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Case reports of patients with significantly elevated CA 19-9 levels without confirmed malignancy

Opis przypadków chorych ze znacznie podwyższonym stężeniem markera CA 19-9 bez potwierdzenia rozpoznania choroby nowotworowej

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Abstract

The CA 19-9 antigen is a marker whose concentration is elevated usually in the presence of gastrointestinal cancer. CA 19-9 is considered to be characteristic for pancreatic and biliary cancer; however, an elevated level of this marker may also indicate a cancer with a different point of origin such as the colon or the stomach. CA 19-9 has limited application in diagnosis; however, the observation of its level makes it possible to monitor treatment progress and can help in the detection of cancer spread. CA 19-9 is a glycoprotein with a molecular mass of 210 kD, produced not only by cancer cells, but also by gastrointestinal and liver cells during foetal development, by salivary glands, mature pancreatic and biliary cells as well as the bronchi. This study presents the cases of patients who were diagnosed with significantly elevated CA 19-9 levels and in whom cancer was excluded in the course of further clinical follow-up. The authors indicate that a very high concentration of CA 19-9 can have a different cause than cancer: in the cases described in the present study it was usually cholestasis caused by benign biliary diseases that led to the elevation of this marker.

Keywords: CA 19-9, acute cholangitis, cholestasis

Streszczenie

Antygen CA 19-9 to marker, którego stężenie jest najczęściej podwyższone w przypadku nowotworów przewodu pokarmowego. Uważa się, że jest charakterystyczny dla raka trzustki i dróg żółciowych, ale jego podwyższone stężenie może także wskazywać na nowotwór o innym punkcie wyjścia, takim jak jelito grube czy żołądek. CA 19-9 ma ograniczone zastosowania w diagnostyce, ale jego kontrola pozwala monitorować postęp leczenia i jest pomocna w wykrywaniu rozsiewu nowotworu. CA 19-9 jest glikoproteiną o masie cząsteczkowej 210 kD, produkowaną nie tylko przez komórki nowotworowe, ale również przez komórki przewodu pokarmowego i wątroby w życiu płodowym, gruczoły ślinowe, dojrzałe komórki trzustki i dróg żółciowych oraz oskrzela. Niniejsza praca przedstawia opis chorych, u których stwierdzono istotnie podwyższone stężenia CA 19-9, a w toku dalszej obserwacji klinicznej wykluczono rozpoznanie nowotworu. Autorzy wskazują, że bardzo wysokie stężenie CA 19-9 może być spowodowane zmianą inną niż rak – w opisanych przypadkach była to głównie cholestaza spowodowana łagodnymi chorobami dróg żółciowych.

Słowa kluczowe: marker CA 19-9, ostre zapalenie dróg żółciowych, cholestaza

INTRODUCTION

The CA 19-9 antigen is a marker whose concentration is elevated usually in the presence of gastrointestinal cancer. CA 19-9 is considered to be characteristic for pancreatic and biliary cancer; however, it is not a specific marker and its elevated level may also indicate a cancer with a different point of origin such as the colon or the stomach. CA 19-9 has limited application in diagnosis; however, it makes it possible to monitor treatment progress and can help in the detection of cancer spread as well. The CA 19-9 antigen is a glycoprotein with a molecular mass of 210 kD⁽¹⁾, produced not only by cancer cells, but also by gastrointestinal and liver cells during foetal development, by salivary glands, mature pancreatic and biliary cells as well as the bronchi. For this reason, low levels of this marker are detected even in healthy individuals. CA 19-9 is a Lewis system antigen derivative; individuals with a rare Lewis system (a-b-), who account for approximately 5% of the Caucasian population, are not able to produce this marker.

In the literature different cut-off points are reported (70.5 U/mL⁽²⁾, 90 U/mL⁽³⁾). They make it possible to diagnose a cancer lesion with a high level of probability, although a diagnosis cannot be made exclusively based on the CA 19-9 value since benign lesions can cause CA 19-9 to rise far beyond these cut-off points. However, the values of > 1,000 U/mL are considered highly specific for biliary and pancreatic cancers.

Below the cases of five patients are described who were hospitalised in 2012–2017 at a single gastroenterological centre. They had significantly elevated CA 19-9 levels (> 20 × normal) with respect to a reference level of < 37 U/mL, which is the upper limit of normal (ULN). In the course of further clinical follow-up cancer was excluded. An immunoenzymatic method was used to assay CA 19-9 levels.

CASE 1

A 76-year-old female patient with iatrogenic bile duct injury and massive bleeding from the right branch of the portal vein during laparoscopic cholecystectomy converted to laparotomy was hospitalised multiple times at the Department of Gastroenterology and Hepatology, University Clinical Centre, beginning from 2012.

