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CLINICAL CASE

Persistent elevation of Ca 19-9 and an unexpected finding. A case report[☆]



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KEYWORDS

Ca 19-9;
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Abstract

Background: Tumour markers are substances produced by the tumour itself, or by the host in response to a tumour. These markers could be measured either in the blood or in body secretions. One of the most common tumour markers used in gastrointestinal diseases is Ca 19-9. It is the marker most used for pancreatic cancer, but can be elevated in many benign processes. Thus, it is not a specific marker.

Clinical case: The case is presented of a male patient with 4 years of moderate abdominal pain, weight loss, and persistent elevation of Ca 19-9. After an extensive work-up, renal and hepatic cysts were found, as well as steatosis and, apparently, a gallbladder polyp. With these findings and the persistent elevation of Ca 19-9, it was decided to operate the patient. An exploratory laparoscopy was performed showing multiple, yellowish nodular lesions all over the hepatic surface suggestive of metastases, as well as simple hepatic cysts. Pathology reported biliary hamartomas, steatosis, and chronic cholecystitis.

After 2 years of follow up, although there is no evidence of malignant neoplasia, there is still an elevation of Ca 19-9.

Conclusion: The persistent elevation of Ca 19-9 is probably due to the presence of multiple benign diseases such as steatosis, urolithiasis, hepatic and renal cysts, and cholecystitis. An algorithm is needed for healthy patients with elevated levels of Ca 19-9 marker, in order to lower costs, avoid misdiagnoses, and improve management.

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PALABRAS CLAVE

Ca 19-9;
Hamartomas;
Biliar;
Von Meyenburg;
Benigno

Elevación persistente de Ca 19-9 y un hallazgo inesperado. Reporte de un caso**Resumen**

Antecedentes: Los marcadores tumorales son sustancias producidas por un tumor o por el huésped en respuesta a dicho tumor. Estos marcadores pueden ser medidos en sangre o en secreciones. Uno de los marcadores más utilizados en enfermedades gastrointestinales es el Ca 19-9. Este marcador es el más utilizado para cáncer de origen biliopancreático, pero puede modificarse en múltiples padecimientos benignos; por tanto, no es un marcador específico.

Caso clínico: Paciente masculino con cuadro de 4 años de evolución, caracterizado por: dolor abdominal difuso, acompañado de pérdida de peso y elevación de Ca 19-9. Posterior a protocolo de estudio extenso, se encontró: quistes renales y hepáticos, esteatosis hepática y un aparente pólipo vesicular. Por elevación persistente del marcador y hallazgos no concluyentes en estudios de extensión, se decidió realizar intervención quirúrgica. Durante la laparoscopia diagnóstica, se observaron: quistes hepáticos simples y múltiples lesiones nodulares, amarillas en la superficie hepática, sugestivas de enfermedad metastásica. El reporte de enfermedad fue: hamartomas biliares, esteatosis hepática y colecistitis crónica, sin reportar malignidad.

A 2 años de seguimiento el paciente presenta evolución favorable, sin evidencia de neoplasia a nivel biliopancreático, pero con una persistente elevación de Ca 19-9.

Conclusión: La elevación persistente de Ca19-9 del caso presentado probablemente sea secundaria a la presencia de enfermedades benignas, como: esteatosis hepática, litiasis renal, quistes renales y hepáticos, y colecistitis. Es necesario un algoritmo para pacientes sanos con elevación persistente de niveles de Ca-19-9 a fin de disminuir costos, evitar diagnósticos erróneos y optimizar el manejo correspondiente.

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Background

Tumour markers are substances produced by the tumour itself, or by the host in response to a tumour. These markers can be measured either in the blood or in body secretions.¹ The ideal marker should be specific to each type of tumour, detected in small tumours, with concentration directly proportional to size, measurable by simple, economical methods and not be elevated in healthy patients or those with benign processes.² The first recognised tumour marker was the protein Bence Jones in patients with multiple myeloma. There are many, diverse tumour markers, and their functions are various. The latter may include hormonal, enzymatic and isoenzymes, among others.^{1,2}

The most common tumour marker used in gastrointestinal diseases is Ca 19-9.³ It is an antigen associated with an isolated tumour and initially used in a mouse spleen cell hybridoma technique with colorectal cancer human cells.⁴ This marker is mostly used in pancreatic tumours for monitoring, as treatment response, prognosis and even the detection of recurrence or metastases.⁵ However, it may be elevated in benign processes such as: hepatic steatosis, cholangitis,^{6,7} cholecystitis, endometriosis, pancreatitis, renal lithiasis, and hepatic or renal cysts,⁸⁻¹⁰ pulmonary fibrosis and atelectasis.⁶⁻¹¹ False positives have also been reported by interference. The most well known are the rheumatoid factor or those owing to the presence of heterophile antibodies.¹² It is therefore not a specific marker.

