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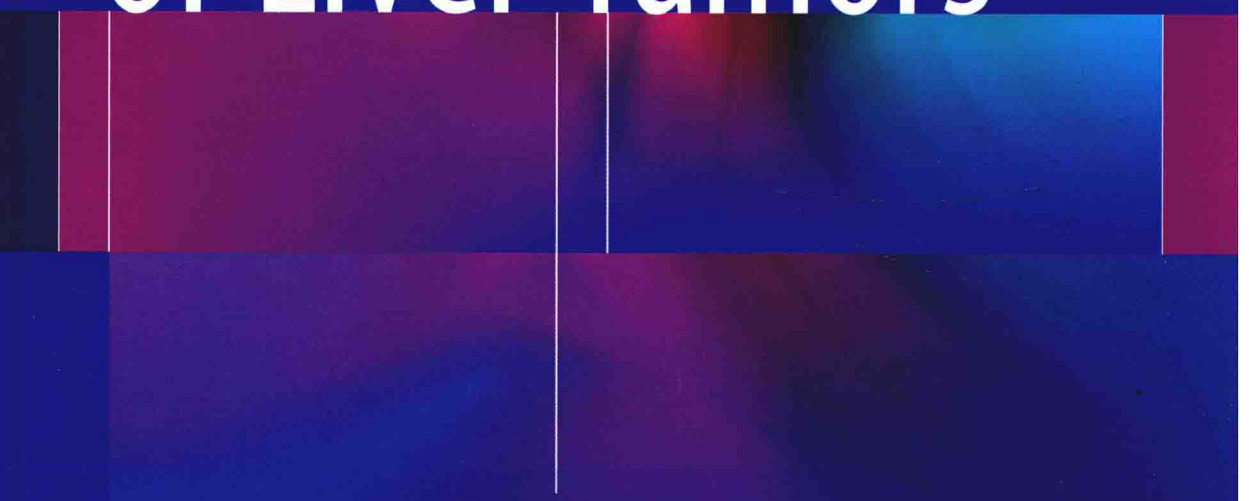
Michael S. Torbenson *Editors*

Surgical Pathology of Liver Tumors



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Preface

The target audience for this book is broad, and we hope this book will be of interest and benefit to those both beginning their training and to those with lots of experience. The pathology of liver tumors is fascinating, diverse, and important. The proper classification of liver tumors is the critical foundation from which derives all subsequent patient management decisions. The pathologist must build this foundation with care and accuracy, for a wrongly classified tumor can lead to a wrongly treated patient. We hope this book helps you in that endeavor. To that end, we wrote this book to provide a resource for diagnostic surgical pathologists, a resource that is focused exclusively on liver tumors and attempts to convey their common appearances, their many variations, and the ways in which they can mimic other tumors. Essentially all benign and malignant primary tumors of the liver are examined, and a full chapter is dedicated to metastatic disease. The integrated use of immunohistochemical stains is discussed, along with the differential diagnosis. The book is extensively illustrated, and the images have been chosen with care, to stand both alone and with the text as an important guide in tumor identification.

All of the authors on this book are from the Mayo Clinic. The Mayo Clinic has a rich history in the field of liver pathology, extending back to the seminal contributions of Jurgen Ludwig and continuing forward through the careers of many outstanding liver pathologists, including Ken Batts, Larry Burgart, and Schuyler Sanderson, among others. We are grateful for this rich heritage and hope this book will continue in that vein. We also benefited enormously from the many consult cases shared with us over the years, cases shared by pathologists both in private practice and by pathologists in academic centers. In fact, many of the rare tumors illustrated in this book came from you! Thank you.

The Mayo Clinic emphasizes a team approach in the practice of medicine, a philosophy that also shaped this book. Ideas, images, and approaches to writing were shared freely by the authors. This group effort was further strengthened by the outstanding administrative support of Alison Smarzyk, whose help kept the book on time and on track.

Finally, this book was written because we really like liver pathology; we enjoy reading about it; we enjoy talking about it; we enjoy writing about it; and we enjoy signing out the cases. We hope this enthusiasm for liver pathology comes through in the book, and we hope this book will contribute in some small way to your own understanding and enjoyment of liver tumor pathology.

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Contents

Pseudotumors

1

Taofic Mounajjed and Vishal S. Chandan

Abstract

A variety of localized non-neoplastic processes can form mass lesions in the liver, mimicking neoplasms. The clinical and pathologic features of this heterogeneous group of entities are discussed. This chapter also illustrates examples of these lesions and examines their differential diagnosis, focusing on features that distinguish them from true neoplastic lesions of the liver.

