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Epithelial Splenic Cysts

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Abstract. *Background: Epithelial splenic cysts (ESC) are uncommon lesions of the spleen. The etiopathogenesis of these cysts is controversial, even if Burrig's theory is the most accredited. The histological distinction between epidermoid and mesothelial cysts may be difficult, particularly for monostratified epithelium. Patients and Methods: In the period between January 1986 and February 2004, 11 patients with ESC were studied. The history, physical findings, all relevant diagnostic studies and treatment were reviewed. All histological material was reviewed in detail with immunohistochemistry for CEA, CA 19-9, cytokeratin and calretinin. Results: Epidermoid cysts were positive for CEA, CA 19-9, and cytokeratin, but negative for calretinin. Mesothelial cysts were positive for cytokeratin and calretinin, but negative for CEA and CA 19-9. Conclusion: Immunohistochemistry allows differential diagnosis between epidermoid and mesothelial cysts. With regard to etiopathogenesis, these data could mean that epidermoid and mesothelial cysts have distinct origins, though at variance with Burrig's theory. Although the ESC in this series were treated by open splenectomy, the recent approach by conservative and laparoscopic techniques offers great promise.*

Splenic cysts are a rare condition with an incidence of 0.07% in a review of 42327 autopsies (1). Fowler, in 1953, reviewed 265 cases from the world literature and proposed the first pathological classification of splenic cysts (2), however this was complex and has been superceded by Martin's simpler, more clinically practical version (3). We report our experience, a series of 11 cases, and a review of the literature.

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Key Words: Epithelial splenic cysts, differential diagnosis, immunohistochemistry.

Patients and Methods

In the period between January 1986 and February 2004, a total of 11 patients with epithelial splenic cyst were referred to the Department of Surgery "Pietro Valdoni" of the University of Rome "La Sapienza", Italy.

There were 9 women and 2 men. Ages ranged from 13 to 47 years, with almost equal numbers in the second, third and fourth decades.

The history, physical findings, all relevant diagnostic studies and treatment were reviewed. All histological material was reviewed in detail by immunohistochemistry, which was performed *via* the avidin-biotin complex method using anti- CEA (DAKO, Denmark), anti- CA 19-9 (NOVOCASTRA, United Kingdom), anti- cytokeratin. (YLEM, Italy), and anti-calretinin antibodies (DAKO).

Results

The presenting symptom in most patients was left upper quadrant discomfort or pain, often accompanied by a feeling of fullness. Fever, vomiting and increase in white blood cells (WBC = 16.000/ UL) were present in a 13-year-old girl with infected epithelial splenic cyst. The cyst contained foul-smelling, brownish-red fluid. Cultures grew *Salmonella*, group B. The cyst wall was lined by non – keratinizing stratified squamous epithelium, with a histological diagnosis of epidermoid cyst. Splenomegaly was evident in all patients with cysts measuring more than 6 cm in diameter.

Cysts in this series measured from 1 cm to 15 cm. The smallest (1 cm) was an incidental finding in a spleen removed for Hodgkin's disease.

The largest of the cysts measured 15 cm in diameter. Excluding a cyst discovered as an incidental finding, the average size in 10 cases was 8.3 cm in diameter. Ultrasonograms and CT scans (Figure 1) were used as imaging studies. All patients underwent a total splenectomy without complication.

The pathological diagnosis on immunohistochemistry (cytokeratin, calretinin, CEA and CA 19-9) was epidermoid cyst in 7 patients, and mesothelial cyst in 4 patients. The epidermoid cysts (Table I) were positive for cytokeratin,

