Case Report

Significant Elevation of CA 19-9 Levels Due to Acute Xanthogranulomatous Cholecystitis and Following mRNA COVID-19 Vaccination: A Case Report and Literature Review

Aphrodite G Fotiadou¹, George Pappas-Gogos¹²*, Konstantinos Tsimogiannis¹, Orestis Petropoulos¹, Christina Kalyvioti¹, Gerasimia D Kyrochristou¹, Athina Tsili³, Georgios K Glantzounis¹

¹HPB Unit, Department of Surgery, University Hospital of Ioannina and Faculty of Medicine, School of Health Sciences, University of Ioannina, Greece
²2nd Department of Surgery, University Hospital of Alexandroupolis and Faculty of Medicine, School of Health Sciences, Democritus University of Thrace, Greece
³Department of Radiology, University Hospital of Ioannina and Faculty of Medicine, School of Health Sciences, University of Ioannina, Greece

*Corresponding author: George Pappas-Gogos, HPB Unit, Department of Surgery, University Hospital of Ioannina and Faculty of Medicine, School of Health Sciences, University of Ioannina, Greece


Received: 17 July 2023, Accepted: 21 July 2023, Published: 24 July 2023

Abstract

Objectives: Carbohydrate antigen (CA 19-9) is a tumour marker usually elevated in upper-gastrointestinal and pancreaticobiliary malignancies, yet some studies reported pathological increments in patients with biliary obstruction. However, extremely high levels of CA 19-9 in the absence of biliary obstruction and malignancy represent a very rare occurrence.

Methods: We report a case of a 61-year-old patient presenting with acute cholecystitis, a segment IVb liver lesion next to the gallbladder and very high CA 19-9 levels (12,500 IU/ml). Results: The patient underwent laparoscopic cholecystectomy, with liver biopsy, due to the suspicion of malignancy. The histopathology showed xanthogranulomatous cholecystitis penetrating the posterior gallbladder wall and entrenched in the liver as a hepatic abscess. After complete remission of the disease, CA 19-9 reached normal values. However, after the third dose of the mRNA vaccine against SARS-CoV-2, CA 19-9 levels incremented abnormally and gradually declined to normal weeks later.

Conclusions: CA 19-9 should never be regarded as a gold standard but rather as a helpful marker in the workup, especially in biliary pathology. Regarding the impact of COVID-19 vaccines on the tumour markers, and especially on CA 19-9, further studies should be performed to investigate this prospect.
Keywords: Carbohydrate Antigen 19-9; Cholelithiasis; Xanthogranulomatous Cholecystitis; Benign Biliary Disease; Mrna COVID-19 Vaccination; Systemic Inflammation

Introduction

The carbohydrate serum antigen 19-9 (CA 19-9) is a glycosphingolipid of the Lewis blood group, normally present in serum in low levels, which can increase in several neoplastic conditions, especially in pancreatic, biliary, and gastrointestinal neoplasms, as well as in benign diseases such as intra or extrahepatic biliary obstruction or respiratory pathologies [1]. It is usually synthetized by both the pancreatic and biliary ductal cells and by the epithelial cells of the stomach, colon, endometrium and salivary glands [2]. The upper limit of normal for CA 19-9 is 37 UI/mL, and with this limit, the assay has an overall sensitivity of 60 to 70% for the diagnosis of biliary malignancies. CA 19-9 values greater than 1,000 UI/mL have a specificity of over 99% for pancreatic cancer [3]. Reports concerning the prognostic value of this marker are conflicting. Nevertheless, this analysis remains a valuable tool that can support diagnosis, detect recurrence in treated neoplasms and monitor treatment response, especially in chemotherapy [4-7]. Regarding its use in the differential diagnosis of biliary stenoses, serum CA 19-9 levels alone cannot differentiate between malignant and benign stenoses upon initial evaluation. However, assessing serum CA 19-9 at specific time points, for example, after the resolution of the obstruction, along with clinical features and imaging results, might have significant potential diagnostic utility [8,9]. Few cases have reported such high levels of CA 19-9 in patients with no signs of malignancy [5,6,8-15]. In this article, we report a case of abnormally high levels of CA 19-9 in a patient with an inflamed gallbladder ruptured to the liver due to multiple episodes of acute cholecystitis, as well as after the booster vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Case Report