Keywords

Accessory lobe • Benign cystic mesothelioma • Echinococcosis • Endometriosis • Focal fatty nodule • Inflammatory pseudotumor • Heterotopia • Juvenile xanthogranuloma • Lobar/lobular compensatory hypertrophy • Nodular regenerative hyperplasia • Post-necrosis regenerative nodule • Pseudolipoma • Pseudocyst • Primary hepatic pregnancy • Segmental atrophy • Nodular elastosis

1.1 Accessory Lobe

An accessory lobe of the liver is a rare congenital anomaly found in 0.44 % of individuals [1]. It consists of hepatic tissue located adjacent to the liver and supported by a pedicle. In contrast to ectopic liver, this hepatic tissue is not completely separate from the liver. Accessory lobes are usually identified on the inferior surface of the liver. The accessory lobe is connected to the liver by a pedicle of either hepatic tissue or a portion of mesentery containing branches of the portal vein, hepatic artery, and bile duct (Fig. 1.1) [2]. By imaging, the accessory lobes may mimic a liver mass or a gastric/perigastric mass [3].

Accessory lobes can measure up to 19 cm [2]. They can become symptomatic due to large size or torsion [1, 2, 4, 5]. Grossly, the cut surface has the appearance of normal liver. Histologically, accessory lobes demonstrate normal liver architecture. However, some vascular abnormalities are common, including aberrant naked arteries (Fig. 1.2). Accessory lobes also often contain

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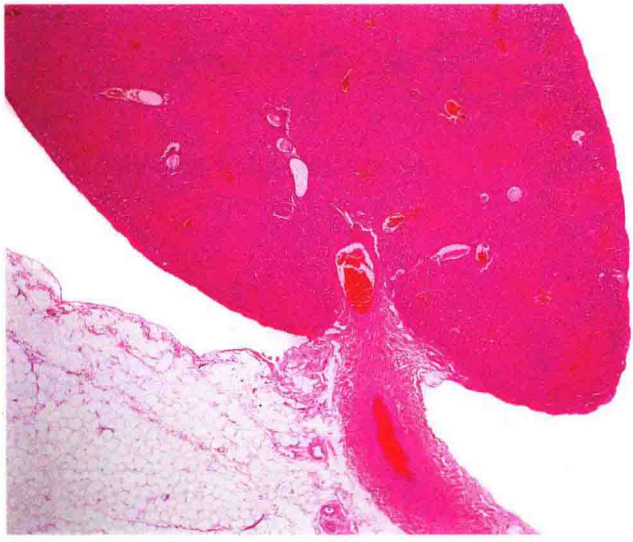

Fig. 1.1 Accessory hepatic lobe. The accessory lobe is attached to the liver by a pedicle of fibrovascular tissue

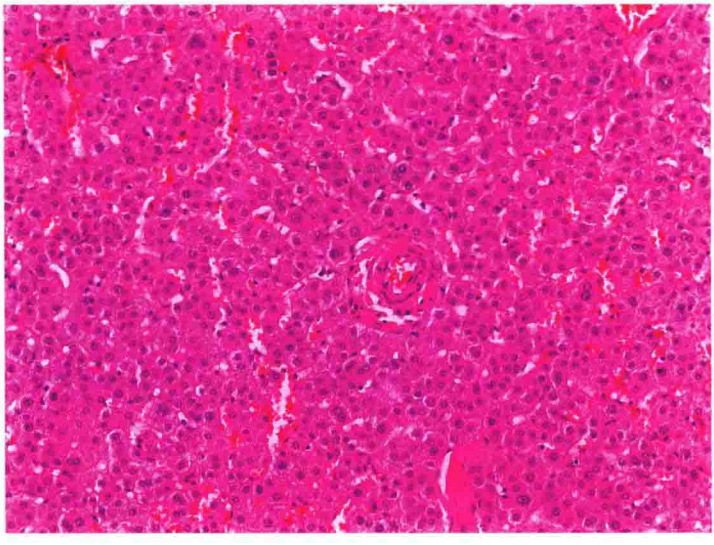

Fig. 1.2 Accessory hepatic lobe. The accessory lobe consists of essentially normal liver parenchyma, though aberrant naked arteries can sometimes be found

mild portal inflammation and bile ductular proliferation. Necrosis or post-necrotic fibrosis can occur in cases of torsion and subsequent infarction [2]. They have a normal reticulin framework (Fig. 1.3) and most have a normal glutamine synthetase-staining pattern (Fig. 1.4). However, some cases will have sufficient abnormalities in their blood flow that they can develop findings that resemble some features of focal nodular hyperplasia, including vague nodularity and abnormal glutamine synthetase staining.