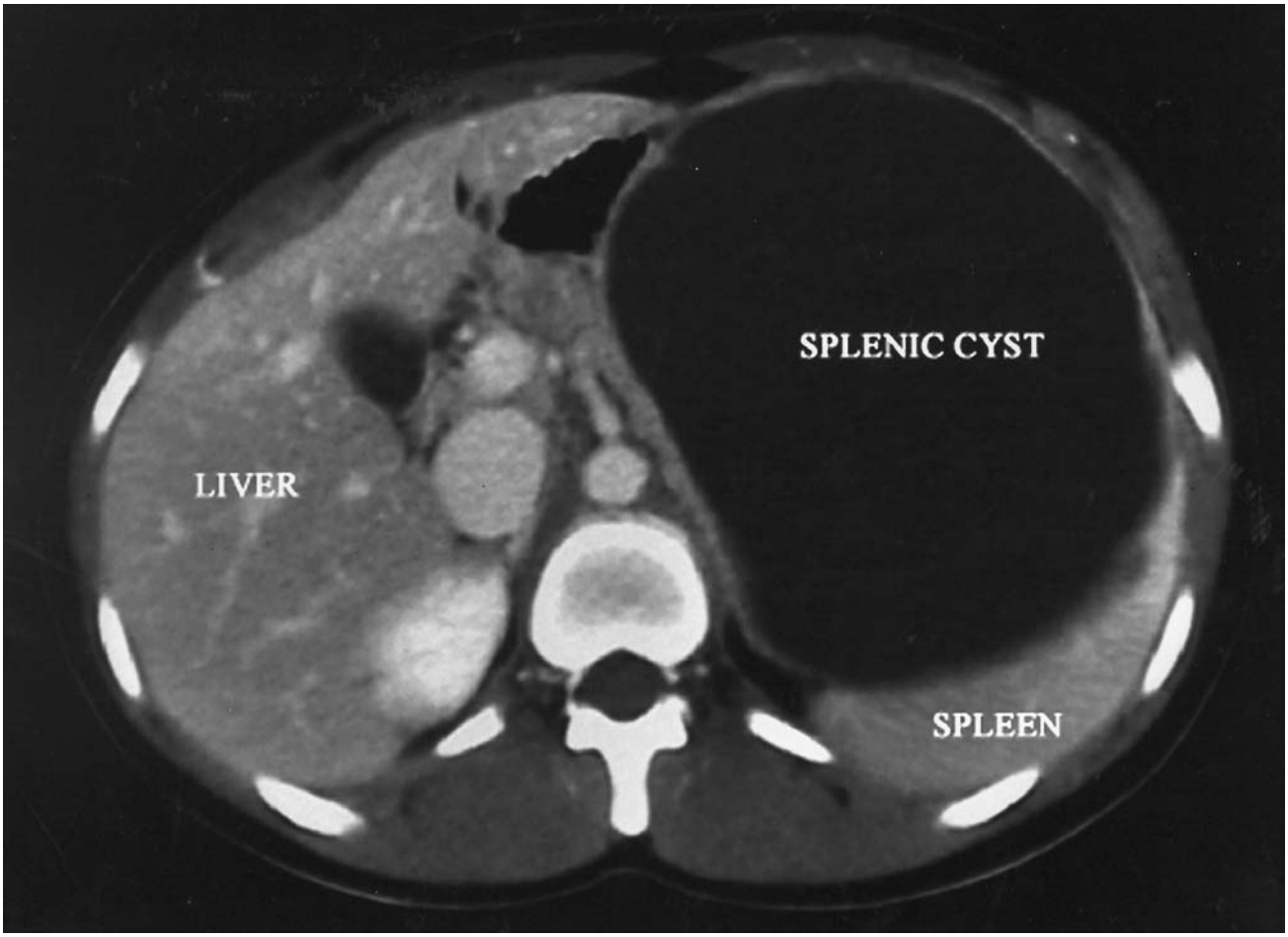

Figure 1. *CT of the abdomen shows a homogeneous and low attenuated giant cyst in contact with the spleen and pancreas.*

CEA and CA 19-9, and negative for calretinin (Figure 2). Mesothelial cysts were positive for cytokeratin and calretinin, but negative for CEA and CA 19-9 (Figure 3).

Two cases had been classified as pseudocysts, on the basis of the absence of a cyst lining. More careful review of the sections and immunohistochemistry results (positive for cytokeratin and calretinin, but negative for CEA and CA 19-9) demonstrated a mesothelial lining, resulting in a revised diagnosis.

