

Can semaglutide influence tumor biomarkers? Insight from a clinical case

Alice Schianchi ^{a,*}, Fabio Mauri ^b, Christian Polli ^b

^a Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale, Lugano, Switzerland

^b Department of Obstetrics and Gynecology, Lugano Regional Hospital, Ente Ospedaliero Cantonale, Lugano, Switzerland

Abstract

To our knowledge, this is the first case reported in literature, regarding an increase in tumoral biomarkers during a treatment with Semaglutide. A 61-year-old patient was referred to our gynecological consultation due to suspected adnexal cysts following an MRI performed for a functional defecation disorder. The patient was on Semaglutide treatment. Gynecological examination and transvaginal ultrasound were normal, with no evidence of adnexal cysts. Tumor biomarker testing revealed a significant increase in CA 19-9 and a mild elevation in CA-125. In an asymptomatic patient, these findings raised suspicion of a possible neoplastic origin involving the pancreas or biliary tract. However, all further investigations yielded normal results. At a follow-up laboratory check one month later, CA 19-9 levels had decreased from 717 to 62 kU/L. A subsequent evaluation two months later confirmed the normalization of tumor biomarkers. Despite the elevation of CA19-9 during pancreatitis, which could be induced by Semaglutide, it is important to recognize that not all patients will experience this side effect. Moreover, an increase in tumor biomarkers can occur even in the absence of a clinically detectable disease, such as pancreatitis or cancer. Further research is needed to explore the potential relationship between Semaglutide and elevated CA 19-9 or CA-125 levels.

Keywords: CA 19-9, CA-125, Pancreatic cancer, Semaglutide, Tumor biomarkers

1. Introduction

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) that has gained significant attention among the public and healthcare professionals due to its efficacy in improving glycemic control and promoting weight loss. The increasing number of patients using it calls for careful consideration of its safety profile [1].

Regarding safety, mild-to-moderate gastrointestinal disorders, as well as biliary diseases, were observed during the SUSTAIN and PIONEER randomized clinical trials (RCTs). No unexpected safety concerns emerged, and Semaglutide's safety profile is comparable to that of other GLP-1RAs [2].

However, some preclinical and pharmacovigilance studies, have suggested a potential

pancreatic cancer risk associated with the use of GLP1-RAs, although the results remain contradictory and the mechanism is not fully understood [2,3]. This uncertainty is partly due to the low incidence of pancreatic cancer (15–24 cases per 100,000 person-years) and the presence of numerous confounding factors, including obesity, pancreatitis, and chronic renal failure [4]. In the years following the introduction of GLP-1RAs, it was suggested that these agents could potentially cause pancreatic cancer, so regulatory agencies such as the FDA and EMA have reviewed the potential risks of pancreatic damage (tumoral or non-tumoral) associated with incretin peptides-based therapies, such as GLP-1RA, concluding that current data do not support a significant association [5]. Still, because of the low incidence and limited statistical power of trials to

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* Corresponding author at: EOC ISFSI, Via Tesserete 44, 6900, Lugano, Switzerland.
E-mail address: alice.schianchi@eoc.ch (A. Schianchi).

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detect such outcomes, an association cannot be ruled out, and post-marketing surveillance continues [5].

We present the case of a patient who experienced a transient increase in tumor biomarkers following Semaglutide use. The informed consent was obtained from the patient for the publication of this case.

2. Case report

A 61-year-old female patient with type 2 diabetes and a BMI of 33.3 kg/m² (height 150 cm, weight 75 kg) started Semaglutide on March 14 2024. The initial dose was 0.5 mg once per week. As the patient did not experience any side effects, the dose was increased to 1 mg weekly. Over approximately 2 months from the start of treatment, she experienced a weight loss of 7 kg (9.3% of her initial weight). Moreover, after four weeks on 1 mg weekly, she developed symptoms of gastroesophageal reflux that significantly affected her quality of life. Consequently, the Semaglutide dose was reduced back to 0.5 mg weekly. Despite adjustment, symptoms persisted, leading the patient to discontinue treatment after two weeks.

After a two-week interruption, considering the disappearance of symptoms (positive dechallenge), the patient attempted to resume treatment at a dose of 0.5 mg per week. However, the recurrence of gastroesophageal reflux symptoms led her to permanently discontinue treatment again after two weeks (positive rechallenge).

