

## Endoscopic ultrasonography in patients with elevated carbohydrate antigen 19-9 of obscure origin

Jae Hoon Cheong, Gwang Ha Kim, Ji Yoon Moon, Bong Eun Lee, Dong Yup Ryu, Dong Uk Kim, Hyung-Il Seo, Geun Am Song

Jae Hoon Cheong, Gwang Ha Kim, Ji Yoon Moon, Bong Eun Lee, Dong Yup Ryu, Dong Uk Kim, Geun Am Song, Department of Internal Medicine, Pusan National University School of Medicine, and Biomedical Research Institute, Pusan National University Hospital, Busan 602-739, South Korea

Hyung-Il Seo, Department of Surgery, Pusan National University School of Medicine, Busan 602-739, South Korea

Author contributions: Kim GH and Song GA designed the research; Moon JY, Lee BE, Ryu DY and Seo HI analyzed the data; Cheong JH and Kim GH wrote the paper; Kim GH and Kim DU performed the research.

Supported by A grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family Affairs, Republic of Korea, No. 0920050; Pusan National University Hospital Clinical Research Grant (2012)

Correspondence to: Dr. Gwang Ha Kim, MD, Department of Internal Medicine, Pusan National University School of Medicine, and Biomedical Research Institute, Pusan National University Hospital, 1-10, Ami-dong, Seo-gu, Busan 602-739, South Korea. doc0224@pusan.ac.kr

Telephone: +82-51-2407869 Fax: +82-51-2448180

Received: May 12, 2012 Revised: September 13, 2012

Accepted: February 5, 2013

Published online: May 16, 2013

**RESULTS:** Of the 17 patients, gallbladder sludge was detected in 16 patients (94.1%) and common bile duct sludge was observed in 3 patients (17.6%). After the administration of ursodeoxycholic acid to 12 of the patients with gallbladder sludge, CA 19-9 levels normalized in 6 of the patients after a median of 4.5 mo.

**CONCLUSION:** EUS is a useful diagnostic method for patients with elevated CA 19-9 levels of obscure origin, even if the reason for abnormal levels of this serum marker cannot be determined through prior examinations, including abdominal CT.

© 2013 Baishideng. All rights reserved.

**Key words:** Carbohydrate antigen 19-9; Endoscopic ultrasonography; Gallbladder; Ursodeoxycholic acid

Cheong JH, Kim GH, Moon JY, Lee BE, Ryu DY, Kim DU, Seo HI, Song GA. Endoscopic ultrasonography in patients with elevated carbohydrate antigen 19-9 of obscure origin. *World J Gastrointest Endosc* 2013; 5(5): 251-254 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/251.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.251>

### Abstract

**AIM:** To evaluate the efficacy of endoscopic ultrasonography (EUS) in patients with elevated carbohydrate antigen (CA) 19-9 levels of obscure origin.

**METHODS:** Patients who had visited Pusan National University Hospital because of elevated serum CA 19-9 levels, between January 2007 and December 2009, were retrospectively enrolled. EUS had been performed on all subjects, in addition to routine blood tests, endoscopy, abdominal computed tomography (CT) and other clinical exams, which had not revealed any abnormal findings suggestive of the origin of the elevated CA 19-9 levels.

### INTRODUCTION

Serum carbohydrate antigen (CA) 19-9 is considered to be the best screening marker for pancreatic cancer because of its relatively high sensitivity (70%-90%) and specificity (70%-98%)<sup>[1,2]</sup>. However, CA 19-9 is also elevated in many other digestive cancers, as well as in a number of benign diseases<sup>[3,4]</sup>. Although the usefulness of CA 19-9 as a screening marker for the detection of malignancies has not yet been validated, it is not uncommon to measure serum CA 19-9 levels in asymptomatic individuals during routine health examinations.

Pancreaticobiliary disease is one of the most common

causes of benign abnormal serum CA 19-9 levels. Herein, we report 17 cases of patients with elevated serum CA 19-9 levels without any obvious pancreaticobiliary system abnormalities, as revealed on abdominal computed tomography (CT); endoscopic ultrasonography (EUS) was performed as an additional part of their diagnostic examination and was useful in these cases.