Where a malignant intestinal disease is suspected, the Ca 19-9 marker has a sensitivity of 80%, a specificity of 90%, a predictive positive value of 69% and a predictive negative value of 90%,^{13,14} but a diagnostic challenge arises when there is elevation of this marker, with no proof of a tumour.^{15,16}

The case is reported of persistent elevation of the Ca 19-9 marker in a patient with chronic abdominal pain and weight loss, together with the surgical approach used and subsequent follow-up. In addition, a review of the literature related to the case was made.

Clinical case

A male patient aged 56, with a history of bilateral renal lithiasis, a double J catheter in 2013 and transurethral resection of the prostate, due to obstructive prostatic hyperplasia on 2 occasions.

He presented with clinical symptoms of 4 year onset, with diffuse abdominal pain radiating to the lumbar region with an intensity of 5/10, colicky, with periods of complete remission, accompanied by chronic constipation, flatulence and abdominal swelling. He also stated that he had lost 8 kg in weight in 3 months for no apparent reason. Medical treatment was administered as treatment for functional gastrointestinal disorder.

Given the persistence of the abdominal pain, constipation and swelling despite medical treatment, an exhaustive study protocol was initiated and Ca 19-9 levels of 115.9 U/ml

were found. The study was complemented by an X-ray of the chest, an enema for the colon, an endoscopy and colonoscopy, with no remarkable findings.

A tumour marker was requested for a second time which resulted in levels of 124.3 U/ml. An ultrasound of the liver and bile ducts were made (Fig. 1) and these were complemented by axial computed tomography (Fig. 2), nuclear magnetic resonance (Fig. 3) and endoscopic ultrasound (Fig. 4). In the studies requested the following were



Figure 1 Hepatic with thick ultrasound scan pattern, suggestive of a chronic inflammatory process. Isoechoic image to the wall is observed, probably suggestive of 14 mm (arrow) polyp in neck.



Figure 2 Hypodense images (arrows), on hepatic parenchyma which are not enhanced on application of contrast medium. Increase in the density of hepatic parenchyma.



Figure 3 Hypo and hyperintense lesions in weighted sequences to T2, with tendency to coalesce and with no union with bile duct (straight arrow). Bilateral renal cysts (curved arrow).

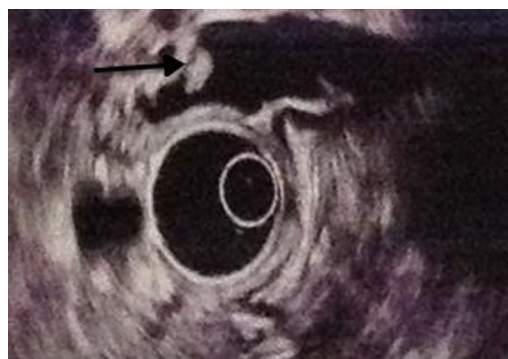


Figure 4 Hyper-echogenic 10 mm lesion on its surface, which does not project a posterior acoustic shadow, which may correspond to a vesicular polyp vs. biliary sludge (arrow).

reported: renal and hepatic cysts, renal lithiasis, chronic inflammatory process of the liver and an image suggestive of gallbladder polyp. Due to these findings the patient was referred to the Gastrointestinal Surgery Service. Assessment began with a new request for a tumour marker and levels of 161.9 U/ml were found.

As a result of these findings and the persistent elevation of Ca 19-9, a surgical approach was decided using diagnostic laparoscopy due to the probability of gallbladder cancer. The laparoscopic procedure was performed without complication, and multiple yellowish nodular lesions were found all over the hepatic surface (Fig. 5) suggestive of liver metastasis, in addition to simple hepatic cysts. A liver biopsy was performed, to confirm the diagnosis and was sent for intra-operative analysis. Pathology reported biliary hamartomas, compatible with von Meyenburg complexes. The procedure continued undertaking standard cholecystectomy. The final pathology report was: chronic cholecystitis without polyp, macro and micro vesicular steatosis below 10% (Fig. 6).