During the treatment with Semaglutide, in addition to experiencing gastroesophageal reflux symptoms, in late March, the patient underwent defecography through a magnetic resonance to investigate potential pelvic floor dysfunctions underlying defecation difficulties. The examination revealed the presence of free abdominal fluid and a suspected adnexal cyst.

As a result, she was referred to the gynecological service. A gynecological examination was performed in May, yielding no significant findings. A transvaginal ultrasound showed normal ovaries, no cystic formations or ascites. Tumor biomarker testing performed on May 15 2024, soon after the first four weeks period at high dosage (1 mg/week), revealed elevated levels of CA-125 (36.4 kU/L) and CA 19-9 (717.0 kU/L), while other tumor biomarkers, such as CA 15-3 and CEA, remained within normal ranges. The patient had normal CA-125 and CA 19-9 values in tests performed the previous year. At the time of laboratory assessment, the patient was asymptomatic, with no alterations or related clinical signs suggestive of pancreatitis.

The case was discussed at a multidisciplinary meeting involving, where it was recommended to perform a contrast-enhanced CT scan of the chest and abdomen, along with a panendoscopy, due to the suspicion of a biliary-pancreatic disorder. These investigations yielded negative results for pathological conditions, neither oncological nor otherwise, that could confirm a biliary-pancreatic disorder.

A follow-up gynecological evaluation on June 11, with repeated tumor biomarker testing, showed significant CA 19-9 (62.8 kU/L) and normalized CA-125 (5.0 kU/L). This examination falls within the two-week rechallenge window (06 June to 13 June) with a lower dose of 0.5 mg/week, following suspension due to side effects. Eventually, a further check-up in August, when the patient had fully suspended Semaglutide therapy, confirmed the normalization of both biomarkers (positive dechallenge) (Fig. 1).

3. Discussion

When a high tumor biomarker value is detected, it is essential to conduct in-depth clinical investigations to determine the underlying cause.

Tumor biomarkers are substances, often proteins, produced by cancer cells or by the body in response to cancer. They can be detected in blood, urine, tissue, or other body fluids and are used in oncology for diagnosis, monitoring, and management.

Carbohydrate antigen 19-9 (CA 19-9) is a tumor biomarker commonly used to monitor patients with pancreatic cancer and other digestive tumors. It has a sensitivity of 79–81% and a specificity of 82–90% for diagnosing pancreatic cancer in symptomatic patients. However, its positive predictive value is low (0.5–0.9%), making it unsuitable for screening asymptomatic individuals [6].

Cancer antigen 125 (CA-125) is a tumor biomarker associated with epithelial ovarian neoplasms, but also found in cells lining various organs, including the endometrium, fallopian tubes, pleura, peritoneum, and pericardium. CA-125 specificity is limited, and fluctuations in its levels can occur even in healthy women at different menstrual phases [7].

A non-exhaustive list of benign conditions associated with elevated CA-125 levels includes menstruation, pregnancy, benign pelvic tumors, pelvic inflammatory disease, endometriosis, ovarian hyperstimulation syndrome, peritonitis, and conditions causing pleural effusion or ascites. It has been proposed as a biomarker for pancreatic neoplasms and that its levels rise in response to inflammation of the abdominal serosa [8].

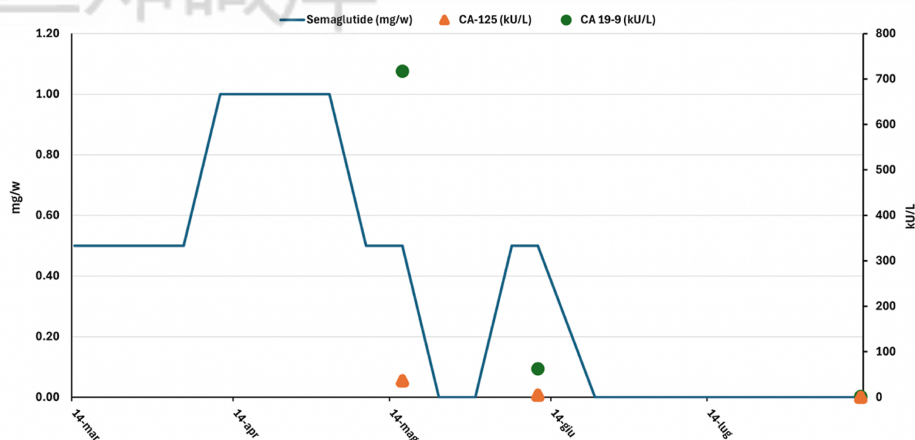


Fig. 1. Tumor biomarkers level in relation to Semaglutide use.

