Cystadenocarcinoma of the liver

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SYNOPSIS  The clinical and pathological findings in a 42-year-old woman with cystadenocarcinoma of the liver are described. The criteria for acceptance of the diagnosis of cystadenoma of the liver or intrahepatic bile ducts are discussed and the previous literature is reviewed. Malignant change in a cystadenoma has not previously been recorded. Intestinal metaplasia with both goblet and argentaffin cells is also described for the first time in this condition.

Hepatic cysts, though uncommon, are not rare. Davis (1937), in a review of 500 reports of cystic disease of the liver collected from the world literature, found 187 cases of unilocular solitary cyst and 20 of multilocular solitary cyst. The majority of those reported to date, including some described as cystadenoma, are developmental or retention cysts. True proliferative neoplastic cysts of the liver are rare and, as malignant change has not previously been recorded, the following case is of interest.

CASE REPORT

A 42-year-old woman was first seen at the Manchester Northern Hospital in November 1965, complaining of colicky right-sided abdominal pain of four months' duration. There was no history of dyspepsia, vomiting, or jaundice. Physical examination showed a healthy woman of average build with slight scleral icterus. A large smooth mass was felt in the right hypochondrium and its presence confirmed by radiological examination. A cholecystogram showed a normally functioning gall bladder displaced downwards by the mass. A Casoni test was negative. At operation a large multilocular cyst was found arising from the antero-inferior surface of the right lobe of the liver and extending well below it. It involved the porta hepatitis, burrowed deeply into the substance of the right lobe and just impinged on the left lobe; the overlying liver was smooth. All abdominal and pelvic viscera were normal to palpation. The cyst was opened and about 1 litre of thick dark green fluid aspirated. On the wall were several fleshy pink polyps, one of which was biopsied. Dilute formalin was injected into the cyst and closure effected. Recovery was marred by the development of a wound discharge which persisted until a second operation in February 1966, when the cyst was excised. At operation the hepatic ducts were noted to be stretched firmly round the sides of the mass and the gall bladder was adherent in the region of the cystic duct though separation was easy. Small bile ducts ran into the cyst wall, and, when severed, some discharged bile from the end attached to the cyst. Post-operative recovery and progress have been uneventful up to the time of writing.

PATHOLOGICAL EXAMINATION

The biopsy consisted of a strip of tissue 3 cm. in length, on which was a raised nodule 1 cm. square containing several small adjacent cysts. As the microscopic findings did not differ significantly from those of the remainder of the cyst, further description will be omitted.

OPERATION SPECIMEN  The cyst was received in two pieces, the smaller measuring 16 × 13 × 3 cm., the larger 26 × 21 × 9 cm. (Fig. 1). The smaller piece came from the upper surface of the cyst where it was most deeply attached to liver. Bile-stained liver tissue was adherent to its roughened external surface. The inferior surface of the larger part was covered by serosa. The cavity was situated superiorly and was ovoid in shape. Its internal surface was congested and roughened with numerous fibrinous plaques; a few small polyps projected into the lumen from the upper wall. The floor was covered by bulky, irregular, pink, fleshy masses which were multilocular on section and measured up to 8 cm. in thickness. Some cysts contained clear, glairy mucus, others opaque, slimy, greenish semi-solid material.

HISTOLOGICAL FINDINGS

The cyst wall was composed of dense fibrous tissue with smooth muscle-like fibres underlying some cysts for variable distances. The interlocular stroma, which varied in amount, also showed similar fibrous tissue condensations. Degenerative changes, with foamy macrophages and foreign body giant cells

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FIG. 1. Section through larger specimen near lateral extremity; cavity indicated by arrow.

FIG. 2. Proliferative pattern; tall columnar epithelium with papillary infoldings and goblet cells (haematoxylin and eosin × 100).