## MATERIALS AND METHODS

All patients with elevated serum CA 19-9 levels of indeterminate cause who underwent EUS in our institution between January 2007 and December 2009 were retrospectively assessed. Elevated serum CA 19-9 levels had been detected during routine cancer screenings and none of the patients had a history of cancers, surgeries or acute infections. To identify the causes of the elevated serum CA 19-9 levels, the patients, prior to the EUS examination, had provided a medical history regarding their smoking and alcohol consumption habits and had undergone a physical examination, routine blood tests (including liver and thyroid function tests), esophagogastroduodenoscopy, colonoscopy, abdominal ultrasonography, abdominal/pelvic CT and for female patients, mammography and breast ultrasonography.

EUS examinations were performed using a radial echoendoscope (GF-UM2000; Olympus, Tokyo, Japan) at either 5 or 7.5 MHz, by one experienced endoscopist. This study was reviewed and approved by the Institutional Review Board at Pusan National University Hospital. Written informed consent was obtained from all patients.

## RESULTS

Of the 17 patients, 13 (76.5%) were female and the median age of the patients was 51 years (range 28-85 years). Two of the patients consumed more than 20 g of alcohol daily. The median serum CA 19-9 level during the screening visit was 64.1 U/mL (range 40.0-381.0 IU/mL). Serum total bilirubin levels were normal in all but 1 patient. This patient had an initial value of 1.6 mg/mL (reference range was < 1.3 mg/mL), which subsequently decreased to within the normal range (1.2 mg/mL) (Table 1).

EUS revealed gallbladder (GB) sludge in 16 of the patients (94.1%) and common bile duct (CBD) sludge in 3 patients (17.6%). Mild CBD dilatation (8 mm) was noted in 1 patient, tiny GB polyps (2-3 mm in size) in 3 patients, and a pancreatic cyst (9 mm in size) was detected in 1 patient.

The median follow-up duration was 12 mo (range 3-51 mo). Of the 16 patients with GB sludge, 12 received ursodeoxycholic acid (UDCA; 600 mg/d) for 3-18 mo (median 6 mo). The median number of CA 19-9 measurements was 3, although subsequent measurements of CA 19-9 were not performed for 2 patients. Six of 11 patients who received UDCA achieved normal CA 19-9 levels after a median of 4.5 mo (range 3-8 mo) (in 1 patient, the subsequent CA 19-9 value was not assessed); 1 of the 4 patients who did not initially receive UDCA did

so 5 mo after the initial testing. Serum CA 19-9 levels remained within the normal range during the follow-up period in all patients who attained levels within the normal range as a result of UDCA therapy.

## DISCUSSION

Biliary sludge, either GB or CBD sludge, is defined as a suspension of crystals (usually cholesterol monohydrate), mucin, glycoproteins, cellular debris, and/or proteinaceous material within the bile<sup>[5-7]</sup>. Many studies have suggested that biliary sludge may be a precursor to stone formation<sup>[8,9]</sup> and a source of potential complications<sup>[10-13]</sup>. The exact mechanism underlying the elevation of serum CA 19-9 levels, associated with GB sludge, remains unclear. However, the mechanism underlying the elevation in CA 19-9 levels in patients with bile duct obstruction is assumed to be as follows. Increased biliary pressure induces bile duct cells to produce CA 19-9<sup>[14]</sup>, which accumulate in the lumen due to biliary obstruction. An increased permeability between the bile duct and the vasculature is believed to result in CA 19-9 reflux into the circulation<sup>[15]</sup>. Increased biliary pressure is suspected to be the main outcome of clinically insignificant biliary obstruction, such as is caused by biliary sludge. Furthermore, we hypothesize that sludge may flow down to the CBD during GB contractions, causing transient obstructions of the CBD outlet and increasing bile duct pressure. In this study, CBD sludge was identified by EUS in 3 of 16 patients with GB sludge, which may support our hypothesis.