A 61-year-old male patient presented to the Emergency Department of the University Hospital of Ioannina on the first days of November 2021, reporting intense pain, localized in the right hypochondrium for more than six days, as well as fever (39°C), discomfort, weakness, nausea, vomiting, and inability to ingest food or water the last 10 hours, as well as the inability of defecation and flatulence for the past two days. Past history revealed cholelithiasis (four small gallstones randomly found during an abdominal U/S in 2017) and two acute cholecystitis episodes in August 2021 and September of the same year. Acute cholecystitis was managed conservatively and was advised to undergo a laparoscopic cholecystectomy in the near future. Concerning the patient’s daily habits, he did not mention smoking or alcohol consumption. However, he said that he was used to a sedentary life. He was not physically active in the past and usually consumed fatty meals, such as dairy products and meat. The laboratory tests revealed elevated liver enzymes (ALP of 149IU/l, TBL of 1.8 mg/dl, AST of 39IU/l, ALT of 41IU/l γ-GT of 146 IU/l, INR = 1.40, aPTT = 46.7 sec) and extremely elevated levels of CA 19-9, reaching 12,500 IU/ml. Complete blood count and serum electrolytes were within the normal range. The last contrast-enhanced abdominal CT performed in September displayed microlithiasis that did not cause intra- and extrahepatic duct dilatation. Also, the portal venous phase revealed a discontinuity of the posterior gallbladder wall and an abnormal connection between the bladder and the IVb liver segment, compatible with a gallbladder rupture and a formation of a hepatic abscess (characteristic “cluster of grapes” radiological sign). The delayed phase also displayed increased vascularization and impaired tissue perfusion of the hepatic lesion (Figure 1). In order to characterize the lesion more accurately, an abdominal MRI was performed subsequently. After applying T1, T2, and diffusion-weighted image sequences, the radiology report noted the existing gallbladder cholelithiasis and the hepatic abscess, visible with high signal intensity in the T2 sequence (Figure 2). The DWI did not show diffusion restriction but a slight difference in that segment’s composition. However, two months later, the patient’s preoperative MRI revealed no sign of the hepatic abscess in the IVb liver segment since it was no longer visible with any imaging technique. During his hospitalization, an increment of serum urea, creatinine, eGFR levels, and clinical signs of dehydrated skin, oral mucosa and anuria underlined an acute kidney disease without peripheral edemas. Nevertheless, the patient had a free past nephrological history. In addition, his kidneys seemed normal in the U/S. The patient was referred to the Nephrology Clinic of the Hospital, where he was diagnosed with acute interstitial nephritis of allergic aetiology since, as mentioned above, the patient was receiving a double antibiotic treatment with ciprofloxacin and metronidazole, combined with non-steroidal anti-inflammatory drugs (NSAA). His antibiotic treatment was switched to meropenem, NSAA were stopped, and after five days, the patient was discharged having normal kidney function. A “demanding” laparoscopic cholecystectomy was performed two weeks later. Biopsies have been taken from the liver to characterize the previously existing hepatic lesion. Histological reports confirmed the absence of malignancy either of the liver or the gallbladder; instead, xanthogranulomatous cells were found, as well as rupture of the gallbladder and inflammatory infiltration of the liver. The postoperative course was uneventful, and the patient was discharged on the 4th postoperative day. CA 19-9 levels steadily declined from the 1st postoperative day (132 IU/ml) to 83.8 IU/ml on the 4th postoperative day (Figure 3). Two months later, a preoperative MRI revealed no sign of the hepatic abscess in the IVb segment since it was no longer visible with any imaging technique. In the context of the postoperative...
recommendations given to the patient to check the tumour marker once a month, a month later, CA 19-9 levels reached 777.9 IU/ml (Figure 3). The most interesting fact was that the patient was vaccinated with the third dose of a mRNA vaccine against SARS-CoV-2 two days before the CA19-9 control. However, the marker steadily declined to 210 IU/ml two weeks later. At the last follow-up, CA 19-9 values returned to normal (27.3 IU/ml). The present report is the first case of CA 19-9 increment after SARS-CoV-2 mRNA vaccination in the literature.

Figure 1: Axial contrast-enhanced C.T. scan of the abdomen shows multiple stones in the gallbladder (yellow arrow) and a hepatic lesion at the IVb liver segment (red arrow).

Figure 2: Axial T2 MRI of the abdomen shows a dilated gallbladder and a hepatic abscess with high signal intensity (arrow: hepatic abscess).

Figure 3: CA 19-9 levels since the first episode until the last measurement.