The patient was hospitalised for the first time in March 2012, 2 weeks after cholecystectomy. Due to bile leakage endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy was performed and a 10 F plastic biliary stent was implanted. The stent was removed 6 months later, as planned, after a single replacement. A year after the first hospitalisation (April 2013) the patient developed signs and symptoms of acute cholangitis (AC). Apart from typical laboratory abnormalities that are the basis for AC diagnosis (ALT: 189 U/L, AST: 147 U/L, GGTP: 821 U/L, bilirubin: 2.64 mg/dL, CRP: 24.4 mg/L), the CA 19-9 level

was assayed in the patient and the result was 1,777 U/mL (48 × ULN). Due to critical common bile duct stenosis a fully coated self-expandable 8 mm by 80 mm stent was inserted into the biliary tract. Two months after the biliary stenting procedure the CA 19-9 value returned to normal (4.2 U/mL) and it was not observed to rise during consecutive hospitalisations associated with repeated stent replacement procedures until February 2017. On abdominal computed tomography performed twice (March 2012, April 2013) no pathology was found in the biliary tract and the pancreas.

CASE 2

A 60-year-old female patient with a history of cholecystectomy many years earlier and choledochotomy in 2010 was hospitalised multiple times in 2010–2014 due to the signs and symptoms of recurrent cholangitis.

On admission to the Department in 2012 enzymatic cholestasis was diagnosed (GGTP: 224 U/L, ALP: 245 U/L) with normal ALT, AST and bilirubin levels. The CA 19-9 concentration was 741.3 U/mL (20 × ULN).

Ultrasound examination did not reveal any abnormalities, while contrast-enhanced abdominal computed tomography demonstrated discrete intra- and extrahepatic bile duct dilation and enlarged lymph nodes in the supradiaphragmatic area near the heart and the porta hepatis; however, their image did not indicate cancer as the cause of the elevated marker level. On magnetic resonance cholangiopancreatography (MRCP) no abnormalities were found in the biliary tract. Liver biopsy was performed. The microscopic image of the specimen was consistent with low-grade chronic hepatitis with grade 3 fibrosis and biliary ductule damage, suggesting primary cholangitis (previously known as primary biliary cirrhosis). Empirical ceftriaxone therapy caused fever to subside and 3-year-long clinical follow-up during ursodeoxycholic acid treatment did not demonstrate the development of cancer.

CASE 3

A 74-year-old female patient with diagnosed cholelithiasis reported to the Department in May 2012 with symptoms of acute cholangitis lasting 5 days. Her previous cholangitis episode occurred 5 months earlier.

Laboratory tests revealed signs of cholestasis (GGTP: 660 U/L, ALP: 256 U/L, bilirubin: 8.81 mg/dL) with a moderate increase in transaminase levels (AST: 73 U/L, ALT: 282 U/L), increased inflammatory markers (CRP: 329 mg/L) and an elevated CA 19-9 level: 2,755.9 U/mL (75 × ULN).

Urgent ERCP with sphincterotomy was performed and a concrement 10 mm in diameter lodged in the terminal common bile duct was revealed. An attempt was made to remove the concrement, however, due to technical difficulties a 7 F, 9 cm-long double pigtail stent was inserted

in order to achieve efficient bile drainage. Gradual resolution of cholestasis and inflammation was observed. The patient was discharged from hospital in good general health. The removal of the concrement was successful during an ERCP procedure performed 5 months later. Two-year clinical follow-up did not demonstrate the development of cancer.

CASE 4

An 83-year-old female patient with a history of cholecystectomy many years earlier was admitted to the Department for endoscopic treatment due to typical cholangitis symptoms (pain in the upper mid and upper right abdomen radiating towards the back, chills, nausea and vomiting, yellow skin and dark urine) associated with ductal cholelithiasis. Laboratory tests revealed signs of inflammation (CRP: 135 mg/L) and cholestasis (ALP: 275 U/L, GGTP: 148 U/L, bilirubin: 8.78 mg/dL) with increased transaminase activity (ALT: 241 U/L, AST: 138 U/L). The CA 19-9 concentration was 5,980 U/mL ($162 \times \text{ULN}$).

Urgent ERCP with endoscopic sphincterotomy was performed and bile duct concretions were removed. After the procedure signs of cholestasis were reduced and the CA 19-9 concentration decreased to 90.2 U/mL. A contrast-enhanced abdominal CT scan did not reveal any pathology. The patient was discharged from hospital in good health and 3-year-long clinical follow-up did not demonstrate the development of cancer.

CASE 5

A 73-year-old male patient was admitted to the Department with signs of acute cholangitis (CRP: 294 mg/L, GGTP: 100 U/L, normal bilirubin: 1.0 mg/dL and elevated transaminase levels: ALT: 25 U/L, AST: 34 U/L). The CA 19-9 concentration was $> 12,000$ U/mL ($324 \times \text{ULN}$).