Riedel's lobe of the liver is a variant of the hepatic accessory lobe that consists of a tongue-like caudal projection from the right lobe of the liver. This can produce a palpable mass in the right upper abdominal quadrant. Most patients are women, ranging in age between 31 and 77 years [6]. Other variants include intra-thoracic accessory hepatic lobes, which have vascular supplies that perforate the diaphragm [7], and can sometimes mimic a pulmonary tumor [8, 9].

Accessory lobes occasionally require surgical treatment because of their large size, torsion, or the presence of other associated defects. At other times, they are resected as potential neoplasms, when the diagnosis is not clear from imaging

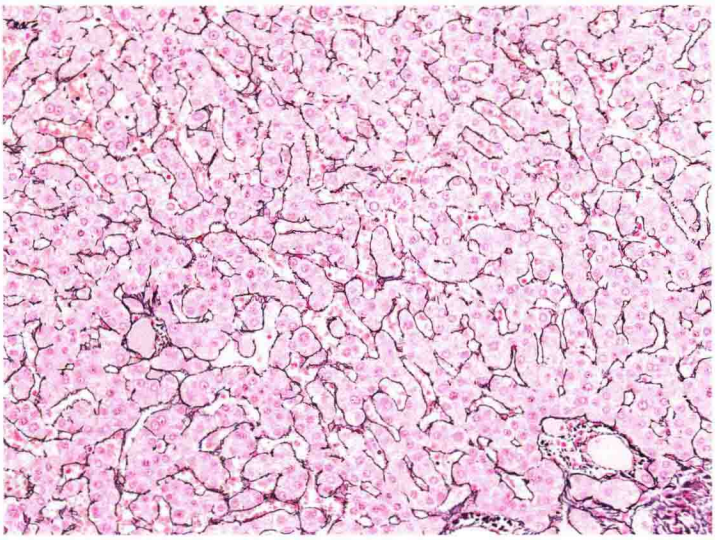

Fig. 1.3 Accessory hepatic lobe. A reticulin stain shows an intact reticulin meshwork

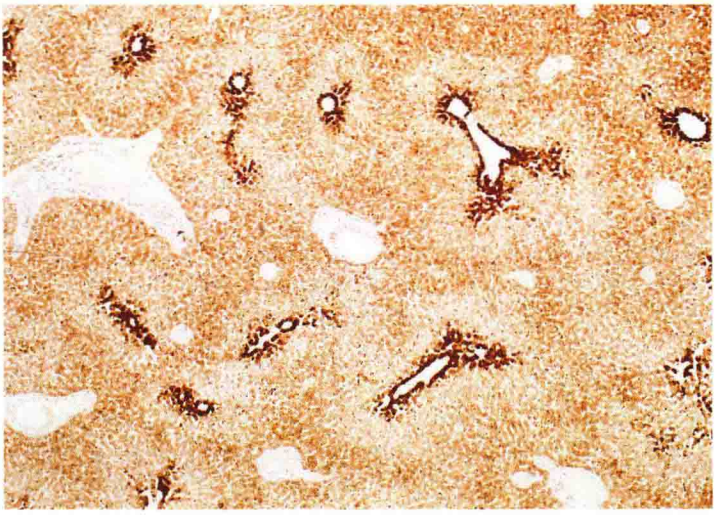

Fig. 1.4 Accessory hepatic lobe. A gluthamine synthetase immunostain shows a normal pattern of zone 3 expression

studies. Benign and malignant lesions such as focal nodular hyperplasia, hepatocellular adenoma, and hepatocellular carcinoma can rarely arise in accessory lobes [10, 11].

1.2 Benign Cystic Mesothelioma

Benign cystic mesotheliomas are relatively rare benign tumors that occur mainly in young women, but they can occur in both genders and any age [12–14]. Synonyms include inflammatory inclusion cyst of the peritoneum, multilocular peritoneal inclusion cyst, and multicystic mesothelial proliferation. They most often arise in the pelvic peritoneum, usually in the tubo-ovarian region, but secondary serosal involvement of other organs has been reported (uterus, kidney, bladder, liver, and colon) [13, 15, 16]. Involvement of the liver is very rare [13–16].