Discussion

Splenic cysts are a rare condition with an incidence of 0.07% in a review of 42327 autopsies (1). Fowler (2), in 1953, reviewed 265 cases from the world literature and proposed the first pathological classification of splenic cysts, however this was complex and has been superseded by Martin's simpler (3), more clinically practical version.

Splenic cysts may be parasitic (75%), most frequently caused by *Echinococcus granulosus*, or non parasitic (25%) (4).Non parasitic cysts are divided into primary or true cysts and secondary or false cysts. Primary or true cysts have an inner cellular lining, which is absent in the false or secondary cysts. False cysts (80% of all non parasitic cysts) are mostly of traumatic or haemorragic origin, but may also be of infectious and degenerative origin.

Lymphangioma or hemangioma (benign tumors of the spleen) are neoplasms of endothelial origin (5). Lymphangioma (6) consists of small lymph vessel – like spaces, while hemangioma forms small vascular spaces. Both lymphangioma and hemangioma have endothelial lining cells. Immunohistochemically they are positive for endothelial markers (CD 31 and factor VIII).

Occasionally the lining of the typical cyst can be mistaken for endothelium, leading to an erroneous diagnosis of lymphangioma or hemangioma. The typical true splenic cyst

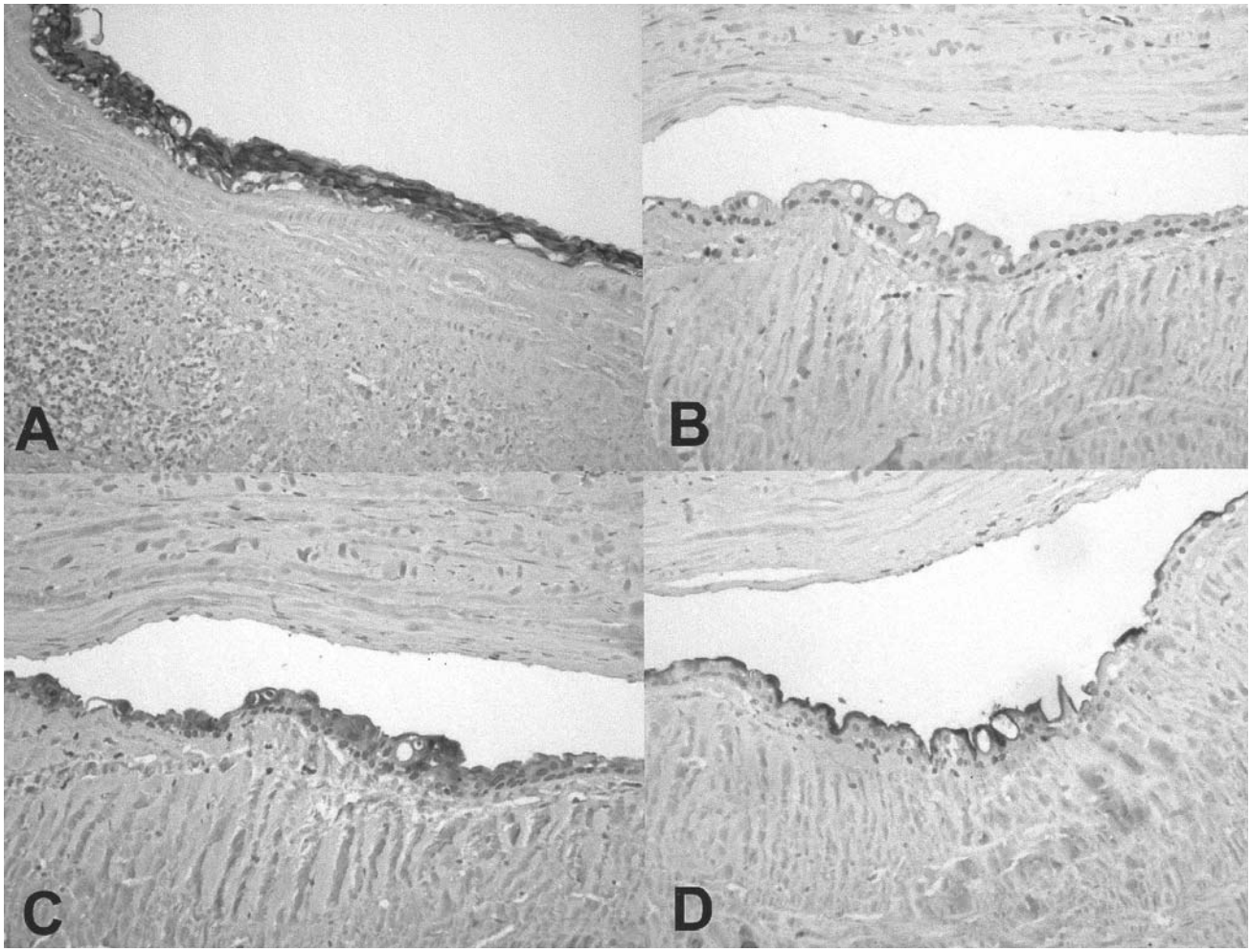

Figure 2. *Immunohistochemistry: Epidermoid cysts are positive for cytokeratin (A), CEA (C), CA 19.9 (D), but negative for calretinin (B).*

lining is positive for keratin (epithelium) and negative for factor VIII (endothelium).