An ultrasound scan revealed an enlarged, porcelain gallbladder of 105×55 mm and with up to 6 mm-thick walls as well as a common bile duct dilated to 17 mm with a suspected concrement in the distal segment.

An urgent ERCP was performed; however, attempted bile duct catheterisation was unsuccessful due to the ampulla of Vater being located in a diverticulum. MRCP did not reveal any lesions suggesting neoplastic proliferation and empyema of the gallbladder was diagnosed. The patient was referred for surgical treatment. Laparotomy was performed during which inflammatory infiltration of the hepatoduodenal ligament was found and an enlarged gallbladder with a 10 mm-thick wall was removed. No ductal cholelithiasis was found during the procedure. The postoperative period was uneventful. Histopathological examination of the gallbladder revealed chronic suppurative inflammation. The patient was discharged in good health. Follow-up examinations performed after 2 years revealed a normal CA 19-9 level (12.7 U/mL).

DISCUSSION

Significantly elevated cancer marker levels should first raise the suspicion of neoplastic proliferation. However, in some cases conditions unrelated to cancer are the cause of significantly elevated CA 19-9 antigen levels. In the cases described in the present study the cause of a significant CA 19-9 increase was cholestasis and similar cases have also been reported in the international medical literature.

Sheen-Chen et al. described the case of a 68-year-old female patient with a baseline CA 19-9 antigen concentration of 5,674 U/mL, in whom bile duct obstruction was diagnosed that was caused by the presence of a large concrement in the distal common bile duct. After surgical removal of the concrement the patient's condition stabilised. Two weeks after the procedure the CA 19-9 concentration decreased to 63.1 U/mL and after a month CA 19-9 levels did not exceed ULN⁽⁴⁾.

Similar cases have been reported by Marcouizos et al.⁽⁵⁾, Murohisa et al.⁽⁶⁾ and Lowe et al.⁽⁷⁾. In all these cases the patients displayed the signs of cholestasis and the initial CA 19-9 levels were 99,070 U/mL, 60,000 U/mL and 4,374 U/mL, respectively. Following surgical treatment and the restoration of bile duct patency these levels decreased: after 2 months, 6 weeks and 5 months, respectively, the CA 19-9 concentrations were < 37 U/mL. No cancer was found in any of these patients.

Murray et al. described the case of a 55-year-old male patient with ulcerative colitis who developed jaundice associated with primary sclerosing cholangitis (PSC) with significant stenosis of the common bile duct. A very high level of the CA 19-9 antigen of 26,321 U/mL was alarming, which, however, decreased to < 37 U/mL after the restoration of bile duct patency. Due to an increased risk of pancreatic and biliary cancer in patients with PSC long-term surveillance was conducted and the development of cancer was not found⁽⁸⁾.

Akdoğan et al. reported the case of a 79-year-old female patient with a pancreatic pseudocyst and the signs and symptoms of cholangitis in whom the initial CA 19-9 value was 35,500 U/mL. After 2 months of treatment the CA 19-9 level decreased to < 37 U/mL. In this case no malignancy was diagnosed either⁽⁹⁾.

It is also worth taking note of the dynamics of CA 19-9 level changes and observing CA 19-9 values after the resolution of signs and symptoms of cholestasis. The validity of CA 19-9 monitoring is demonstrated by Marrelli et al. In their study, in nearly all patients in whom biliary obstruction associated with non-cancerous lesions was found, the CA 19-9 levels decreased following endoscopic drainage of the bile ducts. In contrast, in patients with a malignant lesion the CA 19-9 level decreased in only half of the cases, while in the remaining patients the antigen's level continued to increase or did not change⁽³⁾.

Significantly elevated CA 19-9 levels can also occur in patients with benign lesions located beyond the gastrointestinal tract. Pyeon et al. reported the case of a 37-year-old

female patient hospitalised due to pain in the lower right abdomen. Abdominal computed tomography demonstrated the presence of a cystic ovarian lesion with the dimensions $10 \times 10 \times 6.5$ cm. Cancer marker tests were conducted. Only in the case of CA 19-9 was the level significantly higher than ULN: 2,753 U/mL. The lesion, which turned out to be a benign serous cystadenoma on histopathological examination, was laparoscopically removed. After the operation the CA 19-9 value returned to normal⁽¹⁰⁾.

