Clinical Biochemistry 64 (2019) 53–56

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Case Report

Transient increase of CA 19–9 serum concentrations in a liver transplant recipient with cystic fibrosis and hepatic abscess: a case report and brief literature review

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ABSTRACT

CA 19–9 (carbohydrate antigen 19–9) is a tumor marker widely used for surveillance of patients with pancreatic cancer. However, even high levels of CA 19–9 may not necessarily be cancer-associated thereby complicating the diagnosis. This case report highlights a transient increase of CA 19–9 in a triple transplanted patient with cystic fibrosis and continuous immunosuppression for 20 years who was under antibiotics. This case emphasizes the need for a balanced interpretation of biological results, especially in cases where many confounding factors are present such as diabetes, chronic renal failure, cystic fibrosis and infections. This case also provides an opportunity to formulate a number of recommendations for the interpretation of tumor marker results in order to avoid long and costly further investigations.

1. Introduction

CA 19–9 (carbohydrate antigen 19–9) is a tumor antigen principally used for surveillance of patients with pancreatic cancer. CA 19–9 is defined by its interaction with a murine monoclonal antibody (clone 1116 NS19.9) and was initially detected on the plasma membrane of the SW1116 human colon cancer cell line [1]. CA 19–9 is a polysaccharide containing a sialyl-lacto N-fucopentanose radical. This epitope is structurally similar to the Lewis blood group A antigen.

The CA 19–9 epitope is expressed on a wide variety of carrier glycoproteins such as the heavily O-glycosylated mucins that are present at the surface of epithelial cells and contribute to the lubricant and protective properties of the mucus [2]. Additional protein-carriers have been identified such as the bile globular membrane [3] and other organ-specific carriers [4]. An important limitation in the clinical use of CA 19–9 as a tumor marker is that 5–10% of the Caucasian population is unable to synthesize the antigen due to a deficiency of the fucosyltransferase enzyme. Therefore, whatever the clinical situation, CA 19–9 will necessarily be negative for this subgroup of patients. Moreover, the molecular heterogeneity of CA 19–9 is important and includes partial cleavage, deletion and variations in the nature and degree of glycosylation. The standard CA 19–9 clinical assay captures and detects all CA 19–9 antigens whatever the carrier protein or tissue origin. Some of these glycoproteins are normally expressed at the apical side of human pancreatic and biliary duct cells as well as by gastric, colon, endometrial and salivary epithelia. Small amounts can also be present in the serum of healthy patients.

CA 19–9 concentrations are dramatically increased in the serum and at the surface of the tumor cells for gastrointestinal (GI) cancers including adenocarcinomas of the stomach, intestine, pancreas and cholangiocarcinoma. This is mainly due to secretion of glycoproteins carrying the CA 19–9 epitope at the basal surface of the tumor cells [3]. In pancreatic cancer, CA 19–9 levels are increased in the serum for 70% of the patients whereas the corresponding figure is 50% for gastric, hepatic and colorectal cancers. CA 19–9 can also be expressed, generally at lower levels, in the presence of different benign gastrointestinal disorders (about 5% of cases), rarely exceeding plasma concentrations of 1000 kU/L.

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https://doi.org/10.1016/j.clinbiochem.2018.10.009
Received 19 September 2018; Accepted 17 October 2018
Available online 17 October 2018