While some authors regard this lesion as a true neoplasm, most authorities consider cystic mesothelioma to represent a reactive mesothelial proliferation [15–17]; this is supported by the presence in most cases of identifiable inciting agents, such as previous surgery, pelvic

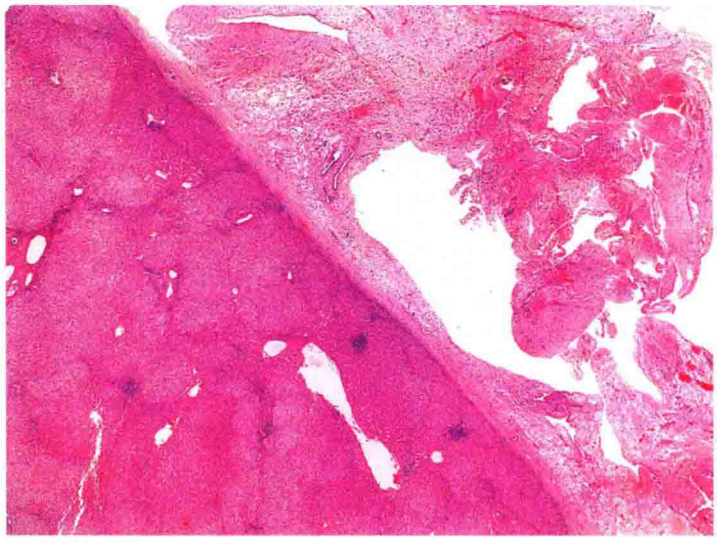

Fig. 1.5 Benign multicystic mesothelioma. This lesion has a subcapsular location

inflammation, endometriosis, or other forms of mesothelial irritation [15, 16]. A hormonal association is suggested by the female predominance and only rare occurrence after menopause [14]. The prognosis of benign cystic mesothelioma is excellent [15, 16], but there can be local recurrence [14].

Benign cystic mesothelioma can range from a small and localized lesion to a diffuse multifocal process [15, 16]. It is typically asymptomatic, but can sometimes present as a palpable mass, with ascites, or constipation [13, 15]. Radiologically, the lesion can be highly vascular and mimic focal nodular hyperplasia or hepatocellular carcinomas [14]. Liver involvement can be accompanied by involvement of other organs such as the pelvic or inguinal region, or rarely the pericardium [18, 19].

Grossly, the tumors are located in the liver immediately beneath the Glisson capsule (Fig. 1.5) and can measure up to 10 cm. They are typically encapsulated and have a soft glistening surface and a cystic (microcystic and macrocystic) configuration [14]. The cysts often contain a gelatinous fluid [14, 18].

Microscopically, the lesion is partially cystic, encapsulated, and features high vascularity. The cysts are lined by flattened cells (Fig. 1.6) with bland, oval to spindled nuclei, sometimes with a hobnail appearance. In addition to the cysts, the lesion contains tubular and gland-like spaces, anastomosing loose cords, as well as areas with solid, reticulated nests of epithelioid cells (Fig. 1.7). The tubular and glandular structures are lined by epithelioid cells with clear, vacuolated cytoplasm. The tumor cells have indented/cleaved nuclei that are moderately pleomorphic and have small rims of cytoplasm. A fibrous stroma featuring a rich vascular proliferation (medium-to large-sized vessels) is interspersed between the cystic spaces (Fig. 1.8). Hemorrhage is often widespread in the lesion. This, along with the overall high tumor vascularity, can mimic a vascular neoplasm [14, 18].

By immunohistochemistry, the lesional cells are positive for keratin, CAM 5.2, HBME-1, D2-40, calretinin, WT-1 (Fig. 1.9), EMA, and CK5/6. Approximately 30 % of tumors show nuclear positivity for estrogen receptor. The proliferative index is less than 1 %. Ultrastructural analysis confirms mesothelial differentiation, characterized by the presence of microvilli and desmosomes [14, 18].

The differential diagnosis includes lymphangioma, which develops in younger individuals and usually spares the pelvis. Furthermore, lymphangiomas are richer in smooth muscle bundles and often contain follicular lymphoid aggregates.

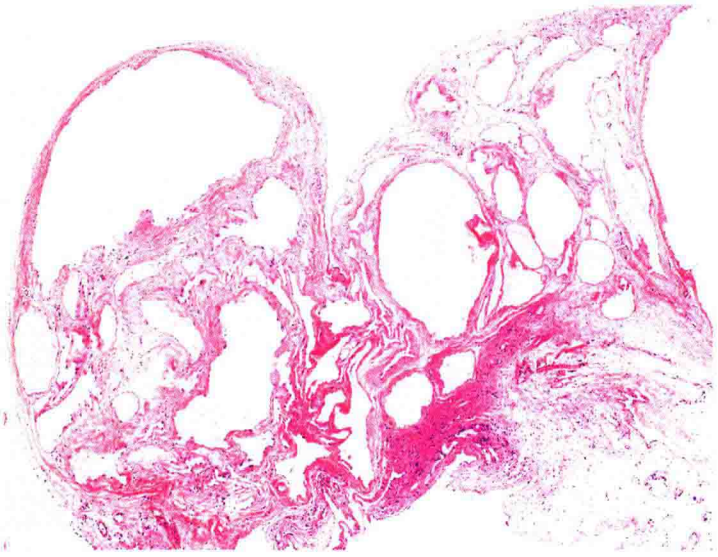

Fig. 1.6 Benign multicystic mesothelioma. The lesion is characterized by cystic spaces lined by flattened mesothelial cells