Discussion

CA 19-9 is produced by the pancreatic and biliary duct cells and from the epithelium of the stomach, the colon, the endometrium, and the salivary glands. CA 19-9 can aid the diagnosis of gastrointestinal malignancy, such as pancreatic, biliary, gastric and colon carcinoma. However, CA 19-9 may increase in benign conditions affecting antigen pathways (secretion, discharge, and metabolism). Pancreatitis, cholangitis, bronchial cysts, pulmonary fibrosis, ovarian cysts, endometriosis, benign conditions that cause biliary obstruction, and diseases such as chronic hepatitis and chronic renal failure may present high levels of CA 19-9 [1]. Nevertheless, since CA 19-9 is highly specific, several examinations are mandatory to rule out the presence of pancreatic or biliary malignancy, or in our case, the presence of gallbladder malignancy (U/S, CT, MRI). Hence, it must be interpreted cautiously, alongside the patient’s medical history, physical and imaging examination, and additional lab analyses. Without an adequate clinical context, the isolated results of the marker could incorrectly lead to costly and unnecessary investigations and misdiagnosis of pancreatic or biliary malignancy. Although the first diagnosis to be considered is a malignant disease, the possibility of benign diseases should not be ruled out [4-9,16,17]. In our case, an explanation for the abnormally high CA 19-9 levels could be the increased production of CA 19-9 from the biliary...
epithelial cells and its decreased hepatobiliary clearance due to cholestasis, which may have contributed to abnormal CA 19-9 elevation in the bloodstream. However, there was no intrahepatic or extrahepatic biliary obstruction. First, bile flow may be blocked due to cystic duct obstruction by gallstones and biliary sludge. Then, the epithelial cells of the gallbladder wall may be impaired by the blocked bile flow, increased internal pressure of the gallbladder, and inflammatory conditions. Subsequently, production of CA 19-9 in the epithelium of the gallbladder may be increased and leak into the blood circulation. It also explains why there was a gradual 3-week reduction of CA 19-9 levels after the cholecystectomy. Several authors reported high serum CA 19-9 levels in patients with benign biliary obstruction and jaundice due to choledocholithiasis, Mirizzi syndrome, or sclerosing cholangitis [4-12,14-16]. In addition, cases of acute cholecystitis, particularly xanthogranulomatous, have been reported with elevated levels of the marker [17,18]. However, such high levels of CA 19-9 (12,500 IU/ml), analogous to our case, have not been described in Occident. The only case reported in the literature comes from Japan and concerns a patient with very high serum levels of CA 19-9 (19,392 IU/ml). This patient had acute cholecystitis, biliary sludge, and a stone incarcerated in the neck of the gallbladder [23]. As in our case, the CA 19-9 reached the normal values after surgery. SARS-COV-2 causes coronavirus disease 2019 (COVID-19), which represents an acute respiratory syndrome. However, patients affected by COVID-19 could be symptomatic or asymptomatic, with an incubation period of 4-7 days approximately. Three categories of COVID-19 (mild, severe, and critical) can be identified according to the severity of the symptoms. The mild may occur with or without mild pneumonia, the severe with dyspnea and acute respiratory stress, while the critical may occur with respiratory or multiple organ dysfunction. CA 19-9 levels may increase in diseases of the respiratory system, such as bronchitis, interstitial lung disease, pulmonary tuberculosis, lung abscess, pneumonia, and pulmonary sequestration, and thus, it has been hypothesized that they could be incremented in patients with COVID-19 [20,24]. CEA and CA 125 were found to increase in cases of mild COVID-19, but CA 19-9 levels increased only in critical cases [24]. On the other hand, in a retrospective cohort study, Purut et al. [25] found that COVID-19 had no impact on tumour markers, including CA 19-9. However, regarding the impact of COVID-19 mRNA vaccines on tumour markers, and especially on CA 19-9, no studies exist so far. It has been shown that mRNA COVID-19 vaccines may induce, in selected individuals, the production of S protein comparable to that during SARS-COV-2 infection. The molecular targets of the S protein are angiotensin-converting enzyme (ACE2), CD147, toll-like receptors (TLRs), estrogen receptor alpha (ERα), as well as the human cells directly. In consequence, binding to ACE2 may trigger platelet aggregation, thrombosis, and inflammation, interacting with CD147 may induce microvascular damage, binding to TLR2 or TLR4 may have implications on innate immunity, and acting directly to the cells may increase the activation of cell growth signalling [26]. Based on the mechanisms mentioned above, several authors reported cases of induced acute liver injury, autoimmune hepatitis, cholangiopathy, and acute pancreatitis, following mRNA COVID-19 vaccination [27-31]. Regarding our case, a potential explanation of the high levels of CA19-9 after the mRNA vaccination could be the implication of the immune reaction due to the vaccination, which may trigger an inflammatory response to a previously inflamed liver, and consequently the production of the CA 19-9.

Conclusion

In conclusion, CA 19-9 should never be regarded as a gold standard but rather as a helpful marker in the workup, especially in biliary pathology. Regarding the impact of COVID-19 vaccines on the tumour markers, and especially on CA 19-9, further studies should be performed to investigate this prospect.

Highlights

Our case highlighted the high levels of CA 19-9 do not necessarily indicate the presence of malignancy. This case illustrates that cholecystitis, especially when accompanied by a liver abscess, is difficult to distinguish from malignancy of the liver or gallbladder, and the diagnosis is considered challenging. Therefore, a complete clinical examination accompanied by second-level radiological tests, such as MRI with diffusion sequences, should confirm or rule out malignancy and create an appropriate management plan. Also, as presented in our case, more research should be conducted to assess the possible elevation of CA 19-9 in systematic inflammatory conditions.

Funding: This research received no funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the University Hospital of Ioannina, Ioannina, Greece.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data for this article are not publicly available to ensure patient anonymity. Requests to access the data should be directed to the corresponding author.

Conflicts of interest: The authors declare no conflicts of interest.

References