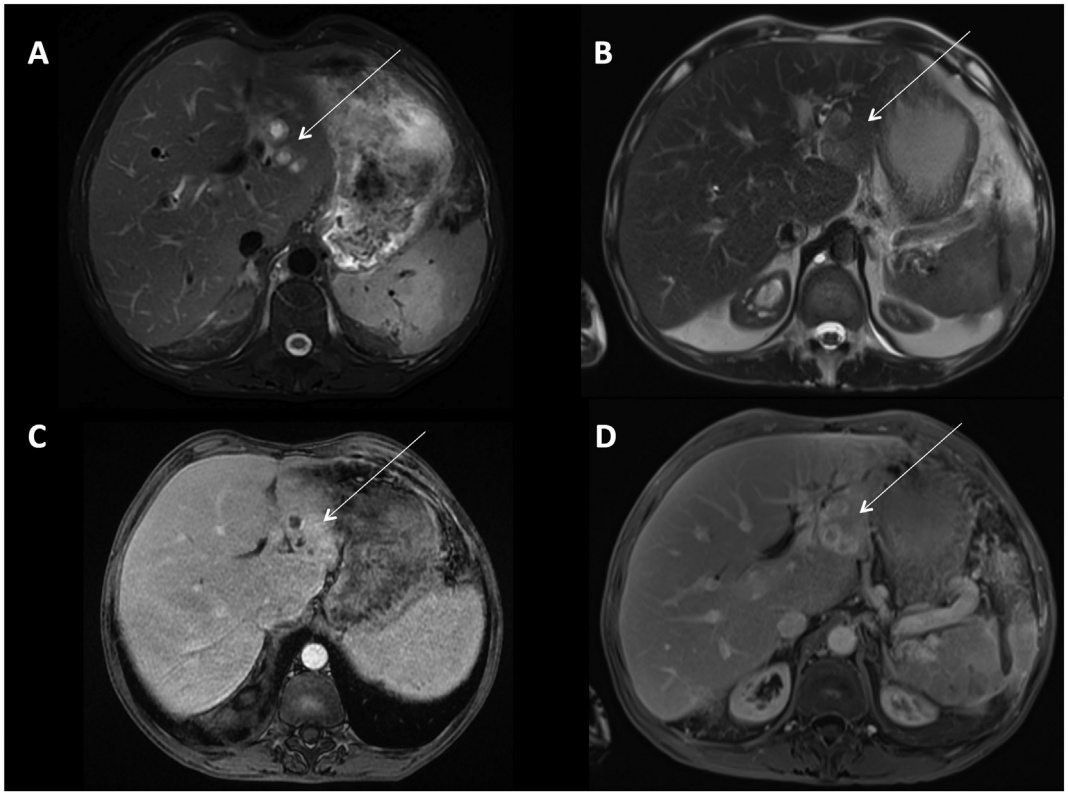

Fig. 1. Hepatic Magnetic Resonance before and after antibiotherapy switch.
A) T2-weighted sequence and C) Hepatocyte-specific, contrast-enhanced portal phase *before* the antibiotic switch, respectively. The three liver lesions (white arrow) in the left liver appear hyperintense in the T2 sequence (A) and with heterogeneous peripheral enhancement and no central enhancement (fluid content) in the portal phase (C).
B) T2-weighted sequence and D) Hepatocyte-specific, contrast-enhanced portal phase *after* the antibiotic switch, respectively. Three liver lesions (white arrow) in the left liver appear as less hyperintense in the T2 sequence (B) and with heterogeneous peripheral and central enhancement (organized, tissular content) in the portal phase (D).

The nature of the CA 19–9 antigen and the presence of patients with deficient fucosyltransferase activities explain, at least in part, the relatively high number of both false positive and false negative results. However, although the CA 19–9 marker is often criticized for its clinical performance, it remains a widely used tumor marker, sometimes wrongly prescribed for the screening of common tumor types. Thus, it is important to better identify clinical situations in which high CA 19–9 levels can be observed in a non-tumor setting in order to avoid misinterpretations that may complicate or delay treatment decisions and lead clinicians to recommend unnecessary and expensive additional examinations for their patients [5]. Here, we reported a transient increase of CA 19–9 in a complex clinical background associating cystic fibrosis and hepatic abscesses in a multi-transplanted patient.

2. Case report

A 35-year-old man with cystic fibrosis, chronic respiratory deficiency and exocrine pancreatic insufficiency, complicated by a type 2 diabetes and a chronic aspergillus infection, cirrhosis and portal hypertension was treated by combined lung and liver transplantation in 1997. The postoperative recovery was complicated by acute bronchiolar rejection, multi-resistant *Staphylococcus aureus*, pyocyanic pneumopathy, supraventricular tachycardia and arterial hypertension. Later, he also developed chronic renal failure attributed to immunosuppressive drugs and was treated by hemodialysis followed by renal transplantation in 2005. The postoperative course included two renal tubulopapillary carcinomas type I of the kidney graft treated by partial nephrectomy.

