Elevated serum CA 19-9 level associated with a splenic cyst: which is the actual clinical management?
Review of the literature

Ann. Ital. Chir., 2015 86: 22-29
pii: S0003469X15023167

Vittorio Bresadola, Riccardo Pravisani, Giovanni Terrosu, Andrea Risaliti

General Surgery and Transplantation Unit, University Hospital of Udine, Italy

Elevated serum CA 19-9 level associated with a splenic cyst: which is the actual clinical management? Review of the literature

Splenic cysts are relatively rare entities. The differential diagnosis for these lesions includes parasite infections, results of previous trauma or infarction, congenital forms, primitive splenic neoplasm or cystic metastasis. They can be either symptomatic, causing mainly abdominal pain, or asymptomatic, thus being diagnosed as in incidental finding during radiological examination for other clinical reasons: among these a raised serum level of CA 19-9 can be a case. It has been demonstrated that epidermoid and mesothelial congenital cyst can be associated with a pathological level of this tumor marker which is usually correlated to biliopancreatic and colonic carcinomas. The aim of the present study is to present the case of an asymptomatic epidermoid splenic cyst associated with a continuous increase of CA 19-9 and to describe the applied clinical workup and surgical management by laparoscopic total splenectomy. Moreover, to analyze the demographics, clinical and pathological features of these infrequent lesions and to confront our therapeutic management with that of the other reported cases, we conducted a systematic review of the literature

KEY WORDS: CA 19-9, Carbohydrate antigen 19-9, Laparoscopic splenectomy, Splenic cyst

Introduction

Splenic cysts are relatively rare entities, with an incidence of 0.07% as reported in a review of 42327 autopsy records [1]. The differential diagnosis for these lesions includes parasite infections, results of previous trauma or infarction, congenital forms, cystic neoplasm of the pancreatic tail, primitive splenic neoplasm or cystic metastasis [2-11]. Moreover congenital epidermoid and mesothelial cystis show an association with increased levels of CA 19-9, a tumor marker for gastrointestinal and biliopancreatic carcinomas [12,13].

In the present paper we report a case of splenic cyst associated with a continuous increase of CA 19-9 and its clinical management by laparoscopic splenectomy. A literature review of clinical characteristics and surgical treatment of splenic cysts with high level of CA 19-9 in the last 20 years is also reported.

Materials and Methods

A comprehensive review of all published cases of splenic cyst associated with elevated CA 19-9 primarily submitted to surgical therapy was conducted through a systematic Medline search in the PubMed database utilizing "splenic cyst", "spleen cyst", "carbohydrate antigen 19-9" and "CA 19-9" as key words. One case was exclud-

Pervenuto in Redazione Giugno 2014. Accettato per la pubblicazione Settembre 2014
Correspondence to: Vittorio Bresadola, MD, Dipartimento di Scienze Mediche e Biologiche, AOU S.M. della Misericordia, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy (e-mail: vittorio.bresadola@uniud.it)

ed since the patient was not submitted to any surgical procedure after failure of percutaneous drainage and injection of tetracycline [14]. For all the others, demographics, clinical, surgical and pathological data were recorded and confronted (Tables I and II).

TABLE I - *Demographic e clinical characteristics of patients with spleen cyst and high CA 19-9before surgery. Data review.*