Sludge may be visualized by abdominal US or EUS. The accuracy of US in detecting cholelithiasis is high, with a reported sensitivity of 92%-96%<sup>[16-19]</sup>. Nevertheless, when stones are less than 3 mm in diameter or located in the GB infundibulum, the sensitivity of US is only 65%<sup>[20]</sup>. By contrast, the sensitivity of EUS is approximately 96%<sup>[21,22]</sup>. Therefore, it is clear that EUS is the most sensitive imaging method for detecting GB sludge.

In patients in whom GB sludge has been detected in the absence of biliary symptoms, the natural history of sludge warrants appropriate management of the sludge. In patients with GB sludge and elevated serum CA 19-9 levels, GB sludge is likely to be responsible for the elevation in CA 19-9 levels. The elevated CA 19-9 levels may result in anxiety for patients regarding a potential malignancy; therefore, empirical treatment with UDCA may also represent a practical management option in such patients. The major role of UDCA is limited to the prevention of sludge formation in patients with predisposing conditions, such as weight reduction or total parenteral nutrition<sup>[23-25]</sup>. Theoretically, however, GB sludge may be more responsive to UDCA treatment than gallstones due to its higher surface-to-volume ratio. Indeed, a prospective, multicenter study showed that UDCA was associated with a 100% dissolution rate for persistent biliary sludge<sup>[26]</sup>. In the current study, 6 of 11 patients (54.5%) with GB sludge showed normalization of CA 19-9 levels after UDCA treatment, compared with 1 of 4 patients

Table 1 Summary of demographic and laboratory data and endoscopic ultrasonography findings in 17 patients with elevated serum carbohydrate antigen 19-9 values

Case	Gender	Age, yr	EUS findings			CA 19-9 level, IU/mL		Time to CA 19-9 normalization, mo	UDCA administration	Duration of UDCA administration, mo	Other findings	Follow-up duration, mo
			CBD size, mm	PD size, mm	GB sludge	CBD sludge	Last visit					
1	F	28	3	1	Yes	Yes	78.3	20.7	Yes	3		6
2	F	51	2	1	Yes	Yes	187.9	25.6	Yes	6		17
3	F	51	3	1	Yes	Yes	63.6	30.2	Yes	6	GB polyp	8
4	F	36	5	0.5	Yes	No	46.1	21.3	Yes	3		36
5	M	68	3	1	Yes	No	73.3	20.6	Yes	3		7
6	M	38	2	0.5	Yes	No	165.3	16	Yes	6		16
7	F	63	8	1	Yes	No	48.2	61.1	Yes	3		51
8	F	59	4	1	Yes	No	46.2	40.4	Yes	18		20
9	F	71	5	2	Yes	No	43.9	57.3	Yes	10		10
10	M	43	2	1	Yes	No	162.7	123.9	Yes	15		17
11	F	64	5	1	Yes	No	141.8	122.2	Yes	12	GB polyp	14
12	F	36	4	1	Yes	No	87.6	-	Yes	3		3
13	M	46	3	2	Yes	No	381	19.4	No	5		5
14	F	30	4	2	Yes	No	64.1	50.4	No			3
15	F	55	3	1	Yes	No	51.4	54.1	No			29
16	F	40	4	1	Yes	No	40	43.9	No			12
17	F	85	6	1	No	No	40.3	-	No		GB polyp, Pancreatic cyst	3

CBD: Common bile duct; PD: Pancreatic duct; GB: Gallbladder; UDCA: Ursodeoxycholic acid.

(25%) who did not receive UDCA. This finding appears to support the proposed relationship between GB sludge and elevated CA 19-9 levels.

Additionally, in this study, the median duration of UDCA administration was 4.5 mo in the 6 patients whose CA 19-9 levels normalized, compared with 12 mo for the patients who did not achieve CA 19-9 level normalization. Therefore, although UDCA treatment appears to be effective for normalizing CA 19-9 levels, it should be discontinued if CA 19-9 levels are not decreased after 6 mo of therapy.

To our knowledge, the utility of EUS in determining the potential cause of CA 19-9 level elevation in patients has not been previously described. This study demonstrated that EUS is a useful diagnostic method in patients with elevated CA 19-9 levels of obscure origin, despite inconclusive results from prior examinations, including endoscopy and abdominal/pelvic CT. In addition, the current findings indicate that UDCA therapy may be effective for normalizing CA 19-9 levels in patients with GB sludge. Additional large, prospective studies may clarify the association between CA 19-9 levels, the present of GB sludge, and UDCA treatment.

