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

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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. 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. Moreover congenital epidermoid and mesothelial cysts show an association with increased levels of CA 19-9, a tumor marker for gastrointestinal and biliopancreatic carcinomas.

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

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

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<td></td>
<td>30</td>
<td>F: 83,3%</td>
<td>M: 16,6%</td>
<td>Symptomatic: 86,7% Asymptomatic: 13,3%</td>
<td>14,8%</td>
<td>15,6 ± 6</td>
<td>6300,7 ± 17234</td>
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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 proteinous content (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.

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 (mainly 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 cysts (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 autotptic 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 35,36,38. 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 35,6,8,11,17,28,38. 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 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 bильно-pancreatic carcinoma 3,10,21 (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 the average CA-19.9 serum level is as high as 6700.3 U/ml (65-85000) which should be confronted to the data that the specificity of this tumor marker is actually 90% for pancreatic cancer when the serum level is 1000 U/ml 1. 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 6,6,9,11,28,39,43,48,49.

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 malignant 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 popolazione generale di circa lo 0.07% e per le quali la diagnosi differenziale include infezioni parasitarie, 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


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