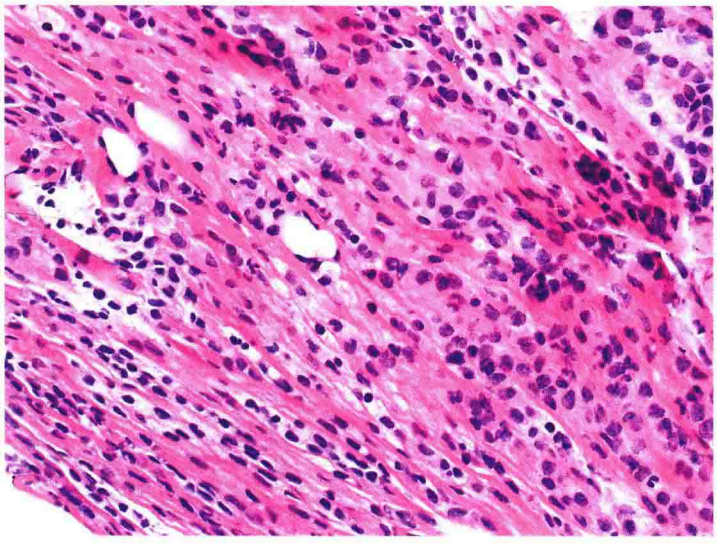

Fig. 1.7 Benign multicystic mesothelioma. In some cases, there may be focal areas of compact growth

By immunostains, lymphangiomas express D2-40, CD31, and CD34 and lack mesothelial marker expression. Hemangiomas have a similar immunostain profile to lymphangiomas, which can distinguish them from benign cystic mesothelioma in challenging cases. Another possibility to consider in the differential diagnosis is metastatic cystic variant of clear cell renal cell carcinoma; this is differentiated from benign cystic mesothelioma by a history of a renal mass, the presence of clusters of clear cells within the cyst wall, immunostain expression of keratin, RCC, and PAX-8, and the lack of expression of mesothelial markers. Benign cystic mesotheliomas can be distinguished from malignant mesothelioma by the lack of cytologic atypia and the lack of complex and/or infiltrative growth, low cellularity, and lack of mitotic activity [14, 18].

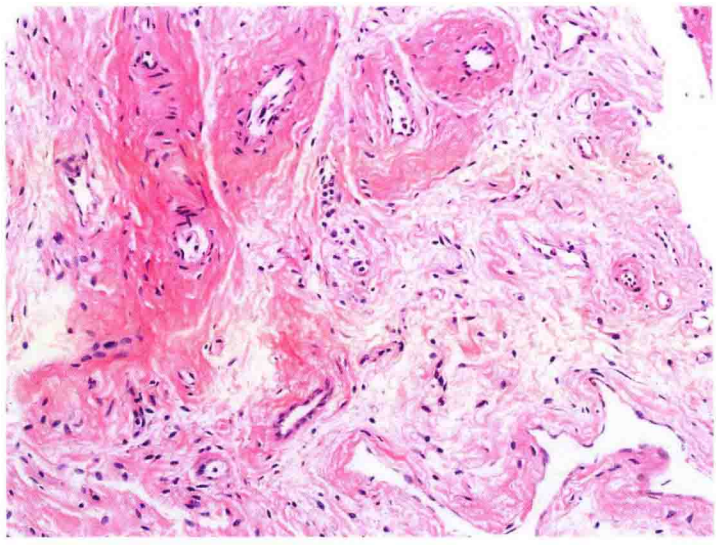

Fig. 1.8 Benign multicystic mesothelioma. A loose fibrous stroma rich in blood vessels is interspersed between the cystic spaces