## COMMENTS

### Background

Serum carbohydrate antigen (CA) 19-9 levels are commonly examined as part of cancer screening among asymptomatic individuals. However, it can also be elevated by conditions other than pancreatic cancer, as well as in the absence of any specific diseases. When physicians encounter a patient with an elevated CA 19-9 level, they search for possible hidden malignancies. In many cases, although several tests are performed, the putative cause remains unknown.

### Research frontiers

Endoscopic ultrasonography (EUS) can detect small lesions in the pancreaticobiliary system that conventional ultrasound (US) or computed tomography (CT) cannot. Therefore, in this study, the authors examined the efficacy of EUS in patients with elevated CA 19-9 levels of obscure origin.

### Innovations and breakthroughs

Using EUS, the authors identified gallbladder and bile duct sludge as possible causes of elevated CA 19-9 levels. The presence of this gallbladder sludge had not been detected by transabdominal US and abdominal CT.

## Applications

EUS can be used to identify causes of elevated CA 19-9 levels in patients when other examinations show non-specific results.

## Peer review

Although this paper is a single center study with a small number of subjects, the novel application of EUS for patients with elevated levels of this tumor marker is an attractive and potentially promising modality for investigating the pancreaticobiliary system.

## REFERENCES

- 1 Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. *J Gastroenterol Hepatol* 2004; **19**: 182-186 [PMID: 14731128 DOI: 10.1111/j.1440-1746.2004.03219.x]
- 2 Nazli O, Bozdog AD, Tansug T, Kir R, Kaymak E. The diagnostic importance of CEA and CA 19-9 for the early diagnosis of pancreatic carcinoma. *Hepatogastroenterology* 2000; **47**: 1750-1752 [PMID: 11149048]
- 3 Kim BJ, Lee KT, Moon TG, Kang P, Lee JK, Kim JJ, Rhee JC. How do we interpret an elevated carbohydrate antigen 19-9 level in asymptomatic subjects? *Dig Liver Dis* 2009; **41**: 364-369 [PMID: 19162573 DOI: 10.1016/j.dld.2008.12.094]
- 4 Ventrucci M, Pozzato P, Cipolla A, Uomo G. Persistent elevation of serum CA 19-9 with no evidence of malignant disease. *Dig Liver Dis* 2009; **41**: 357-363 [PMID: 18602352 DOI: 10.1016/j.dld.2008.04.002]
- 5 Carey MC, Cahalane MJ. Whither biliary sludge? *Gastroenterology* 1988; **95**: 508-523 [PMID: 3292341]
- 6 Lee SP, Nicholls JF. Nature and composition of biliary sludge. *Gastroenterology* 1986; **90**: 677-686 [PMID: 3943697]
- 7 Allen B, Bernhoft R, Blanckaert N, Svanvik J, Filly R, Gooding G, Way L. Sludge is calcium bilirubinate associated with bile stasis. *Am J Surg* 1981; **141**: 51-56 [PMID: 7457727 DOI: 10.1016/0002-9610(81)90011-8]
- 8 Lee SP, Maher K, Nicholls JF. Origin and fate of biliary sludge. *Gastroenterology* 1988; **94**: 170-176 [PMID: 3275565]
- 9 Johnston DE, Kaplan MM. Pathogenesis and treatment of gallstones. *N Engl J Med* 1993; **328**: 412-421 [PMID: 8421460 DOI: 10.1056/NEJM199302113280608]
- 10 Janowitz P, Kratzer W, Zemmler T, Tudyka J, Wechsler JG. Gallbladder sludge: spontaneous course and incidence of complications in patients without stones. *Hepatology* 1994; **20**: 291-294 [PMID: 8045489 DOI: 10.1002/hep.1840200204]
- 11 Ohara N, Schaefer J. Clinical significance of biliary sludge. *J Clin Gastroenterol* 1990; **12**: 291-294 [PMID: 2193981 DOI: 10.1097/00004836-199006000-00011]
