



# A woman with abdominal pain, jaundice and elevated CA 19.9

Alessandra Fusco<sup>1</sup> · Francesca Baorda<sup>1</sup> · Lorenzo Porta<sup>2</sup> · Alessandro A. Lemos<sup>3</sup> · Lucio Caccamo<sup>4</sup> · Eleonora Tobaldini<sup>1</sup> · Giorgio Costantino<sup>1</sup>

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## Case presentation

### Francesca Baorda and Alessandra Fusco

A 54-year-old woman presented to the emergency department (ED) complaining of severe epigastric and right hypochondrial pain with back radiation, weight loss of 14 kg within the previous 3 months, asthenia, hyperchromic urine (for the last 7 days) and jaundice (for the last 3 days). For these symptoms, the general practitioner prescribed ciprofloxacin 500 mg twice a day and esomeprazole. Her past medical history was unremarkable.

The blood tests indicated elevated hepatic markers—serum glutamic oxaloacetic transaminase (SGOT) 403 IU/l (reference range RR: 10–35 IU/l), serum glutamic pyruvate transaminase (SGPT) 650 IU/l (RR: 10–40 IU/l in female), total bilirubin 7.2 mg/dl (RR: 0.2–1.2 mg/dl), conjugated bilirubin 6.90 mg/dl (RR: <0.3 mg/dl) and slightly elevated C-reactive protein (CRP) 4.33 mg/dl (RR: <0.5 mg/dl)—and normal complete blood count and electrolytes.

For the presence of jaundice, the patient underwent an upper abdominal ultrasound, which revealed a distended gallbladder with diffuse wall thickening, but no obvious evidence of calcific gallstones. Intra- and extrahepatic bile

ducts, as well as the common bile duct, appeared dilated and the intrapancreatic portion of the bile duct seemed partially occupied by a hyperechogenic material, suggesting the presence of a distal cholangiocarcinoma.

Given the suspicion of malignancy, the patient was admitted to the medical department.

To confirm our hypothesis, we decided first to dose the CA 19.9, which was reported as extremely elevated: 9606.00 IU/ml (RR: 0–27 IU/ml).

CA 19.9 is a carbohydrate antigen usually synthesized by both the pancreatic and biliary ductal cells and by the epithelial cells of the stomach, colon, endometrium and salivary glands. Normally present in serum in small quantities, its levels can increase in several neoplastic and benign conditions. The usefulness of this tumoral marker is still debated in the literature, especially because of the high costs and the poor significance if improperly requested. Nevertheless, this examination is easily available and its use in the differential diagnosis of biliary stenosis is supported by several published investigations [1, 2]. Since values higher than 1000 IU/ml have a theoretically 100% specificity for a malignancy [3], we interpreted our result as highly specific for a cholangiocarcinoma [4].

Consequently, we decided to perform a contrast-enhanced abdominal computed tomography (CT) to characterize the infiltration of the tumor and to decide on the best therapeutic strategy.

### Alessandro Lemos

Contrast-enhanced CT scan of the abdomen showed a normal liver with no evidence of focal lesions. The wall of the gallbladder was diffusely calcified and moderately thickened, keeping with “milk of calcium gallbladder” (Fig. 1).

Milk of calcium is a term given to dependent, sedimented calcification within a cystic structure or hollow organ. This

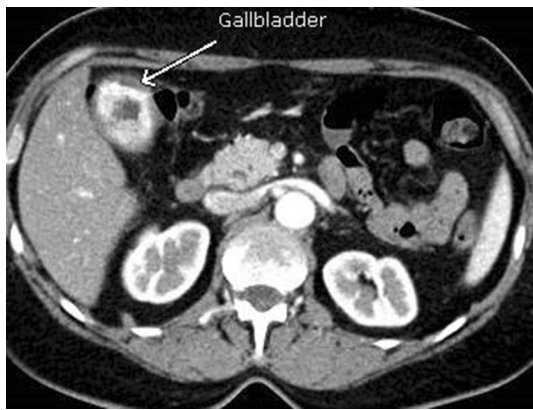
✉ Alessandra Fusco  
ales.fusco@gmail.com

<sup>1</sup> Department of Internal Medicine, Ca' Granda IRCCS Foundation, Policlinico Hospital, Via F. Sforza 35, Milan, Italy

<sup>2</sup> Department of Biomedical and Clinical Sciences, “L. Sacco” University of Milan, Milan, Italy

<sup>3</sup> Department of Radiology, Ca' Granda IRCCS Foundation, Policlinico Hospital, Milan, Italy

