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Case Report

A Remarkable Case of Elevated Carcinoembryonic Antigen after Surgical Treatment of Rectal Cancer: A Search for its Mysterious Cause

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ABSTRACT

Introduction: Measuring carcinoembryonic antigen (CEA) serum levels is frequently used as a biomarker for recurrent disease in follow-up after treatment of colorectal cancer. However, it is also elevated to a significant degree in a number of other malignant and non-malignant conditions. In this case, we present a patient with ongoing elevated CEA levels without a clear cause.

Case Presentation: A 57-year-old female patient with adenocarcinoma of the rectum underwent neoadjuvant chemoradiation and a laparoscopic low anterior resection. During follow-up she presented without any clear symptoms but with an ongoing elevation of serum CEA levels, for which she underwent four sequential PET-CT scans within one year without any sign of malignancy. Other causes of elevated CEA levels were investigated and excluded by additional blood tests and imaging studies. Available literature was extensively reviewed but revealed no further possible explanations for the high CEA serum level.

Conclusion: The manifestation of an exponential rise of CEA levels following the treatment of colorectal cancer in the absence of abnormalities is a rare presentation and remains a mystery. The cause of the elevated CEA is yet to be elucidated.

Introduction

Serial measurements of carcinoembryonic antigen (CEA) serum levels can be indicative of recurrent disease after treatment of colorectal carcinoma and is therefore frequently used as a biomarker in follow-up [1]. However, it is also elevated to a significant degree in a number of other malignant and non-malignant conditions. This is due to its diverse functions in cell adhesion, in intracellular and intercellular signaling, and during complex biological processes such as cancer progression, inflammation, angiogenesis, and metastasis [2]. Common malignant causes for an elevated carcinoembryonic antigen include ovarian cancer, breast cancer, thyroid cancer and non-small cell lung cancer [3]. Benign causes contain cigarette smoking, mucinous cystadenoma of ovary/appendix, cholecystitis, liver cirrhosis, pancreatitis, inflammatory bowel disease and several medications [4].

In this case, we present a patient with ongoing elevating CEA levels without a clear cause.

Case Presentation

A 57-year-old female with a 32 pack per year smoking history and a past medical history of bilateral fibroadenoma and cataract and a family history of cardiovascular disease presented with a persistent change in bowel habits with rectal bleeding. Patient received no medication at the time and did not have any known allergies. During colonoscopy, a malignant looking tumour was found at 11cm from the anal verge. Pathological findings confirmed the diagnosis of adenocarcinoma of the

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rectum. The CEA level was elevated, 10.4ng/ml (normal level <5ng/ml), and CT and MRI imaging showed a cT3N2 rectal tumour without evidence of distant metastases. Additional findings on the 18F-FDG PET-CT scan were benign nodules in the lung, described as calcifications and a pancreas cyst with a homogenous aspect without solid components for which follow-up was advised. The patient received neoadjuvant chemoradiation therapy (25x2Gy + 1300mg capecitabine on treatment days). The capecitabine was discontinued after the first dose because of coronary spasms. Radiotherapy was continued and 6 weeks after final treatment, a re-staging MRI was performed. This showed a partial response (ycT2N1) and a laparoscopic low anterior resection with an end-to-end stapled anastomosis was performed.

Despite initial good clinical recovery, patient developed a leucocytosis on day 4 postoperatively and a CT-scan was executed which revealed anastomotic leakage. A re-laparoscopy with a deviating ileostomy was performed, together with placement of a pre-sacral drain and ceftriaxone/metronidazole intravenously. After this, recovery looked promising until patient developed a pre-sacral abscess for which she received an Endo-sponge® for drainage. At the same time, patient suffered from stoma dermatitis which was healed after surgical revision of the ileostomy. Further recovery was without further complications. Final pathology revealed γpT3N0 adenocarcinoma. Patient underwent regular follow-up according to the Dutch National Oncological Guidelines and the ileostomy was closed 3,5 months after the initial surgery [5].

I Follow-up - the Rise of CEA

The first postoperative CEA level was 2.8, followed by 4.4 three months later. Patient was asymptomatic and during this early follow-up, she underwent ileostomy closure surgery without complications. Because of the rise of CEA, 18F-FDG PET-CT scan was performed without any signs of recurrent disease. Three months later, patient was seen again, this time complaining about changing bowel movements resulting in frequent defecation up to 8 times a day. On rectal examination, the anastomosis was palpated and was considered unremarkable and no palpable rectal mass was found. CEA further increased to 10.0 and therefore another 18F-FDG PET-CT scan was executed, again no abnormalities were found. Three months later, patient had similar complaints and experienced mild weight loss and this time CEA had risen to 25.6. Again, a 18F-FDG PET-CT scan was performed showing no signs of recurrent disease. Three months later, patient was seen again, this time with a CEA level of 57.2.