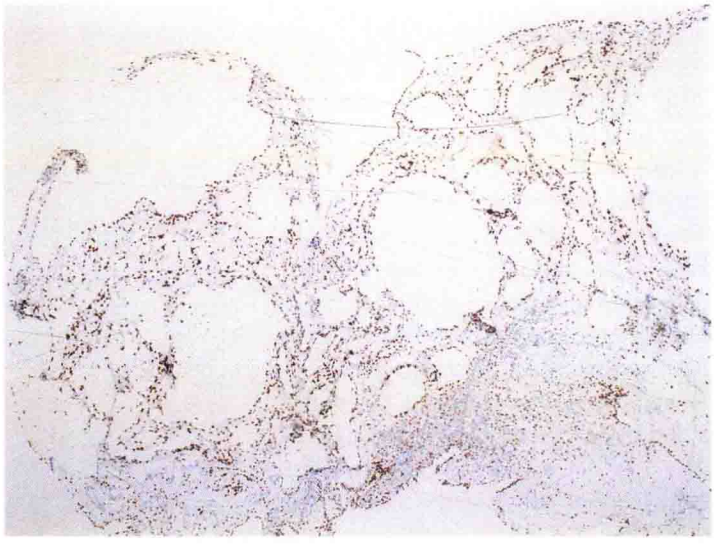

Fig. 1.9 Benign multicystic mesothelioma. The mesothelial cystic lining expresses WT-1

1.3 Echinococcosis

Echinococcosis is an infectious disease caused by larva of *Taeniid cestodes* (tapeworms) belonging to the Echinococcus species [20]. The cystic form is also known as "hydatid cyst." Humans are infected by ingesting Echinococcus eggs, which are excreted by infected animals [20–22].

Echinococcosis has two main forms, a cystic form characterized by large cystic lesions and an alveolar form featuring alveolar structures (1 mm to 3 cm) [23]. Cystic Echinococcosis is most common in temperate zones such as the Mediterranean, Australia, Central Asia, and some parts of America [24], whereas alveolar Echinococcosis is endemic in the northern hemisphere (North America, Asia, China, Japan, and Europe) [21, 25]. The hepatic lesions grow very slowly in the liver (1–5 mm/year). Therefore, the disease remains asymptomatic for long periods of time [23]. Symptoms eventually result from

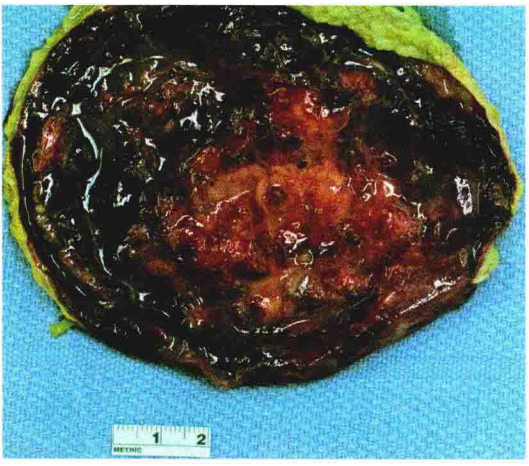

Fig. 1.10 Echinococcal cyst, gross. Grossly, the cystic form of Echinococcosis is characterized by a spherical cyst surrounded by a fibrous rim. Although this example is unilocular, most cases are multilocular, featuring multiple daughter cysts within the main cyst

the mass effect exerted by the cyst/alveolar lesions or by cyst rupture, which can lead to anaphylactic shock (intraperitoneal rupture) or secondary cholangitis (rupture into biliary system) [20, 23]. The alveolar form can also lead to liver failure due to infiltrative growth and potential spread to other organs (through rupture into the abdominal cavity or biliary tree) [26, 27].

The diagnosis is typically made by ultrasound findings and positive serology [23, 28–30]. Because of this, Echinococcosis-related liver lesions rarely get evaluated by the surgical pathologist. However, there can be atypical imaging findings that lead to biopsies or to resections. In resection specimens, the typical cystic form is characterized by a spherical cyst (Fig. 1.10), measuring up to 30 cm, and has a fibrous rim. The cyst can be unilocular but more frequently contains several daughter cysts, developed by growth and invagination of the germinal membrane.

The cyst wall consists of four layers, though in any given histological section some of the layers may not be apparent.

1. The outer layer is composed of the host response, which commonly includes a fibrous rim of variable thickness (Fig. 1.11). Eosinophils are not prominent, but if the cyst ruptures they can become more conspicuous, and often are accompanied by granulomas (Fig. 1.12).
2. An outer membrane (also called the middle layer) is eosinophilic, anucleated, and laminated and measures approximately 1 mm in thickness (Fig. 1.13). This layer is white, refractile, friable, and slippery to touch. It is positive for PAS and GMS.
3. The transparent germinal layer (also called inner layer) measures 10–25 μm in thickness and contains nuclei (Fig. 1.14). This layer gives rise to brood capsules, attached by short stalks, in infectious (fertile) cysts.
4. In the center of the cyst, protoscolices (hydatid sand) can sometimes be found, measuring approximately 100 μm each (Fig. 1.15). These are oval structures containing round suckers and refractile, birefringent, acid-fast hooklets. They may not be present in all cases, depending in part on the age of the cyst, extent of sampling, and whether there has been treatment prior to resection. Protoscolices are usually attached to the germinal layer or budding from it. The hooklets are more commonly found and in fact may be the only component seen in many cases, but are diagnostic (Fig. 1.16).