<sup>4</sup> General Surgery and Liver Transplant Unit, Ca' Granda IRCCS Foundation, Policlinico Hospital, Milan, Italy



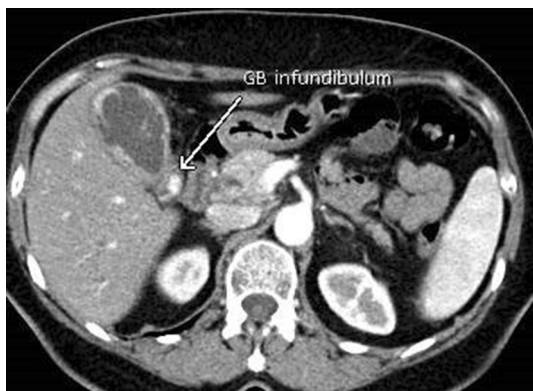
**Fig. 1** Axial contrast-enhanced CT scan of the abdomen shows diffusely calcified gallbladder wall in keeping with “milk of calcium” gallbladder (arrow)

sort of colloidal calcium suspension layering is a benign condition and can occur in various regions: renal cysts (most common), breast cysts, gallbladder, mesenteric cyst and tunica albuginea (less common) [5].

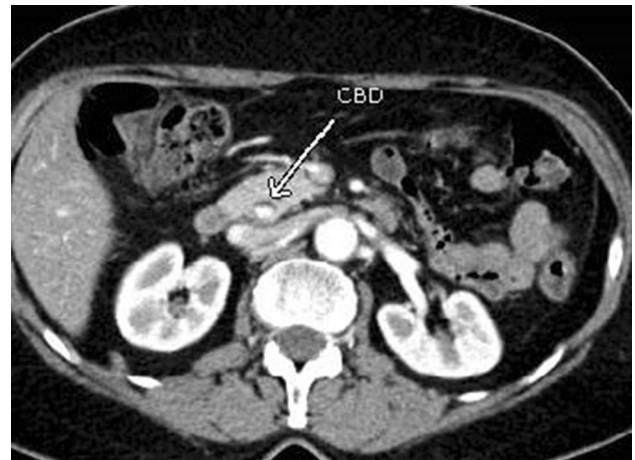
In addition, there was evidence of a calcified gallstone at the infundibulum of the gallbladder and two hyperdense stones in the common bile duct (CBD, Figs. 2, 3), causing significant biliary dilatation.

Ultrasonography (US) has a sensitivity and specificity for cholangiocarcinoma of 73.5 and 61.5%, respectively [6]. CT is generally more sensitive and provides a comprehensive evaluation of solid organs, retroperitoneal space and vascular structures. However, according to a retrospective study by Heinzow et al., the accuracy of CT in detecting bile duct malignancies is only 79%. Thus, the absence of an obvious mass does not entirely exclude the presence of malignancy [7].

Since there were discordant results between CA 19.9, US and CT findings, a CT/positron emission tomography (PET)



**Fig. 2** An impacted calcified gallstone at the neck of the gallbladder is seen (arrow)



**Fig. 3** The common bile duct (CBD) is dilated and there is an obstructing calculus in the distal CBD (arrow)

and an endoscopic ultrasound (EUS) were necessary to rule out the possibility of malignancy.

The images of the CT/PET were not suggestive for a pathological accumulation of focal glucose analogs, which would have confirmed the presence of the malignancy. A recent meta-analysis by Annunziata et al. provides the following results: sensitivity 82% (95% confidence interval, CI 78–85%) and specificity 75% (95% CI 65–84%), with an area under the curve (AUC) of 0.89 [8].

### Giorgio Costantino and Lorenzo Porta

Though the patient spontaneously started to gradually feel better (the jaundice and the abdominal pain decreased, the blood tests revealed a reduction in the inflammation markers and an improvement in the hepatic function), we performed an EUS to evaluate the possible neoplastic mass. The examination revealed the presence of dilatation of the common biliary duct (CBD) (maximum diameter of 9.3 mm) and biliary sludge at the confluence of the cystic and the common hepatic duct. Biliary sludge and a biliary calculus of 8.9 mm diameter were also present in the CBD behind the ampulla of Vater. The gallbladder was full of stones, with slightly thickened walls (max 5 mm) and without any sign of vascularization. The examination confirmed the absence of malignancy and showed choledocholithiasis and gallstones only.