After renal transplantation, the patient was hospitalized for different infectious episodes. The first time, in December 2016, was due to *E. coli* producing an extended-spectrum β-lactamase septicemia, treated by vancomycin, amikacine and imipenem followed by meropenem. Then, he developed a *Pseudomonas aeruginosa* pneumopathy that was treated with ceftazidime and ciprofloxacin.

In January 2017, the patient was again hospitalized for fever (39 °C) and cholestasis. The initial infection evaluations were negative (lung, sinus, teeth, digestive and urinary tract, cardiac valves) except for the hepatic MRI that showed small lesions compatible with, but not typical of, liver abscesses (Fig. 1a). The evolution was characterized by the persistence of fever despite treatment with tazocilline (piperacilline and tazobactam). A new MRI showed an increased number of liver lesions and a change in the appearance (Fig. 1b) without dilation of the bile ducts. Then, the patient was switched to imipenem, amikacine and ceftriaxone. The infectious balance was negative (negative viral PCRs including HCV and HEV, respiratory viruses, blood cultures and cytobacteriological examination of the urine). Faced with a persistent fever despite the anitbiotics, a search for neoplasia was undertaken focusing on cholangiocarcinoma. The tumor markers showed an isolated increase in CA 19–9 at 974.5 kU/L on Jan 26, 2017 confirmed on Feb 1 at 3399 kU/L. All other tumor markers, including alpha-fetoprotein, carcinoembryonic antigen (CEA), carbohydrate 125 and 15–3 (CA 125, CA 15–3) were within the normal range (Table 1). Additional testing designed to neutralize potential heterophilic antibodies present in the plasma sample confirmed the original CA 19–9 results. Subsequent measurements showed a progressive decrease of CA 19–9 (282 kU/L 5 days after the last line of antibiotics) and then a progressive return to normal values (Fig. 2). Biological assessment at the time of the CA 19–9 peak also showed a peak of cholestasis with elevated alkaline

Table 1
Biology report at the time of the CA 19–9 peak.

Parameters	Results	Normal
Biochemistry		
Sodium	140 mmol/L	135–145
Potassium	3.2 mmol/L	3.5–5.0
Chloride	103 mmol/L	95–105
Bicarbonate	19 mmol/L	22–29
Total protein	65 g/L	67–82
Anion gap	22	
Creatinine	157 µmol/L	62–106
Urea	6.1 mmol.L	2.5–7.0
Uric acid	289 µmol/L	200–420
Calcium	1.95 mmol/L	2.10–2.65
Phosphates	0.83 mmol/L	0.81–1.45
Magnesium	0.52 mmol/L	0.74–0.87
Albumin	23 g/L	35–52
Total bilirubin	4 µmol/L	2–17
Alkaline phosphatase (ALP)	339 U/L	40–120
Aspartate transaminase (AST)	25 U/L	20–32
Alanine aminotransferase (ALT)	30 U/L	16–35
γ-glutamyltransferase (ϒ-GT)	209 U/L	12–55
c-reactive protein (CRP)	64 mg/L	< 5
Procalcitonin (PCT)	0.32 µg/L	< 0.1
MDRD	44 mL/min/1.73m^{2}*	See legend*
Tumor markers		
Alpha-feto protein (AFP)	3.5 ng/mL	< 13
CA 125	11.6 kU/L	< 35
CA 15–3	19.6 kU/L	< 35
CA 19–9	3399 kU/L	< 37

Immunoassays for tumor markers were performed using Kryptor analyzer (B.R.A.H.M.S., Hennigsdorf, Germany) while the other parameters was determined using Modular (Roche Diagnostics).