Author	Year	Cases (n°)	Sex	Age (Years)	Symptoms	Acute complication	Maxdiameter (cm)	Preoperative CA 19-9 serum level (U/mL)	Other increasedser ummarkers
Terada[12]	1994	1	F	21	acuteabdominalpain	-	16	830	-
Walz[13]	1994	1	M	25	no	-	7	618	-
Higaki[48]	1998	3	F	33	fever, diarrhea, acute abdominalpain	-	11	85000	CEA
			M	25	peritonitis	hematoma + abscess	15	1600	-
			F	46	chronic back and abdominal pain	-	3	201	-
Sardi[39]	1998	1	M	16	chronicabdominalpain	-	20	1264	CEA
Ishibashi[16]	1999	1	F	19	fever, loss of appetite	-	20	4929	CA 125
Sakamoto[38]	1999	1	F	26	chronicabdominalpain	-	16	217	-
Van Lacum[2]	2000	1	M	22	chronicabdominalpain	-	25	502	-
Matsubayashi[50]	2001	1	F	36	acuteabdominalpain	rupture	14	24000	-
Soudack[18]	2001	1	F	24	chronicabdominalpain	-	-	1200	-
Trompetas[3]	2002	1	F	21	fever, dyspepsia	-	20	1240	-
Galizia[45]	2003	1	F	21	chronic abdominal pain, weight loss	-	20	892	CEA, CA 50, CA 125, TPA
Hashimoto[49]	2003	1	F	18	acuteabdominalpain	-	28	2887	CA 125, IL-2
Lieto [17]	2003	1	F	21	chronic abdominal pain, palpable mass, weight loss	-	20	892	CEA, CA 125, CA 50, TPA
Madia[5]	2003	1	F	19	dyspepsia, palpableabdominal mass	-	18	273	CEA
Chiarugi [47]	2006	1	F	28	acuteabdominalpain	-	15	3284	CA 125
Paskoy[25]	2006	1	F	28	chronicabdominalpain	-	7	57	-
Yigitbasi[51]	2006	1	F	30	chronicabdominalpain	-	10	268	-
Uludag[21]	2009	1	F	19	chronic abdominal pain, palpable mass	-	20	349	CA 125
Inokuna[8]	2010	1	F	20	peritonitis	rupture + abscess	11	43000	CEA, CA 125
Papadopoulos[9]	2010	1	F	21	acute abdominalpain	-	12,2	478	-
Brauer[10]	2012	1	F	32	chronic abdominal pain, weight loss, dyspepsia	-	-	1300	CEA
Morandi [41]	2012	1	F	32	no	-	26	eleveted	-
Graziani[45]	2013	1	M	32	acute abdominalpain	-	13,5	3103	
Hoshino[43]	2013	1	F	33	acute abdominalpain	-	10	3347	
Yoh[42]	2013	1	F	22	acute abdominalpain	hematoma	25	65	-
Vo[11]	2013	1	F	18	acute abdominalpain	-	20	88	-
Takagi [44]	2014	1	F	36	No..	-	8,5	244	
Present case	2013	1	F	48	no	-	8	593	-
Total		30	F: 83,3% M: 16,6%	26,4 ± 8 (mean±ds)	Symptomatic: 86.7% Asymptomtic: 13,3%	14,8%	15,6 ± 6 (mean±ds)	6300,7 ± 17234 (mean±ds)	

TABLE II - *Perioperative aspects in patients submitted to splenic surgery for a cyst lesion plus high CA 19-9. Data review.*

Case	Surgical indication	Timing	Laparotomy vs laparoscopy	Surgical procedure	Histology	cysticliquidlevel	postoperative decreasing trend	latency for postop normalization (week)
1	symptoms	elective	laparotomy	splenectomy	epidermoid	10150000	yes	-
2	diagnosis	elective	laparotomy	cystectomy	mesothelial	-	yes	12
3	symptoms	elective	not specified	splenectomy	epidermoid	990	yes	-
4	complications	urgent	not specified	splenectomy	epidermoid	-	yes	-
5	symptoms	elective	not specified	splenectomy	epidermoid	-	yes	-
6	symptoms	elective	laparoscopy	cystectomy	mesothelial	48275	yes	-
7	symptoms	elective	laparotomy	splenectomy	epidermoid	14970000	yes	12
8	symptoms	elective	laparoscopy	splenectomy	epidermoid	925466	yes	0,5
9	symptoms	elective	laparotomy	partialsplenectomy	epidermoid	50000	yes	-
10	complications	elective	laparotomy	splenectomy	epidermoid	24000	yes	12
11	symptoms	elective	laparotomy	splenectomy	epidermoid	-	-	-
12	symptoms	elective	laparotomy	splenectomy	mesothelial	-	yes	8
13	symptoms	elective	laparotomy	splenectomy	epidermoid	52875	yes	4
14	symptoms	elective	notspecified	splenectomy	epidermoid	2165550	yes	-
15	symptoms	elective	laparotomy	splenectomy	epidermoid	52875	yes	4
16	symptoms	elective	laparoscopy	splenectomy	epidermoid	2546	yes	4
17	symptoms	elective	laparoscopy	splenectomy	epidermoid	5000	yes	20
18	symptoms	elective	laparoscopy	cystectomy	epidermoid	-	yes	12
19	symptoms	elective	laparotomy	splenectomy	epidermoid	-	yes	6
20	symptoms	elective	laparotomy	splenectomy	epidermoid	48217	yes	12
21	complications	urgent	laparotomy	splenectomy	epidermoid	-	yes	-
22	symptoms	elective	laparotomy	cystectomy	epidermoid	-	yes	24
23	symptoms	elective	laparotomy	splenectomy	epidermoid	-	yes	-
24	diagnosis	elective	laparoscopy	splenectomy	epidermoid	eleveted	-	-
25	symptom	elective	not specified	splenectomy	epidermoid	-	yes	4
26	diagnosis	elective	laparoscopy	splenectomy	epidermoid	462000	yes	2
27	complications	urgent	laparoscopy	splenectomy	epidermoid	805570	yes	4
28	symptoms	elective	laparoscopy	splenectomy	epidermoid	-	-	-
29	diagnosis	elective	not specified	splenectomy	epidermoid	-	-	-
30	diagnosis	elective	laparoscopy	splenectomy	epidermoid	6938970	yes	8
Total		elective: 90% urgent: 10%	laparotomy: 58,3% laparoscopic: 41,7%	splenectomy: 80% other: 20%	epidermoid: 90% mesothelial: 10%	2293895,8 (Mean)	100%	8,4 ± 6 (mean±ds)

Case Report

A 48-year-old woman in overall good clinical conditions, asymptomatic, without any comorbidity, previous abdominal trauma or recent infections, was referred to our Surgical Unit with an abnormal CA 19-9 level associated with the presence of a splenic cyst.