The use of an endoscopic approach such as the endoscopic retrograde cholangiopancreatography (ERCP) or EUS is crucial in establishing a diagnosis of a cholangiocarcinoma. Among these two, EUS is highly accurate and less invasive than ERCP. Thus, EUS is recommended to differentiate benign conditions such as gallstones from malignant biliary obstructions and to establish the extent of the neoplastic infiltration. According to a study by Sotoudehmanesh et al., the sensitivity, specificity and accuracy of EUS for

**Table 1** Sensitivity, specificity, accuracy and positive and negative likelihood ratio of the diagnostic tools

	Sensitivity (%)	Specificity (%)	Accuracy (%)	Likelihood ratio +	Likelihood ratio –
Abdominal ultrasound (US) [6]	73.5	61.5	70.9	1.91 <sup>a</sup>	0.43 <sup>a</sup>
Computer tomography (CT) [7]	67	82	79	3.72 <sup>a</sup>	0.4 <sup>a</sup>
Endoscopic ultrasound (EUS) [9]	89	100	90.9	89 <sup>a</sup>	0.11 <sup>a</sup>
Endoscopic retrograde cholangiopancreatography (ERCP) [12]	49	96.33	60.66	13.35 <sup>a</sup>	0.53 <sup>a</sup>
Magnetic resonance (MR) [13]	83.3	100	98	83.3 <sup>a</sup>	0.17 <sup>a</sup>
Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) [8]	82	75	–	3.28 <sup>a</sup>	0.24 <sup>a</sup>
Carbohydrate antigen (CA) 19.9 > normal values [2]	72	84	–	4.93 <sup>a</sup>	0.35 <sup>a</sup>
<sup>b</sup> CA 19.9 > 1000 U/ml [3]	–	100	–	–	–

<sup>a</sup>These values were calculated using the sensitivity and specificity reported in literature; some values could not be calculated

<sup>b</sup>Theoretic values for maximizing SE and SP, calculated by La Grega et al.

– Missing values are due to lack of published data on the issue

diagnosing a malignancy are, respectively, 89.5, 100 and 90.9% [9]. Furthermore, a study by Saifuku et al. demonstrates a high diagnostic ability of EUS with a sensitivity of 90.5%, a specificity of 100% and an accuracy of 94.1%. They also compared the accuracy of both the EUS and the CA 19.9 in differentiating malignant and benign pathologies, with a sensitivity, specificity and accuracy, respectively, of 94.1, 82.3, 88.2% for EUS, 76.5, 70.6, 73.5% for values of CA 19.9 > 37 U/ml and 53, 82.4, 67.7% for values of CA 19.9 > 100 U/ml [10].

### Lucio Caccamo

Apart from the first US, all the other imaging techniques (CT, PET and EUS) failed to demonstrate the presence of a mass. Only two calcific stones were found in the distal portion of the common bile duct, as well as a stone in the infundibulum of the gallbladder. Since a clinical spontaneous improvement was observed and due to the presence of a dilated biliary tree secondary to a distal lithiasic obstruction, we decided to perform an ERCP (Table 1).

The examination confirmed the presence of gallstones that were hence removed. The patient felt better, and both bilirubin and transaminases levels normalized. In 5 days, the CA 19.9 showed an important reduction, though still over the threshold: 600 U/ml (with a normal value < 27 U/ml). This reduction was interpreted as a consequence of the cholestatic improvement, and the patient was discharged with the program of an elective laparoscopic cholecystectomy. The operation was performed after 1 month, the specimen did not reveal any presence of malignancy and the postoperative course was regular. Three months after surgery, the patient is in good shape, with some weight gain and a CA 19.9 level of 12.5 U/ml.

## Conclusion

**Francesca Baorda, Lucio Caccamo, Giorgio Costantino, Alessandra Fusco, Alessandro Lemos, Lorenzo Porta and Eleonora Tobaldini**

In our case, US and CA 19.9 results were strongly suggestive of malignancy. One of the reasons why the CA 19.9 levels were abnormally high might be that it is produced by the epithelium of the biliary duct and then secreted into the biliary system. Therefore, the presence of an obstruction (even benign) of the biliary tract promoted the excretion, increased absorption and transfer to serum of this oncological marker. This is the reason why after restoration of the biliary flow, there was a reduction of CA 19.9 level.

Some investigators report significantly high CA 19.9 levels in the absence of malignancy [11]. Nevertheless, since the CA 19.9 is highly specific (the level we found has a theoretical specificity of 100%), several second-level examinations were mandatory to rule out the presence of a cholangiocarcinoma (CT, EU, ERCP). As demonstrated in our case, high levels of CA 19.9 do not necessarily indicate the presence of malignancy. Therefore, second-level examinations are mandatory to confirm or rule out malignancy.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statement of human and animal rights** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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