As three sequential 18F-FDG PET-CT scans had previously not shown any sign of recurrent disease, patient was referred to a tertiary oncological centre for additional advice. A fourth 18F-FDG PET-CT scan within one year was performed, this time together with a MRI scan of the rectum, both without any abnormalities. On all scans, the calcifications in the lung and the pancreas cyst did not differ from previous findings. Colonoscopy was performed and was negative for recurrent disease. After the second opinion – without new insights – patient underwent follow-up and at her following visit, CEA levels continued to rise, up to 163.6. Again, a 18F-FDG PET-CT scan was made without abnormalities. At this visit patient complained of headaches, abdominal pain and further weight loss (3kg in 3 months). She was referred to the neurologist for further consultation. An MRI of the brain showed no sign of metastatic disease or other abnormalities. After one year of follow-up – without any signs of recurrence, despite an extremely elevated CEA – diagnostic laparoscopy was performed as a last resort. The entire abdomen was evaluated but no signs of recurrent disease were found.

II Other Examination for Causes of CEA Elevated Levels

During follow-up, several additional blood tests and imaging were performed to rule out other causes of elevated CEA. Since CEA is often elevated in other malignant diseases, additional tumour markers such as carbohydrate antigen 19.9 were tested but were within normal values (CA 19.9 11.7u/ml (<37u/ml)). Thyroid hormones were tested, both to rule out thyroid cancer as well as endocrinological disorders, since hypothyroidism is a common endocrinological disorder in which CEA levels can rise [6]. Neither thyroid (stimulating) hormones, nor parathyroid hormones were abnormal. Patient had a pack year history of 32 years but had stopped smoking for over 9 years at the time of diagnosis and did not restart during illness or follow-up. Other types of cancer (breast, NSCLC) and inflammatory disease (cholecystitis, pancreatitis, IBD) that are potential causes of elevated CEA were all ruled out by the sequential 18F-FDG PET-CT scans.

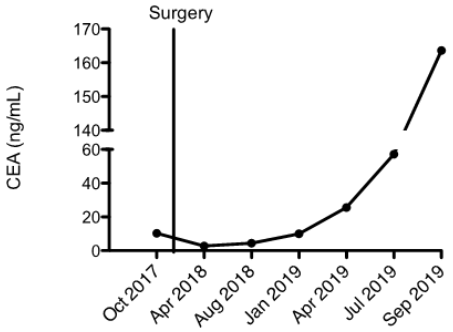

Figure 1: CEA elevation over time in patient case.

Discussion

CEA levels have been shown to be associated with tumour burden in patients with colorectal cancer and can therefore be used as marker in follow up [1]. It can however also be elevated in a number of benign conditions and other malignancies. In the present case the more commonly known conditions that cause an elevated CEA were excluded: ovarian cancer, pancreatic cancer, gastric cancer and thyroid cancer [3]. In addition, a literature search revealed several case reports presenting rare entities that cause elevated CEA levels, such as head and neck cancer, mucinous adenocarcinoma of the lip, hypothyroidism, a apocrine hidrocystoma and lithium use, but none of these were helpful for our patient [7-12]. With elevated CEA levels as high as in our patient, distant or local recurrence of the rectal cancer was on the top of our differential diagnosis list, followed by a second primary tumour. The patient underwent four sequential 18F-FDG PET-CT scans that did however not reveal a recurrence or a second primary tumour, and more specifically no change in the pancreatic cyst or the benign looking lung nodules. A recent study shows that 18F-FDG PET-CT is sensitive, specific, and accurate in investigating patient with elevated CEA and without known primary malignancy [13]. When CEA serum levels rise above 14.31ng/L, the diagnostic value of 18F-FDG PET-CT for malignant tumours becomes even more reliable [14]. Peritoneal metastases are

known to elude standard imaging, and because our patient had some abdominal complaints and weight loss eventually a diagnostic laparoscopy was performed [15].

For the patient the most difficult part in the follow up has been how to cope with the distress of the uncertainty. The second opinion in a dedicated oncology referral centre, while not providing any definitive answers, mainly served to alleviate some of this distress. Both the patient and the doctor know there is an increasing likelihood of recurrent disease with at present no signs or clues where this would be located, and if there would still be a chance for cure. It could turn out to be a solitary metastasis that can be surgically removed, it could be diffuse bone marrow invasion with a dire prognosis, or it could be something entirely different. The only option we currently have is to wait and repeat the imaging, mindful of Sir William Osler's quote: "medicine is a science of uncertainty and an art of probability".

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