The alveolar form, on the other hand, features multilocular, necrotic, cystic cavities, containing thick pasty material and lacking a fibrous wall. Histologically, the cysts have a laminated membrane, but no germinal membrane or protoscolices. Hooklets can be found. The laminated membrane is often fragmented; a PAS stain may be necessary to highlight it. The cysts in the alveolar form invade necrotic liver tissue in a manner similar to malignant neoplasms. The host response is variable and may contain a granulomatous reaction with neutrophils and eosinophils, or feature a peripheral rim of extensive necrosis, fibrosis, and calcification.

Mortality from Echinococcosis is uncommon in developed countries, but death rate from Echinococcosis is as high as 5 % worldwide [23, 28, 31]. The treatment of choice for the cystic form is puncture aspiration, injection, and reaspiration (PAIR), which results in parasitological

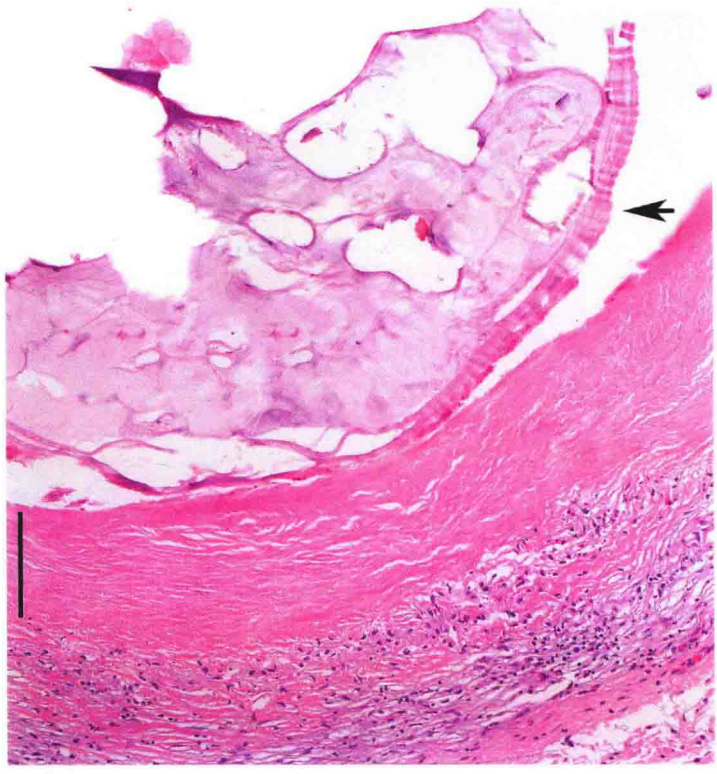

Fig. 1.11 Echinococcal cyst, cyst wall. Microscopically, Echinococcal cysts feature an outer rim of host reaction, an outer anucleated membrane (marked by *vertical line*), and a germinal layer that often separates upon sectioning (*arrow*)

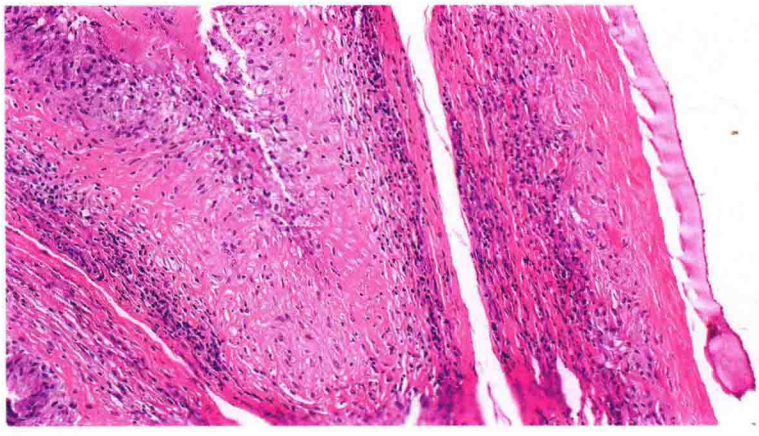

Fig. 1.12 Echinococcal cyst, host reaction. The host reaction to Echinococcal cysts (*right*) can produce granulomatous inflammation (*middle* and *left*)

clearance in 96 % of cases [32]. In this form of treatment, the cysts are aspirated and then re-injected with ethanol or hypertonic saline, which is left in the cyst for a short time before removal by re-aspiration. Treatment of the alveolar form, on the other hand, is similar to treatment for malignancies and consists of radical surgery followed by chemotherapy [20].