Only those cysts with an epithelial lining should be designated as true splenic cysts. Depending on the type of lining, these true splenic cysts are classified as epidermoid (stratified non keratinising squamous), dermoid (squamous lining with skin appendages, hair follicles and sebaceous glands) (7), mesothelial (low cuboidal to low columnar) types.

To date the main subject of controversy is whether epithelial splenic cysts result from the developmental displacement of epithelial tissue or whether they arise from the peritoneal mesothelium. Embryonal inclusions from epithelial cells of adjacent structures during splenic development with subsequent metaplasia has been proposed.

These include germinal cells from the gonads according to Lubarsch (8), the dorsal mesogastrium suggested by Harding (9) and the Wolffian duct proposed by Santy(10).

Concerning the histogenesis of epithelial true splenic cysts Burrig (11) and Ough *et al.* (12) reported that these cysts originate from invagination of capsular peritoneal mesothelium or collections of peritoneal mesothelial cells trapped in splenic sulci.

The mesothelium subsequently undergoes squamous metaplasia, probably secondary to chronic irritation. In fact, Shatz and Colgan reported that injections of a strongly irritating mixture of Sudan III and sodium cholate in olive oil into rabbit pleural cavities resulted in development of focal transitional and stratified squamous epithelium (13). While some authors suggest a traumatic origin, others support the idea of an embryonic disturbance as a result of a mesothelial inclusion into the spleen (11, 12, 14). According to Touloukian *et al.* (15), the possibility exists that splenic epithelial cysts result from secondary fluid collection after injury or spontaneous intrasplenic bleeding. The likelihood