The clinical history started with a routinely gynecological checkup. Due to the clinical suspect of an ovarian neoplasm, tumor markers serum dosage and an abdominal ultrasound examination were programmed. Tumor markers profile resulted as sequent (normal value): CA 19-9 318.6 U/ml (<37), CEA 1.5 ug/L (<5), CA 15 13.9 U/ml (<35), CA15-3 26.3 U/ml (<30). Abdominal ultrasound examination excluded the suspect of an ovarian lesion but revealed the presence of a splenic cyst. Serological tests for parasitic infection by *Echinococcus Granulosus* were negative and hemocrome with formula, liver and renal function tests were normal. Physical examination was negative. Since the patient was asymptomatic, and the isolated abnormal CA 19-9 level could be a false positive a follow up surveillance was programmed. The seriated tumor markers dosage showed a raising trend of the CA 19-9 up to 593.3 UI/ml after 4 months, therefore an MRI scan was performed. No other pathological finding could be demonstrated a part from the splenic cyst which appeared to occupy the upper and middle pole of the spleen (which was otherwise within the size range) without any relationship with the pancreas tail, 7.5x8cm in diameter, not associated with any solid mass and filled of a proteinou scontent (Fig. 1). No percutaneous fine needle aspiration was planned. In accordance with the oncologists we decided to perform a laparoscopic splenectomy to make sure the relationship between the marker's level and the cyst and to exclude any potential malignant origin (either occult primary or secondary). No intraoperative complication occurred. The postoperative course was uneventful and the patient was discharged on postoperative day 3. The level of CA 19-9 in the cystic content was 6938970 U/ml. Histological examination confirmed the diagnosis of a benign epidermoid cyst. In the immunostaining analysis the epithelium was positive for CA 19-9 and CEA. During the follow up the CA 19-9 value progressively decreased and became normal 2 months after splenectomy, conclusively excluding any other concomitant cause for its initial abnormal level. Perioperative trend of the tumor marker is described in Fig. 2.

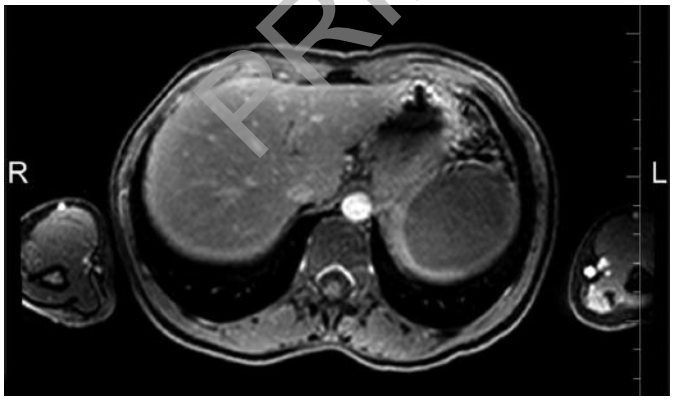

Fig. 1: Preoperative MRI scan showed the splenic cyst.

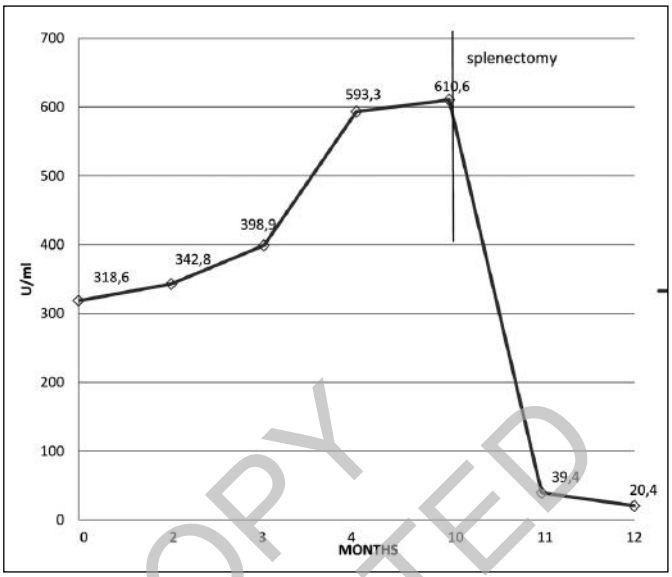

Fig. 2. CA 19-9 trend before and after splenectomy. Case report.