1.4 Endometriosis

Endometriosis is a common condition that most frequently involves the pelvis [33]. Endometriosis is rarely found in extra-pelvic locations; and when this occurs, it is termed "atypical endometriosis" [34]. Atypical endometriosis can involve

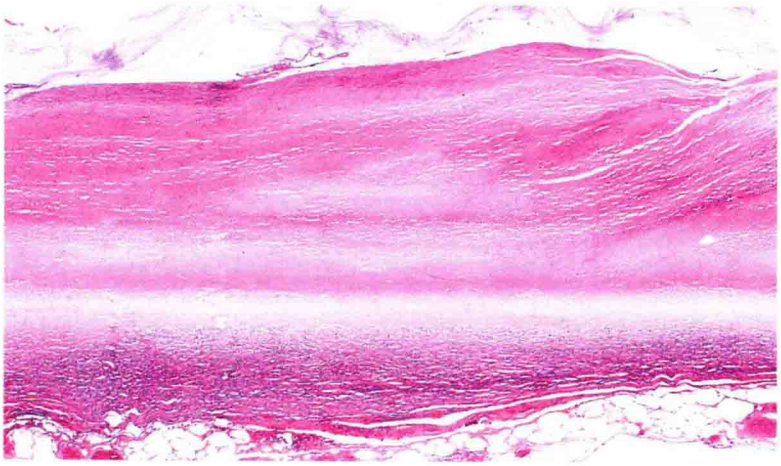

Fig. 1.13 Echinococcal cyst, outer layer. The anucleated laminated membrane is seen

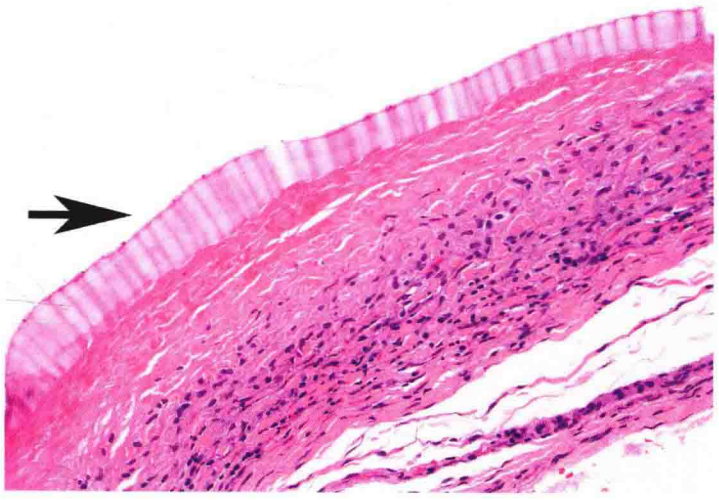

Fig. 1.14 Echinococcal cyst, inner layer. The germinal layer (*arrow*) is seen as a thin layer on top of the laminated membrane

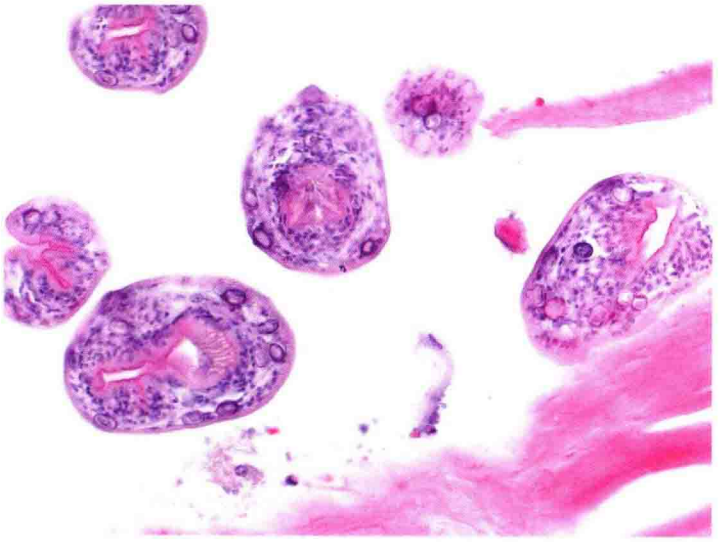

Fig. 1.15 Echinococcal cyst, hydatid sand. Protoscolices are characteristic of Echinococcal cysts. These oval structures contain round suckers and retractile hooklets and are found budding from the germinal layer