* Glomerular filtration rate estimated by the MDRD formula. This result must be multiplied by 1212 if the patient is neither Caucasian nor Asian. Classification of Chronic Kidney Disease (CKD) Stage 1 DFG > 90 mL/min/1.73 m2 MRC ∗ with normal or increased DFG Stage 2 DFG between 60 and 89 MRC ∗ with DFG slightly decreased Stage 3 DFG between 30 and 59 CK moderate stage 4 DFG between 15 and 29 severe CKD Stage 5 DFG < 15 CRI terminal.

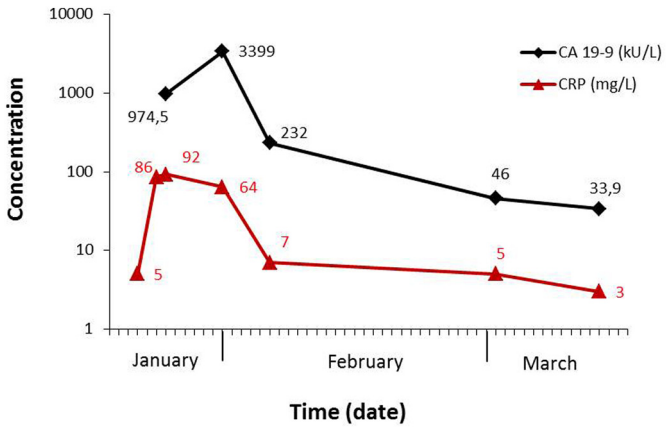

Fig. 2. Kinetics of CA19–9 and CRP.

phosphatase (10 times the upper limit of normal (ULN)) as well as of gamma-glutamyl transferase (12 × ULN) without an increase of bilirubinemia or a significant increase of transaminases (ALT: 2 × ULN). Additional biological investigations revealed a correlation between CA 19–9 serum concentrations and C-reactive protein (CRP). Pro-calcitonin (PCT) was also slightly increased at the time of the CA 19–9 peak and was associated with increased leucocyte (12.2 × 10^9/L, normal range: 4–10 × 10^9/L) and neutrophil counts (8.8 × 10^9/L, normal range: 2–7.5 × 10^9/L), whereas lymphocyte numbers (2.7 × 10^9/L, normal range: 1.5–4 × 10^9/L) remained within the normal range. Finally, a glycaemia at 23 mmol/L was also detected at the time of the CA 19–9 peak. Three and six months later, MRI confirmed the disappearance of the hepatic abscesses while the CA 19–9 level had returned to normal.

3. Discussion

When a high CA 19–9 value is discovered, additional clinical information should systematically be collected. In the absence of confirmed neoplasia, the first thing to determine is if the abnormal value could be due to the presence of heterophilic antibodies against external antigens (heterophilic antigens) in the serum of the patient. Heterophilic antibodies are antibodies induced by external antigens such as Epstein-Barr virus (EBV) as well as toward more poorly defined antigens. Heterophilic antibodies show broad reactivity toward polyclonal antibodies of non-human origin (which are part of the immunological assays) and can therefore cause significant interference with immunoassay testing resulting in both false positive and false negative results [6].