Discussion

Carbohydrate antigen 19-9 (CA 19-9) is a glycoprotein produced in ductal epithelial cells of salivary glands, biliary and pancreatic ducts and in metaplastic mesothelial cells. Elevated levels are associated with pancreatic, biliary and gastrointestinal carcinomas [10,11,15]. In these cases CA 19-9 is used for diagnosis and as surveillance marker in the follow up with a sensitivity and specificity of 77-88% and 84-90% respectively [3,16-23]. However also benign conditions such as cirrhosis, cholangitis, cystic fibrosis, pancreatitis can determine abnormal CA 19-9 levels, resulting in false positive data [17,18,24,25]. Combining the pathogenic mechanism and microscopic characteristics, splenic cysts are classified as parasitic (maily caused by *Echinococcus Granulosus* infection) or non-parasitic. The latter are further subdivided into primary or secondary in relation to the presence or absence of an epithelial lining. Secondary cyst or pseudocyst are usually post-traumatic or caused by infarction of the spleen. Primary non-parasitic cysts can be congenital or neoplastic. The histological features of the epithelial lining within congenital forms imply an additional subclassification:

– epidermoid cyst (stratified non keratinizing squamous epithelium), which accounts for 90% of congenital cyst;
– dermoid cyts (squamous lining with dermal structures);
– mesothelial cysts (low cuboidal or low columnar epithelium);
– angiomatous cyst (derived from endothelium) which represents lymphangiomas and hemangioma [2-11].

Primary non-parasitic splenic cyst can also be of neoplastic nature, either primitive or secondary [6,10,26-28].

There have been reported in Literature cases of primary splenic cystadenocarcinomas [26,27] and of splenic lymphoma presenting as a splenic cyst [29,30]. Isolated splenic metastasis are diagnosed in only 5.2% of case on autoptic studies [31,32]. They are mostly secondary to melanoma, and cancer of the breast, lung, ovary, colon, stomach and pancreas [31-34]. Although they usually appears as solid lesions, hemorrhagic phenomena, cystic or necrotic degenerations can occur, conferring to the metastasis a cystic feature [33,35,36]. Moreover a cystic adenoma-adenocarcinoma of the pancreatic tail, extended within the splenic parenchyma should be excluded [10,37].

The first report about the association between serum levels of CA 19-9 and a splenic cyst was in 1994: a case of a young woman with a huge splenic cyst and a marker level of 800 U/ml who was submitted to open splenectomy with subsequent CA 19-9 level normalization [12]. Since then, similar clinical pictures have been reported in a small number of cases (Tab. I). The pathogenesis responsible for this correlation could be explained by the demonstration with immunohistochemical analyses that the epithelium lining of primary epidermoid cyst produces and secretes CA 19-9 or other tumor markers [3,5,6,8-11,17,28,38]. The increased serum level would be the result of diffusion phenomena of the antigens from the liquid content of the cyst to the vascular system, where the serum concentration would depend on the degree of proliferation of the epithelium, capsule thickness, and presence of capillaries in connective tissue surrounding the cyst [3,8,10,17,28].

It has been reported in several cases that also mesothelial cyst can be associated to elevated CA 19.9 serum level [3,13,39].

Because of the limited number of cases reported in Literature, it was not possible to evaluate with a statistical significance the possible correlation between serum level of CA 19-9, intracystic level and cystic dimension. However by descriptive analysis it seems that these parameters are not reciprocally dependent. As reported, other tumor markers, particularly CA 125 and CEA, are associated with epidermoid/mesothelial cysts (Tab. I).

This is the first case report where the trend of CA 19-9 levels is preoperatively monitored over time with a seriated frequency. This additional data with its increasing trend was a relevant element in the clinical management of the case, considering the asymptomatic state of the patient.

Hoshino recently reported of a patient who had interval increase of CA 19-9 associated with a splenic cyst, but the time span was of 5 years without any follow-up which limits the significance of the data[43].

Since the prevalence of splenic cyst is very low and the pathogenesis of the CA 19-9 secreting epithelium lining is not completely understood, in contrast to a well-established association between CA 19-9 and bilio-pancreatic carcinoma [3,18,21] (despite negative imaging investigation), the possibility of excluding a concomitant life-threatening disease through cyst resection or splenectomy is, in our opinion, a crucial indication for surgical intervention. Moreover it is particularly relevant in the case of young patients as those epidemiologically most affected by splenic cysts (Tab. I).

In our case, percutaneous aspiration of the cyst was refused either as diagnostic or therapeutic tool since this procedure not only doesn't offer any conclusive diagnostic information but also carries the risk of recurrence, rupture, abscess formation [8,14,21,40-43] and of seeding malignant cells into the peritoneum or along the needle tract [6,43].