- 12 Grier JF, Cohen SW, Grafton WD, Gholson CF. Acute suppurative cholangitis associated with choledochal sludge. *Am J Gastroenterol* 1994; **89**: 617-619 [PMID: 8147369]
- 13 Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N Engl J Med* 1992; **326**: 589-593 [PMID: 1734248 DOI: 10.1056/NEJM199202273260902]
- 14 Tolliver BA, O'Brien BL. Elevated tumor-associated antigen CA 19-9 in a patient with an enlarged pancreas: does it always imply malignancy? *South Med J* 1997; **90**: 89-90 [PMID: 9003836 DOI: 10.1097/00007611-199701000-00023]
- 15 Murohisa T, Sugaya H, Tetsuka I, Suzuki T, Harada T. A case of common bile duct stone with cholangitis presenting an extraordinarily high serum CA19-9 value. *Intern Med* 1992; **31**: 516-520 [PMID: 1633361 DOI: 10.2169/internalmedicine.31.516]
- 16 Hessler PC, Hill DS, Deforie FM, Rocco AF. High accuracy sonographic recognition of gallstones. *AJR Am J Roentgenol* 1981; **136**: 517-520 [PMID: 6781288]
- 17 Cooperberg PL, Burhenne HJ. Real-time ultrasonography. Diagnostic technique of choice in calculous gallbladder disease. *N Engl J Med* 1980; **302**: 1277-1279 [PMID: 7366693 DOI: 10.1056/NEJM198006053022303]
- 18 Lee CL, Wu CH, Chen TK, Lai YC, Yang SS, Huang CS, Chen DF. Prospective study of abdominal ultrasonography before laparoscopic cholecystectomy. *J Clin Gastroenterol* 1993; **16**: 113-116 [PMID: 8463613 DOI: 10.1097/00004836-199303000-00007]
- 19 McIntosh DM, Penney HF. Gray-scale ultrasonography as a screening procedure in the detection of gallbladder disease. *Radiology* 1980; **136**: 725-727 [PMID: 7403554]
- 20 Kurol M, Forsberg L. Ultrasonography in the diagnosis of acute cholecystitis. *Acta Radiol Diagn (Stockh)* 1984; **25**: 379-383 [PMID: 6391092]
- 21 Dahan P, Andant C, Lévy P, Amouyal P, Amouyal G, Dumont M, Erlinger S, Sauvanet A, Belghiti J, Zins M, Vilgrain V, Bernades P. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. *Gut* 1996; **38**: 277-281 [PMID: 8801211 DOI: 10.1136/gut.38.2.277]
- 22 Dill JE, Hill S, Callis J, Berkhouse L, Evans P, Martin D, Palmer ST. Combined endoscopic ultrasound and stimulated biliary drainage in cholecystitis and microlithiasis--diagnoses and outcomes. *Endoscopy* 1995; **27**: 424-427 [PMID: 8549438 DOI: 10.1055/s-2007-1005734]
- 23 Broomfield PH, Chopra R, Sheinbaum RC, Bonorris GG, Silverman A, Schoenfield LJ, Marks JW. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. *N Engl J Med* 1988; **319**: 1567-1572 [PMID: 3200265 DOI: 10.1056/NEJM198812153192403]
- 24 Shiffman ML, Kaplan GD, Brinkman-Kaplan V, Vickers FF. Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. *Ann Intern Med* 1995; **122**: 899-905 [PMID: 7755224]
- 25 Worobetz LJ, Inglis FG, Shaffer EA. The effect of ursodeoxycholic acid therapy on gallstone formation in the morbidly obese during rapid weight loss. *Am J Gastroenterol* 1993; **88**: 1705-1710 [PMID: 8213711]
- 26 Guma C, Viola L, Apestegui C, Pinchuk L, Groppa J, Michelini J, Martínez B, Bolaños R, Toselli L. [Therapeutic efficacy of ursodeoxycholic acid in persistent gallbladder lithiasis and persistent biliary sludge: preliminary results of a multicenter experience]. *Acta Gastroenterol Latinoam* 1994; **24**: 233-237 [PMID: 7701907]

P- Reviewer Eysselein VE S- Editor Song XX  
L- Editor Roemmele A E- Editor Zhang DN