If the high concentration of CA 19–9 is confirmed, a discussion should be undertaken between the biologist and the clinicians to facilitate the interpretation of the results. In the present case, the biological interpretation of the high CA 19–9 value in serum was rendered particularly difficult due to the past medical history. Cystic fibrosis (CF) may cause a non-specific increase of CA 19–9 [7] with values of up to 500 kU/L having been reported [8,9]. CF is due to a mutation in the CTFR (Cystic Fibrosis Transmembrane conductance Regulator) gene, which is coding for a chloride channel. The main manifestations include the respiratory and digestive tracts although almost all organs can be affected. Cystic fibrosis causes a thickening of mucus secreted by the mucous membranes of the sinuses, bronchi, intestine, pancreas, liver and reproductive system. In CF, increased serum concentrations of CA 19–9 seem to be correlated with pulmonary exacerbation of the disease as well as with the amount of sputum in the lung [10,11]. Interestingly, the CA 19–9 antigen in CF seems to be distinct and can, if needed, be detected by using a specific antibody [12]. In the present case, the patient was also diabetic with a glycaemia of > 20 mmol/L at the time of the CA 19–9 peak. Different reports have suggested the occurrence of higher CA 19–9 levels in diabetic patients, even in the absence of malignancy [13], possibly due to a prolonged half-life of CA 19–9 in the serum. [14]. However, similar levels of CA 19–9 have not previously been reported in diabetic patients, suggesting that diabetes alone cannot explain the transient increase. In contrast, we have identified a correlation between CA 19–9 kinetics and C-reactive protein (CRP) suggesting that the elevation may be associated with an inflammatory flare. Both pancreatitis and cholangitis have been associated with important non-specific serum concentrations of CA 19–9. Acute pancreatitis is possible in CF but only in case of pancreatic insufficiency. Cholangitis is also a cause of increased CA 19–9 due to high concentrations of CA 19–9 in the bile that can translocate into the blood in case of inflammation. An infectious cholangitis related to bacterial translocation from the digestive tract or reflux in the bilio-digestive anastomosis is possible in the present case and would be favored by the slowed intestinal transit characteristic of cystic fibrosis. Elevated CRP, PCT and leucocyte/neutrophils counts concomitant with the CA 19–9 peak are all in favor of an ongoing infection. In agreement with this hypothesis, a different study has reported the case of a 72-old woman with respiratory infections due to *Mycobacterium avium* and *Pseudomonas aeruginosa* that was associated with increased CA 19–9 levels, which abruptly decreased when the infection was, controlled [15]. In another study, elevated levels of CA 19–9 and CA 125 were associated with *pseudomonas* colonization and lung function [16]. In our case report, CA 125 was normal. The CA 125 antigen is present in serosa and is typically used as a marker for ovarian tumors and mucinous cystadenocarcinoma. However, it can also be increased in the case of serous inflammation. The normal levels of CA 125 in our case suggest that the inflammatory origin is likely extra-pulmonary. In one report, markedly

elevated CA 19–9 in the pus and the serum was observed in a patient with pyogenic liver abscesses [17,18] while a different study suggests that CA 19–9 may serve as a marker for treatment response in patients with liver abscesses since it was observed that the serological levels of CA 19–9 decreased upon exposure to antibiotics [18]. Indeed, the rapid return to normal levels of CA 19–9 in our patient after change of antibiotics suggests that CA 19–9 may serve as an indicator of response to treatment whereas high persistent levels could indicate potential resistance. A better understanding of the proteins carrying the CA 19–9 epitope would facilitate the interpretation of the clinical findings.

4. Conclusions

This case report describes an isolated increase of CA 19–9 in a triple transplanted patient with cystic fibrosis associated with persistent fever in spite of treatment with antibiotics. This case emphasizes the need for a balanced interpretation of biological results, especially in a case like the present where many confounding factors are present including cystic fibrosis, infection, diabetes and chronic renal failure which are all non-specific causes of increased CA 19–9 levels. This case also allows us to summary the use and interpretation of CA 19–9 results as a tumor marker in order to avoid long and costly investigations. CA 19–9 dosage is useful to distinguish between pancreatic cancer and benign pancreatic lesions, since CA 19–9 is elevated in 93% of pancreatic adenocarcinoma but only in 4% of benign disease. It is also useful for the monitoring of patients with pancreatic cancer under treatment and to monitor recurrence after surgery. Finally, it can be used for the follow-up of colorectal cancer patients (in association with CEA), as well as for post-operative monitoring of gastric cancers (in association with CEA and CA 72.4) and for mucinous ovarian cancer.

In contrast, CA 19–9 is not recommended as a screening or diagnostic tool because of its limited performance, which can be either reassuring or worrisome. If high CA 19–9 levels are observed it should be keep in mind that there is about 20% false positive results for CA 19–9. Therefore, high CA 19–9 alone cannot justify a long, expensive, stressful and unnecessary investigation for the patient. If the patient is infected, the biological interpretation is particularly hazardous. In the present case, repeated CA 19–9 measurements revealed normalization of CA 19–9 levels after the infection was cured.

Conflicts of interest

The authors have no conflict of interest to declare.

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