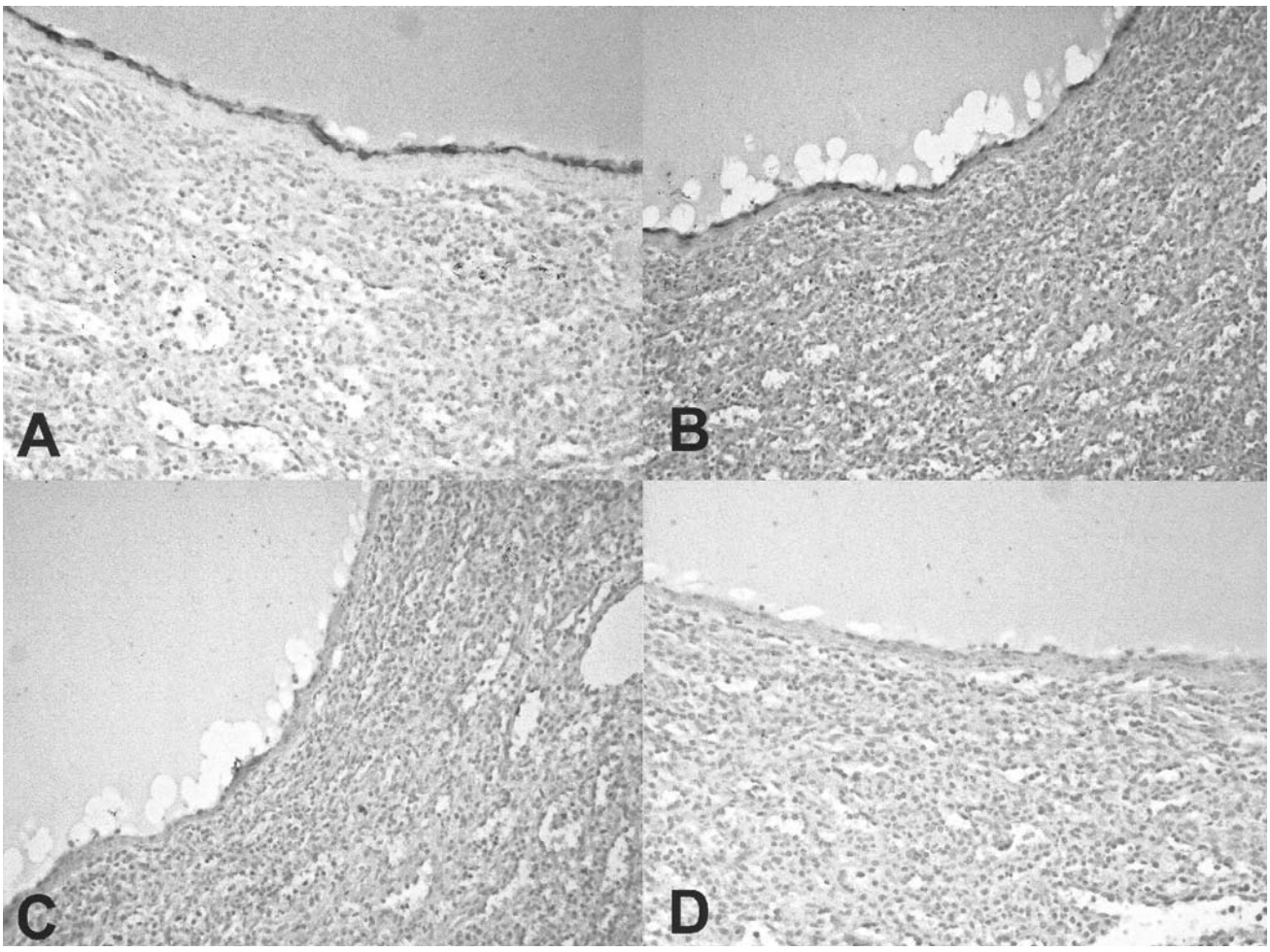

Figure 3. *Immunohistochemistry: Mesothelial cysts are positive for cytokeratin (A), and calretinin (B), but negative for CEA (C) and CA 19.9 (D).*

that bleeding preceded the development of splenic cysts is supported by the presence of hemosiderin – containing fluid within the cyst and embedded in the wall. Intracystic hemorrage from ectatic veins within the wall was suggested as one cause of initial cyst formation with further enlargement secondary to the osmotic effect of the retained fluid. Touloukian's findings are similar to those reported by Lee and Teh (16) who also found that CEA and keratin were positive in squamous epithelium lining cysts, whereas BerEP4 (conventionally positive in cells of epithelial origin) was negative. This gives rise to the possibility of an immature metaplastic phenomenon occurring in the lining of these cysts, in which epithelial intermediate filaments (keratin and cam 5.2) are found, and surface epithelial markers (CEA) are weakly expressed. Additional epithelial markers such as BerEP4 are probably absent because of incomplete epithelial development. Other studies contradict Burrig's theory.

Lifschtz – Mercer *et al.* (17) studied the stratified squamous epithelium of a splenic epidermoid cyst with a battery of monoclonal antibodies to cytokeratin (CK) proteins. The CK profile of the stratified squamous epithelium of the epidermoid splenic cyst was compared to stratified squamous epithelia of ovarian mature cystic teratoma, fetal epidermis, adult epidermis and squamous metaplasia in a peritoneal cyst.

The CK profile of the stratified squamous epithelium of the splenic cyst was similar to the CK profile observed in stratified squamous epithelium of ovarian mature cystic teratoma and of fetal epidermis.