Review of the demographics data shows that splenic cysts with raised CA-19.9 level, when symptomatic, cause mainly upper abdomen discomfort/pain, either acute or chronic. The present case and other two [13,41,42,44] are the only reports with asymptomatic patients. Female young adults are the most frequent patients: average age is 25 years old (range 18-46) and female sex represents the 85.2% of cases. At diagnosis, average CA-19.9 serum level is as high as 6770.3 UI/ml (65-85000) which should be confronted to the data that the specificity of this tumor marker is actually of 99% for pancreatic cancer when the serum level is 1000 U/ml[3]. Maximum diameter at radiological examination is 16.3 cm (range 3-28). Acute complications are represented by rupture, hemorrhage, abscessualization and constitute the clinical picture at diagnosis in the 11.1% of cases (Tab. I).

Indications for surgery are presence of symptoms, acute complications or increased risk of complication (diameter > 5cm) [5,6,8,10,17,21,42,44]. Timing and types of treatments for asymptomatic epidermoid splenic cysts remain unclear in the absence of standard guidelines [8,10,21].

The proposed surgical modalities for treatment include splenectomy, partial splenectomy, marsupialisation, cystectomy and cystic decapitation [6,17,25,28,41,42]. The rationale sustaining spleen-preserving procedures is the possibility to minimize the infectious risks associated with the loss of splenic function [6,25,28,45]. However the routine use of vaccination against capsulated bacteria post splenectomy has reduced such risk. Furthermore, if it is taken into consideration that the average dimension at diagnosis of the epidermoid cysts is 16.3 cm (Tab. I) the possibility to leave a viable and functioning splenic remnant (>25% in volume) appears difficult to perform as the majority of the spleen has already been substituted by the cyst [10,11,21,25,28,41-48]. As a matter of fact, even a minimally invasive approach was used just in 39% of cases (if included also our case) probably due to clinical complications such rupture or technical difficulties secondary to the cyst dimension or adhesion(Tab. II). On the other hand spleen-preserving procedures are actually associated with several and critical risks: intraoperative and postoperative hemorrhage to due insufficient hemostasis, recurrence and incomplete oncological radicality [4,6,9,11,28,39,42,48,49].

These are the reason why we currently consider laparoscopic splenectomy the gold standard for the treatment of splenic cysts associated with increased CA 19-9. In

particular, laparoscopy for splenic surgery has been established as a safe and feasible approach which can reduce morbidity and mortality, shorter hospital stay and hasten functional recovery [4-6,11,25,42,50,51].
After surgical resection, all cases demonstrated a decreasing trend of the CA-19.9 serum level, establishing a definitive etiologic association with the resected splenic cyst. Average interval between operation and normalization of tumor marker's dosage was 9,2 weeks (Tab. II). In agreement with other reports [43], we regard high serum level of CA19-9 at diagnosis or an increasing trend during tight follow up of small asymptomatic lesions, an important indication for surgery which should be included to the aforementioned standard criteria.

Conclusion

Splenic cysts associated with elevated CA 19-9 serum levels are rare diagnostic entities but the increasing use in the clinical routine of serum marker dosage and radiological examinations may increase their frequency in the future.
Symptoms represent the major and absolute indication for surgical treatment in the management of splenic cysts. In case of incidental diagnosis, parallel to a lesion diameter greater than 5 cm, which is considered a high risk factor for complications, also high serum level of CA19-9 at diagnosis or an increasing trend during tight follow up might be an indication for resection. With the aim to exclude an occult malign neoplasm either primitive of the spleen or of the biliopancreatic system, laparoscopic splenectomy with seriated postoperative tumor marker dosage and its expected normalization could be considered as the definitive examination for the differential diagnosis of the aforementioned pathologies. Spleen preserving procedures as partial splenectomy, marsupialisation, cystectomy and cystic decapitation would be advisable to minimize the risk of immunological deficit. However, considering the average large dimensions of the cysts (16.5 cm) and significant incidence of cystic acute complications (11%) at diagnosis, the risk of intraoperative or early postoperative complications of these surgical approaches, when compared with total splenectomy, seems not counterbalanced by their long term protective effects. Moreover it is questionable the effective function of the spleen remnant after a major debulking procedure required by the cystic resection. Conclusively laparoscopic total splenectomy can be considered the surgical procedure with best results in terms of feasibility, safety and efficacy.