The postsurgical period evolved satisfactorily, with no complications and the patient was discharged 24 h after surgery. After 2 years of follow up, at the outpatient department, the patient stated he had a slight improvement of symptoms, without any more weight loss but with persistence of slightly swollen abdomen and constipation, and with occasional abdominal pain. The latest Ca 19-9 control showed levels of 187.8 U/ml. Analysis revealed no evidence of biliopancreatic disease or gastrointestinal tumours. Only



Figure 5 Multiple lesions throughout the hepatic, suggestive of carcinomatosis, in addition to simple hepatic cysts.

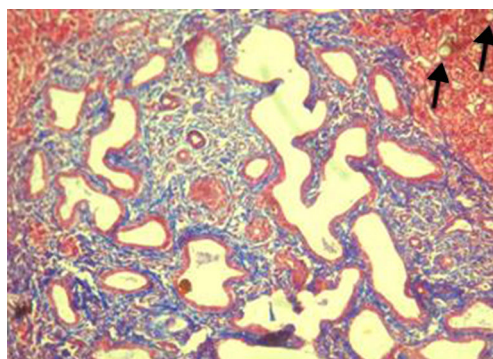


Figure 6 Microscopic image with Masson technique, where biliary hamartomas and fatty corpuscles are observed, in hepatic parenchyma (arrows) (Masson's trichrome stain; 10× enlarged).

that reported previously (hepatic and renal cysts, renal lithiasis) was found.

Discussion

The elevation of Ca 19-9 with no proof of neoplasia is a diagnostic problem. A study in China demonstrated that out of 62,976 healthy and asymptomatic patients, 1.3% presented with significant elevation of Ca 19-9 and required further tests to rule out the presence of malignancies making use of public resources without, in some cases, reaching a definitive diagnosis.¹⁷ Up until now, there have been no specific guidelines, although in this study a study algorithm is recommended for patients with elevation of this marker, and would consist of monthly, quarterly and half-yearly follow-up of patients with control marker levels and additional consultancy studies.¹⁷

The case we present is of a patient with elevation of Ca 19-9 for over one year, where malignancies were ruled out, but with multiple benign diseases associated with the elevation of the marker. It was decided that surgery be performed due to the finding of a gallbladder polyp over 10 mm, with suspicion of gallbladder cancer. On undertaking the diagnostic laparoscopy, multiple nodular lesions suggestive of hepatic metastases were observed. However, the intra-operative studies reported von Meyenburg complexes, also known as biliary hamartomas.

This benign disease is characterised by circular, isolated and irregular bell-shaped lesions.¹⁸ They are located below the Glisson capsule, are of firm consistency, grey or yellow, surrounded by a thick fibrous stroma. A cystic dilation of the bile ducts covered with a single layer of simple cubic epithelium was also determined under the microscope. It has a prevalence of 0.68–2.9%. They are clinically asymptomatic and, at the same time, are discovered incidentally.^{19,20} When symptoms are present, they generally produce signs of cholangitis with recurrent fever or diffuse abdominal pain. They do not affect liver functioning tests.¹⁸

In computed axial tomography, lesions under 1.5 cm with irregular edges were observed, which did not appear enhanced when a contrast medium was applied. In the magnetic resonance, in T1, hypointense cystic lesions may be observed and in T2 hyperintense lesions with no

bile duct union were observed.²⁰ Differential diagnosis included: hepatic metastasis,²¹ hepatocellular carcinoma, microabscesses, schistosomiasis, granulomatous diseases, and hepatic cysts.¹⁹

In accordance with that reviewed in the literature, a few cases of malignant degeneration to cholangiocarcinoma²² were reported, or even hepatocarcinoma, and regular monitoring is therefore important.

It is noteworthy that, in the case of our patient, high Ca 19-9 figures were present and these were even higher than in previous controls, but with no evidence of malignancy. The cause of elevation of this marker appears to be linked to the hepatic steatosis reported in the biopsy, together with the presence of renal lithiasis and both hepatic and renal cysts.²¹

Finally, this case represents a diagnostic challenge since despite tumour marker elevation, there is no evidence of tumour. Several diseases associated with the elevation of this protein do exist and close monitoring of the patient is therefore necessary. Furthermore an algorithm is needed for healthy patients with elevated levels of Ca 19-9 marker to lower costs and improve healthcare quality.

Conflict of interests

The authors have no conflict of interests to declare.

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