From these comparisons it emerges that the epidermoid splenic cyst is either of teratomatous derivation or originates from inclusion of fetal squamous epithelium. Squamous metaplasia of mesothelium or inclusions of mature squamous epithelium appear to be unlikely sources of origin of these cysts.

Table I. *Data on pathological diagnosis.*

Case	Cyst lining	CK	Calretinin	CEA	CA 19-9
2654/86	Squamous pluristratified	+	–	+	+
1091/90	Flat/cubic mono-pluristratified	+	–	+	+
1306/90	Flat monostratified	+	+	–	–
2300/91	Flat monostratified*	+	+	–	–
2667/92	Flat monostratified*	+	+	–	–
1207/ 95	Flat monostratified	+	+	–	–
727/ 98	Flat squamous monostratified	+	–	+	+
2126/02	squamous	+	–	+	+
1837/02	Flat monostratified	+	–	+	+
8715/03	Flat monostratified	+	–	+	+
702/04	Flat pluristratified	+	–	+	+

*These two cases were originally diagnosed as pseudocysts. More careful review of the sections and especially immunohistochemistry results demonstrated a mesothelial lining. Revised diagnosis.

The etiopathogenesis of splenic epithelial cysts is controversial, unclarified. Recent reports on splenic epidermoid cysts indicate that lining cells produce CEA and CA 19-9 because high serum CEA and CA 19-9 levels before surgery returned to their normal ranges after surgery, and squamous epithelium that forms the cyst wall was immunohistochemically positive for anti-CEA antibody or anti-CA 19-9 antibody (18 - 22).

According to the literature about human mesothelioma cell lines, the best positive markers for differentiating these cells with immunohistochemistry are calretinin, thrombomodulin, keratin 5/6, keratin AE 1/3 and HBME –1. Calretinin appears to be more specific for mesothelioma. Negative markers for mesothelioma are Ber-EP4, CA 19-9, CEA, Leu-M1, MOC 31 and B72.3 (23-26). The histological distinction between epidermoid and mesothelial cysts may be difficult. Immunohistochemistry allows differential diagnosis, particularly needed for monostratified epithelium.

In our study epidermoid cysts were positive for CEA, CA 19-9, and cytokeratin, but negative for calretinin. Mesothelial cysts were positive for cytokeratin and calretinin, but negative for CEA and CA 19-9. With regard to etiopathogenesis, these data could mean that epidermoid and mesothelial cysts have distinct origin, being at variance with Burrig's theory. Furthermore in our series two cysts originally diagnosed as pseudocysts, were mesothelial at revised diagnosis. In epithelial cysts, portions of the cyst wall can be found where the lining has been desquamated and no lining exists. If sufficient sections are taken and carefully studied, remnants of the lining can be identified. Failure to identify scant remnants of the epithelial lining has led to erroneous classifications of many cysts (5).

Epithelial splenic cysts are commonly diagnosed in the second and third decade of life. Approximately two - thirds of the patients are females. The clinical manifestations of splenic cysts are not specific. Most frequently the patient complains of diffuse abdominal pain or a heavy feeling and a pathological lump is found in the left hypocondrium. Other symptoms (27)are explained by the pressure of the cyst on other organs such as the stomach (pyrosis, reflux-oesophagitis), the kidney or left renal artery (hydronephrosis, arterial hypertension), the diaphragm (coughing and pain in the left shoulder)or the heart (arrhythmias). Thirty percent of the cysts are without symptoms and are found only by chance. The complications (28) consist of rupture, infection and intracystic hemorrhage. Spontaneous or traumatic rupture of a splenic cyst can cause massive haemoperitoneum or peritonitis (29, 30). Only one case of possible malignant transformation has been reported (31). Cystic infection can lead to splenic abscess or sepsis. Infection associated with the *Salmonella* group is particularly common (32).