Riassunto

Le cisti spleniche sono lesioni che dimostrano un'incidenza nella polopazione generale di circa lo 0.07% e per le quali la diagnosi differenziale include infezioni parassitarie, esiti di pregressi traumi o infarti, forme congenite, tumori splenici primitivi o metastasi. Possono condizionare l'insorgenza di sintomi, più frequentemente dolore addominale, o essere oggetto di diagnosi incidentale in corso di accertamenti radiologici per altre ragioni cliniche, tra cui il riscontro di elevati livelli sierici del marker tumorale CA 19-9. È stato dimostrato che le cisti congenite epidermoidi e mesoteliali della milza possono essere associate a livelli patologici di tale marker che nella pratica clinica però viene di solito correlato ai carcinomi biliopancreatici e colo-rettali. L'obiettivo del presente studio è di presentare la revisione sistematica della Letteratura di tutti i casi di cisti splenica associata a livelli patologici di CA 19-9 al fine di analizzare le caratteristiche cliniche di tali lesioni e la loro gestione terapeutica, ponendo particolare attenzione all'impatto prognostico che una corretta diagnosi differenziale può assumere in questi pazienti. Verrà inoltre presentata la nostra personale esperienza di un caso di cisti splenica epidermoide asintomatica con livelli sierici crescenti di CA 19-9 al fine di descrivere le basi razionali sulle quali è stato strutturato un percorso diagnostico-terapeutico che ha identificato la surrenectomia totale laparoscopica come procedura definitiva, finalizzata ad una corretta diagnosi di benignità.

References

1. Robbins FG, Yellin AE, Lingua RW, Craig JR, Turrill FL, et al.: *Splenic epidermoid cysts*. Ann Surg, 1978; 187(3):231-35.

2. Van Lacum MW, Hessels RA, Kremer GD, Jaspers CA: *A splenic cyst and a high serum CA 19-9: A case report.* Eur J Intern Med, 2000; 11(2):104-07.

3. Trompetas V, Panagopoulos E, Priovolou-Papaevangelou M, Ramantanis G: *Giant benign true cyst of the spleen with high serum level of CA 19-9.* Eur J Gastroenterol Hepatol, 2002; 14(1):85-88.

4. Tagaya N, Oda N, Furihata M, Nemoto T, Suzuki N, et al.: *Experience with laparoscopic management of solitary symptomatic splenic cysts*. Surg Laparosc Endosc Percutan Tech, 2002; 12(4):279-82.

5. Madia C, Lumachi F, Veroux M, Fiamingo P, Gringeri E, et al.: *Giant splenic epithelial cyst with elevated serum markers CEA and CA 19-9 levels: An incidental association?* Anticancer Res, 2003; 23(1B):773-76.

6. Hansen MB, Moller AC: *Splenic cysts.* Surg Laparosc Endosc Percutan Tech, 2004; 14(6):316-22.

7. Mirilas P, Mentessidou A, Skandalakis JE: *Splenic cysts: Are there so many types?* J Am Coll Surg, 2007; 204:459-65.

8. Inokuma T, Minami S, Suga K, Kusano Y, Chiba K, et al.: *Spontaneously ruptured giant splenic cyst with elevated serum levels of CA 19-9, CA 125 and Carcinoembryonic Antigen*. Case Rep Gastroenterol, 2010; 11; 4(2):191-97.

9. Papadopoulos IN, Davatzikos A, Kasabalis G, Manti C, Konstantoudakis G: *Primary epithelial splenic cyst with micro-rupture and raised carbohydrate antigen CA 19-9: A paradigm of manage-*

ment. BMJ Case Rep, 2010. pii: bcr0620103125. doi: 10.1136/bcr.06.2010.3125.

10. Brauner E, Person B, Ben-Ishay O, Kluger Y: *Huge splenic cyst with high level of CA 19-9: the rule or the exception?* Isr Med Assoc J, 2012; 14(11):710-11.

11. Vo QD, Monnard E, Hoogewoud HM: *Epidermoid cyst of the spleen*. BMJ Case Rep, 2013; 9; 2013. pii: bcr2013009707. doi: 10.1136/bcr-2013-009707.

12. Terada T, Yasoshima M, Yoshimitsu Y, Nakanuma Y: *Carbohydrate antigen 19-9 producing giant epithelial cyst of the spleen in a young woman*. J Clin Gastroenterol, 1994; 18(1):57-61.

13. Walz MK, Metz KA, Sastry M, Eigler FW, Leder LD: *Benignmesothelial splenic cyst may cause high serum concentration of CA 19-9.* Eur J Surg, 1994; 160(6-7):389-91.

14. Yoshikane H, Suzuki T, Yoshioka N, Ogawa Y, Hayashi Y, et al.: *Giant splenic cyst with high serum concentration of CA 19-9. Failure of treatment with percutaneous transcatheter drainage and injection of tetracycline.* Scand J Gastroenterol, 1996; 31(5):524-26.