Several reports have suggested that elevated CA 19-9 levels may occur in diabetic patients, possibly due to a prolonged half-life of CA 19-9 in the serum [9]. However, in the present case, both CA-125 and CA 19-9 were within normal limits in the year preceding Semaglutide initiation, making a transient increase solely linked to diabetes unlikely.

After ruling out other conditions that could explain this laboratory trend like tumors of the biliary-pancreatic tract, infections, or bile duct obstruction, the observed temporal pattern suggests an association between Semaglutide exposure and tumor biomarker elevation. This association is supported by normalization of both CA 19-9 and CA-125 following definitive drug discontinuation (positive dechallenge) (Fig. 1). During Semaglutide rechallenge at a lower dose, CA-125 concentration returned to baseline values, whereas persistently elevated CA 19-9 levels continued to suggest a potential correlation.

Nonetheless, this observation must be interpreted with caution. Although a positive rechallenge was clinically documented through the recurrence of gastrointestinal symptoms, only CA 19-9 remained elevated, whereas CA 125 had normalized. This discrepancy may reflect residual effects of the prior drug interruption and the associated reduction in Semaglutide plasma levels. This explanation remains speculative, as comparable biomarker assessment was not performed during the initial dechallenge phase, limiting the strength of this interpretation. The present case therefore underpins a temporal association rather than a definitive causal relationship between Semaglutide use and tumor biomarker elevation.

The Swiss Summary of Product Characteristics for Semaglutide products (Ozempic® and Wegovy®) does not list pancreatic cancer or increases in tumor

biomarkers among side effects. To our knowledge, this is the first reported case in the peer-reviewed literature of concomitant CA 19-9 and CA-125 elevation during Semaglutide treatment with subsequent normalization after drug withdrawal. Reports of tumor biomarker elevation associated with Semaglutide have been recorded in pharmacovigilance databases such as VigiBase, indicating that similar events may have occurred but were not fully characterized. In fact, a search in VigiBase pharmacovigilance databases (07 May 2025), identified nine spontaneous safety reports of tumor biomarker elevations associated with Semaglutide use [10]. Specifically, one case involved increased CA-125 levels, and seven cases involved increased CA-9 levels, in addition to our case, where both biomarkers were elevated. The primary contribution of this report therefore lies not in precedence, but in the comprehensive clinical evaluation, longitudinal follow-up, and thorough exclusion of malignant and inflammatory disease.

Although the exact mechanism by which Semaglutide might influence tumor biomarkers remain unknown, one possible hypothesis is that it induces an inflammatory response in pancreatic cells, leading to the release of CA 19-9 into the bloodstream. This is similar to the proposed mechanism underlying GLP-1RA-induced pancreatitis [2]. A similar process, involving peritoneal cells, could potentially explain the increase in CA-125 levels. This hypothesis is supported by the observed correlation between CRP and CA 19-9, suggesting an association with an inflammatory flare [9]. However, biomarkers associated with pancreatic injury (e.g., CRP, lipase, amylase) were not available for this case, thus these hypotheses remain speculative and cannot be directly demonstrated.

While concerns about GLP-1RA-induced pancreatic disease exist, current evidence does not indicate a significant increase in risk associated with Semaglutide use. Despite the elevation of CA19-9 during pancreatitis, which could be induced by this drug, it is important to recognize that not all patients will experience this side effect. Individual variability in response to Semaglutide, along with the presence of other underlying conditions, can influence CA 19-9 and CA-125 levels. Moreover, an increase in these biomarkers can occur even in the absence of a clinically detectable disease, such as pancreatitis or cancer. From a clinical perspective, as with any iatrogenic event, pharmacological causes should be considered a diagnosis of exclusion. Therefore, when evaluating isolated biomarker abnormalities, clinicians must conduct a thorough differential diagnosis before attributing the findings to a drug-related cause.

Further research is needed to explore the potential relationship between Semaglutide and elevated CA 19-9 or CA-125 levels.

Conflicts of interest statement

The authors declare that they have no competing interests.

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