https://doi.org/10.1200/JCO.2017.35.15_suppl.e23051.

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