15. Urban D, Catane R: *Serum tumor markers in oncology.* Isr Med Assoc J, 2009; 11(2):103-4.

16. Ishibashi R, Sakai T, Yamashita Y, Maekawa T, Hideshima T, et al.: *Benign epithelial cyst of the spleen with a high production of carbohydrate antigen 19-9*. Int Surg, 1999; 84(2):151-54.

17. Lieto E, Castellano P, Ferraraccio F, Orditura M, De Vita F, et al.: *Normal interleukin-10 serum level opposed to high serum levels of carbohydrate antigen 19-9 and cancer antigens 125 and 50 in a case of true splenic cyst*. Arch Med Res, 2003; 34(2):145-48.

18. Soudack M, Ben-Nun A, Toledano C: *Elevated carbohydrate antigen 19-9 in patients with true (epithelial) splenic cysts. Rare or undiscovered?* Can J Gastroenterol, 2001; 15(2):125-26.

19. Qin XL, Wang ZR, Shi JS, Lu M, Wang L, et al.: *Utility of serum CA 19-9 in diagnosis of cholangiocarcinoma: in comparison with CEA*. World J Gastroenterol, 2004; 10(3):427-32.

20. Goonetilleke KS, Siriwardena AK: *Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer*. Eur J Surg Oncol, 2007; 33(3):266-70.

21. Uludag M, Yetkin G, Citgez B, Karakoc S, Polat N, et al:. *Giant true cyst of the spleen with elevated serum markers, carbohydrate antigen 19-9 and cancer antigen 125.* BMJ Case Rep. 2009. pii: bcr03.2009.1691. doi: 10.1136/bcr.03.2009.1691.

22. Molina V, Visa L, Conill C, Navarro S, Escudero JM, et al. : *CA 19-9 in pancreatic cancer: Retrospective evaluation of patients with suspicion of pancreatic cancer*. Tumour Biol, 2012; 33(3):799-807. doi: 10.1007/s13277-011-0297-8.

23. Mourtzikou A, Stamouli M, Kroupis C, Christodoulou S, Skondra M, et al.: *Evaluation of carcinoembryonic antigen (CEA), epidermal growth factor receptor (EGFR), epithelial cell adhesion molecule EpCAM (GA733-2), and carbohydrate antigen 19-9 (CA 19-9) levels in colorectal cancer patients and correlation with clinicopathological characteristics*. Clin Lab, 2012; 58(5-6):441-48.

24. Ito S, Gejyo F: *Elevation of serum CA 19-9 levels in benign diseases.* Intern Med, 1999; 38(11):840-41.

25. Paksoy M, Karabicak I, Kusaslan R, Demiryas S, Ayan F, et al.: *Laparoscopic splenic total cystectomy in a patient with elevated CA 19-9.* JSLS, 2006; 10(4):507-10.

26. Elit L, Aylward B: *Splenic cyst carcinoma presenting in pregnancy.* Am J Hematol, 1989; 32(1):57-60.

27. Morinaga S, Ohyama R, Koizumi J*: Low-grade mucinous cystadenocarcinoma in the spleen*. Am J Surg Pathol, 1992; 16(9):903-08.

28. Palmieri I, Natale E, Crafa F, Cavallaro A, Mingazzini PL: *Epithelial splenic cysts.* Anticancer Res, 2005; 25(1B):515-21.

29. Nakashima A, Nakashima K, Seto H, Kamei T, Kakishita M, et al.: *Primary splenic lymphoma presenting as a large cyst*. Radiat Med, 1994; 12(1):42-45.

30. Takabe K, Al-Refaie W, Chin B, Chu PK, Baird SM, et al.: C*an large B-cell lymphoma mimic cystic lesions of the spleen?* Int J Gastrointest Cancer, 2005; 35(1):83-88.

31. Lam KY, Tang V: *Metastatic tumors to the spleen: a 25-year clinicopathologic study.* Arch Pathol Lab Med, 2000; 124(4):526-30.

32. Schön CA, Görg C, Ramaswamy A, Barth PJ: *Splenic metastases in a large unselected autopsy series.* Pathol Res Pract, 2006; 202(5):351-6.

33. Compérat E, Bardier-Dupas A, Camparo P, Capron F, Charlotte F. *Splenic metastases: Clinicopathologic presentation, differential diagnosis, and pathogenesis*. Arch Pathol Lab Med, 2007; 131(6):965-69.

34. Delaunoit T, Peny MO, Mignon M, Dili A: *Splenic metastasis from gastrointestinal neoplasms: A review.* Acta Gastroenterol Belg, 2012; 75(1):3-4.

35. Urrutia M, Mergo PJ, Ros LH, Torres GM, Ros PR: *Cystic masses of the spleen: radiologic-pathologic correlation.* Radiographics, 1996; 16(1):107-29.