Cases of elevated CA 19-9 levels associated with another non-malignant ovarian neoplasm, dermoid cyst, have also been reported. Madaan et al.⁽¹¹⁾ and Nanayakkara et al.⁽¹²⁾ presented the cases of two patients in whom cystic ovarian lesions were diagnosed at 27 and 57 years old, respectively. The significant elevation of the CA 19-9 antigen level in both patients was alarming: it was 1,826 U/mL and 436 U/mL, respectively. The levels of the remaining cancer markers tested (CA 125, CEA, AFP, β -hCG) in both cases did not exceed ULN. On histopathological examination of the postoperative material the presence of a dermoid cyst with no malignant component was demonstrated. In the patients the CA 19-9 level returned to normal 2 months and 6 weeks after surgery, respectively.

In 1989, Okubo et al. described an interesting case. A 35-year-old patient was admitted to hospital due to sudden retrosternal pain, dysphagia, high fever and tachycardia. On chest radiograph a 7×9 cm nodular lesion of the mediastinum was observed. Laboratory tests revealed elevated signs of inflammation and a high level of the CA 19-9 antigen: 934 U/mL, without other cancer markers being increased. After steroid therapy and antibiotic therapy the patient's clinical condition improved. CA 19-9 values decreased after 2 weeks to 48 U/mL. Following surgical removal CA 19-9 dropped to 23 U/mL. Histopathological examination revealed a bronchogenic cyst of the mediastinum without signs of malignancy and a highly elevated CA 19-9 concentration in the fluid collected from the cyst, which was 1,162,100 U/mL. Most probably the cyst secreted CA 19-9 into the lumen of the lesion and the high serum level of the antigen was caused by the inflammation of the cyst. This case shows that an elevated CA 19-9 level and an abnormal mediastinal shadow on radiograph may be caused by a benign bronchial or pulmonary disease⁽¹³⁾.

High CA 19-9 values have also been observed in gallbladder diseases. Akimoto et al. described the case of a 65-year-old woman hospitalised due to severe abdominal pain and fever (38.5°C) lasting a few days. On admission the following laboratory test results were obtained: CRP: 7.7 mg/dL, bilirubin: 0.5 mg/dL, AST: 19 U/L, ALT: 18 U/L, CEA: 1.9 ng/mL, CA 19-9: 19,392 U/mL. On abdominal ultrasound scan the presence of cholecystolithiasis with gallbladder wall thickening was revealed and calculous cholecystitis was diagnosed. The diagnosis was confirmed on abdominal CT scan. Antibiotic therapy was administered and after

11 days CRP and CA 19-9 levels decreased to 0.11 mg/dL and 1,049 U/mL, respectively. Cholecystectomy was performed 33 days after the beginning of antibiotic therapy. The procedure revealed an inflamed gallbladder and the presence of a concrement near the neck of the gallbladder; no lesions suggesting cancer were found, which was confirmed on histopathological examination. After 21 days from surgery CA 19-9 was 45 U/mL⁽¹⁴⁾.

Shah et al. observed high levels of the CA 19-9 marker in the very rare Mirizzi's syndrome. They described the case of a 51-year-old man with a long history of alcohol abuse who was admitted to hospital with abdominal pain lasting 10 days and progressing jaundice with associated dark urine. The patient denied nausea, vomiting and fever. On physical examination significant hepatomegaly was found. On admission, blood tests revealed significantly elevated liver indicators (bilirubin: 18 mg/dL, AST: 167 U/L, ALT: 497 U/L, GGTP: 1,180 U/L). The CA 19-9 level was 4,618 U/mL and the CEA level was 2.4 ng/mL. On computed tomography scan the presence of a calculus in the lumen of the gallbladder and in the distal cystic duct with intrahepatic bile duct dilation was found. Endoscopic ultrasonography (EUS) and ERCP confirmed the presence of a 14 mm-long concrement in the cystic duct causing compression of the bile ducts. During ERCP a stent was inserted into the bile ducts, which led to the resolution of jaundice and the normalisation of liver indicators. A scheduled cholecystectomy was performed after a month. Histopathological examination of the collected material excluded cancer lesions. After the procedure CA 19-9 levels were checked in outpatient settings and after a few months from cholecystectomy they were within the normal range⁽¹⁵⁾.

These reports indicate that a CA 19-9 level cannot be used to confirm or exclude a malignant lesion with certainty. A very high concentration of CA 19-9 can have a different cause than cancer: in the cases described in the present study it was usually cholestasis associated with benign biliary diseases or benign ovarian or pulmonary neoplasms that led to the elevation of this marker. In order to confirm the diagnosis one needs to utilise other diagnostic tools as well such as, for example, ultrasound, computed tomography and, in specific cases, invasive methods. It is also important to monitor CA 19-9 levels after the resolution of symptoms since a long-term decrease of CA 19-9 is evidence for a benign abnormality, while an increase raises the suspicion of a malignant lesion and requires further diagnostic investigation.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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