With regard to diagnosis, ultrasonography allows the distinction to be made between cysts (anechoic or hypoechoic) and solid masses (isoechoic or hyperechoic). An abdominal CT scan is helpful in determing both the cyst's site of origin and its relationship to surrounding structures. Epithelial splenic cysts are characteristically unilocular anaechoic lesions with smooth, well-defined margins. This is the most common pattern in small (< 5 cm) cysts. The echogenicity, which is the most common finding in large (> 5 cm) cysts, is due to cholesterol crystals or other breakdown products of hematoma. The smaller size of the anechoic cysts compared with the echogenic ones suggests that large cysts are more prone to episodes of intracystic hemorrhage (33, 34). Epithelial and post-traumatic cysts are usually indistinguishable on imaging studies, but post- traumatic cysts tend to have a thicker fibrous wall, more often eggshell – like wall calcifications and internal debris. Only by histology, is it possible to know whether the cyst is primary (cellular lining) or secondary (no cellular lining) and to determine its precise nature. Other differential diagnoses include hydatic cysts, cystic neoplasms of endothelial origin (lymphangioma, hemangioma), cystic metastases, splenic abscess, splenic infarction, pancreatic

pseudocyst or cystic malignant tumors of the spleen. To our knowledge, there is a only case of mucinous cystadenocarcinoma of the spleen (35).

If the splenic cyst is small (< 5 cm) or asymptomatic, usually no treatment is needed. If it is big (> 5 cm) or located at the hilus of spleen or complicated with secondary infection, intracystic hemorrhage, rupture or causes symptoms, it should be treated. In our opinion, indication to treatment is also age-correlated, because an elderly patient performs less physical activity, so he has lower risk of traumatic rupture. Furthermore, in the literature, there are not many reports about abscesses, peritonitis and hemorrhage as complications of epithelial splenic cysts, and the possibility of malignant trasformation is very rare. Therefore, in an elderly and asymptomatic patient the cut – off for treatment can be raised.

Surgery is the gold- standard therapy. There are different modalities of surgical treatment according to the age of the patient and the size, position and nature of the cyst. These different modalities are: splenectomy, partial splenectomy, cystectomy, partial cystectomy or splenic decapsulation. The first splenectomy for a splenic cyst was performed by Pean in 1867 and this operation was considered safe and successful for many decades. Considering the short and long – term complications of splenectomy in children (increased risk of serious infections caused by encapsulated bacteria), the management should be as conservative as possible. However, splenectomy remains the treatment of choice if the cyst is big enough to involve all the spleen, which is reduced to a small remnant, or if the cyst involves the hilum.

Partial splenectomy, the best known spleen-preserving surgical procedure, is based on the segmentation of the vascularization of the spleen through which, segmentary resections of the spleen are possible. The first successful partial splenectomy for an epidermoid splenic cyst was performed by Morgenstern and Shapiro in 1980 (36); a review of this technique was reported in 1997 (37). This procedure, however, is not easy and implies the risk of major blood loss during the operation itself, and of secondary bleeding of the spleen due to insufficient haemostasis afterwards. Some authors report that splenic resection with the use of a TA-stapler minimizes the blood loss since its simple operating technique speeds the procedure (38).

Cystectomy is resection of the cyst and a portion of the contiguous splenic parenchyma. Removing the cyst wall and lining in its entirety is the only treatment with definitive assurance that no cyst remnant remains. Some authors have proposed leaving the portion of cyst wall contiguous with the splenic parenchyma *in situ*. This procedure has been called splenic decapsulation (39). Its advantages include a simpler and more rapidly performed procedure, with less blood loss. Disadvantages include the possibility of cyst recurrence, because a portion of the cyst lining has been left intact. Instillation into the cyst of a sclerosing agent (tetracycline or alcohol) following puncture is not recommended, owing to the high risk of recurrence (40,41). With the advent of laparoscopic surgery, it was inevitabile that surgical treatment of the splenic cyst would be performed laparoscopically. In fact, in literature there are many recent reports about splenectomy, partial splenectomy, cystectomy and decapsulation, performed successfully by the laparoscopic approach (19, 20, 42 - 45). It is likely that the laparoscopic approach for the treatment of the splenic cyst will become the preferred method, since it offers better cosmesis, much less pain, and a shorter hospital stay compared with the traditional open procedure.

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