36. Kaza RK, Azar S, Al-Hawary MM, Francis IR: *Primary and secondary neoplasms of the spleen*. Cancer Imaging, 2010; 10:173-82. doi: 10.1102/1470-7330.2010.0026.

37. Adas G, Karatepe O, Altiok M, Battal M, Bender O, et al.: *Diagnostic problems with parasitic and non-parasitic splenic cysts.* BMC Surg, 2009; 29; 9:9. doi: 10.1186/1471-2482-9-9.

38. Sakamoto Y, Yunotani S, Edakuni G, Mori M, Iyama A, et al.: *Laparoscopic splenectomy for a giant splenic epidermoid cyst: Report of a case*. Surg Today, 1999; 29(12):1268-272.

39. Sardi A, Ojeda HF, King D Jr.: *Laparoscopic resection of a benign true cyst of the spleen with the harmonic scalpel producing high levels of CA 19-9 and carcinoembryonic antigen.* Am Surg, 1998; 64(12):1149-154.

40. Mahomed A, Merry C, Guiney EJ: *Splenic cysts. Aspiration or partial splenic decapsulation?* S Afr J Surg, 1998; 36(3):84-86.

41. Morandi E, Castoldi M, Merlini DA, Vignati G, Milanesi M: *Is there a role of percutaneous drainage in non-parasitic splenic cysts? Case report*. G Chir, 2012; 33(10):343-45.

42. Yoh T, Wada S, Kobayashi A, Nakamura Y, Kato T, et al.: *Laparoscopic splenectomy for a large multilocular splenic cyst with elevated CA 19-9: Report of a case*. Int J Surg Case Rep, 2013; 4(3):319-21. doi: 10.1016/j.ijscr.2013.01.003.

43. Hoshino A, Nakamura Y, Suzuki H, Mizutani S, Chihara N, et al.: *Giant epidermoid cyst of the spleen with elevated CA 19-9 production managed laparoscopically: Report of a case.* J Nippon Med Sch, 2013; 80(6):470-74.

44. Takagi Kl, Takayama T, Moriguchi M, Hasegawa H, Niide O, et al.: *Gastrointestinal: Case of accidentally discovered splenic epidermoid cyst with serum CA19-9 elevation.* J Gastroenterol Hepatol, 2014b; 29(2):231.

45. Kaiwa Y, Kurokawa Y, Namiki K, Matsumoto H, Satomi S: *Laparoscopic partial splenectomies for true splenic cysts. A report of two case*s Surg Endosc, 2000; 14(9):865.

46. Di Carlo I, Fasone MA, Toro A: *Epidermoid cyst of the spleen in the laparoscopic era.* Dig Surg, 2005; 22(1-2):53-4.

47. Galizia G, Lieto E, Ferraraccio F, Castellano P, De Vita F, et al.: *A true splenic cyst producing carbohydrate antigen 19-9 and cancer antigens 50 and 125, but not interleukin 10*. Dig Surg, 2003; 20(1):71-4.

48. Balzan SM, Riedner CE, Santos LM, Pazzinatto MC, Fontes PR: *Posttraumatic splenic cysts and partial splenectomy: Report of a case.* Surg Today. 2001; 31(3):262-65.

49. Chiarugi M, Galatioto C, Battini A, Panicucci S, Lippolis P, et al.: *Giant epidermoid cyst of the spleen with carbohydrate and cancer antigen production managed laparoscopically*. Ann Ital Chir, 2006; 77(5):443-46.

50. Higaki K, Jimi A, Watanabe J, Kusaba A, Kojiro M: *Epidermoid cyst of the spleen with CA 19-9 or carcinoembryonic antigen productions: Report of three cases*. Am J Surg Pathol, 1998; 22(6):704-08.

51. Hashimoto T, Sugino T, Fukuda T, Hoshi N, Ogura G, et al.: *Multiple epithelial cysts of the spleen and on the splenic capsule, and high serum levels of CA 19-9, CA125 and soluble IL-2 receptor*. Pathol Int, 2004; 54(5):349-54.

52. Matsubayashi H, Kuraoka K, Kobayashi Y, Yokota T, Iiri Y, et al.: *Ruptured epidermoid cyst and haematoma of spleen: A diagnostic clue of high levels of serum carcinoembryonic antigen, carbohydrate antigen 19-9 and Sialyl Lewis x*. Dig Liver Dis, 2001; 33(7):595-99.

53. Yigitbasi R, Karabicak I, Aydogan F, Erturk S, Bican O, et al.: *Benign splenic epithelial cyst accompanied by elevated Ca 19-9 level: A case report.* Mt Sinai J Med, 2006; 73(6):871-73.

54. Graziani G1, Cucchiari D, Podestà MA, Quagliuolo V, Montanelli A: *Abdominal pain and increased CA19-9*. Clin Chem, 2013; 59(11):1678-679.