FIG. 3. Pale mucinous epithelium similar to ovarian cystadenoma (haematoxylin and eosin × 160).
aggregated round cholesterol clefts, were present in the stroma near the surface of the polyps. There was an overlying fibrinous exudate and the adjoining epithelium showed polymorphonuclear leucocytic infiltration and marked papillary infolding. These changes probably resulted from trauma sustained at the first operation. Some proliferation of bile ductules was seen at the cyst periphery and there was evidence of obstructive jaundice in the adjacent liver. The tumour was composed of loculi of varying size, filled with mucin and epithelial debris, mostly lined by tall eosinophilic, columnar epithelium in which goblet cells were plentiful (Fig. 2). A few acini had a unicellular epithelial lining of tall, pale, mucinous columnar cells (Fig. 3), and some a lining of flattened low columnar epithelium; more commonly there was multilayering with frequent papillary infoldings. Daughter cyst proliferation was pronounced in some areas. Cellular pleomorphism was moderate, nuclei varying from low, ovoid and basal in the flattened parts, to plump or elongated and spindly and central or eccentric in the papillary epithelium. Mitoses occurred with moderate frequency. A different picture was seen in one of the smaller polyps from the upper wall (Fig. 4). The acini were closely packed with obliteration of intervening stroma in places, and marked irregularities were present in the multilayered epithelium. Highly pleomorphic cells with giant nuclei adjoined others with hyperchromatic, large nuclei in which were two or more eosinophilic nucleoli (Fig. 5); tripolar and other abnormal mitoses were present and the frequency of mitosis was considerably increased. Intraluminal desquamation of giant malignant cells was a further feature. Malignant change was confined to the centre of the polyp and there was no capsular penetration. The tumour was regarded as a carcinoma arising in an actively proliferating cystadenoma of intrahepatic bile duct origin.

With the periodic-acid-Schiff reaction and Southgate’s mucicarmine stain most of the cells were shown to contain mucin, especially along their free borders. Towards the base of the cell only a few mucinous granules could be seen. The goblet cells were packed with mucicarminephilic and Schiff-positive material. Best’s carmine stain with diastase control indicated the presence of a considerable amount of glycogen, mainly in the lumina, but granules could also be seen scattered diffusely throughout the epithelial cells. They were present in greatest numbers near the free border. Van Gieson and Masson’s trichrome stains were used to identify muscle fibres in the stroma; in all cases the reactions were those of collagen except in one small area where the result was equivocal. The Masson-Fontana technique and the diazo reaction, as described by Fox,
Kazzaz, and Langley (1964), were used to demonstrate the presence of argentaffin granules in some of the epithelial cells (Fig. 6). No fat could be demonstrated by Sudan IV staining.

**DISCUSSION**

Although bile duct retention cysts and proliferative cysts (cystadenomata) are listed separately in the commonly cited classifications of Sonntag (1913) and Jones (1923), several later case reports have failed to make this distinction. The differential diagnosis can be difficult since, as a result of compression, the epithelium may be identical, but the presence of multiloculation is greatly in favour of a proliferative type of cyst. In any cystadenoma, the appearance is the resultant of two opposing forces, namely, the constant multiplication of loculi because of the proliferative properties of the tumour epithelium, and the diminution of the numbers of loculi from pressure atrophy of the intervening septa. Thus, if there are several compartments, these almost certainly represent unobliterated septa since, in a simple cyst due to blockage and subsequent swelling, little opportunity for septation can arise. Edmondson (1958) stresses the importance of multiloculation, suggesting that the diagnosis of bile duct cystadenoma be confined to multilocular cystic tumours lined by columnar epithelium and showing a densely cellular stroma. Corrin (1962), who reported a unilocular cystadenoma, felt that the presence of papillary infoldings and a multilayered tall columnar epithelium were the most helpful features in assessing whether a cyst was neoplastic, but conceded that their absence did not invalidate the diagnosis. Not all case reports include adequate photomicrographs or detailed accounts of the histological patterns present in the cyst epithelium, so that in reviewing reported cases, Edmondson's criteria are more valuable. Warren and Polk (1958) include, as their second example of solitary non-parasitic liver cyst, a large multiloculated mass measuring $25 \times 30$ cm. arising from the inferior surface of the liver and involving both lobes, removed from a 32-year-old woman. It contained thick bile-stained fluid and the right and left hepatic ducts were observed in the base of the cyst. The cysts were of varying size and devoid of papillary elements; the pathological diagnosis was multiloculated pseudomucinous cystadenoma.

Clagett and Hawkins (1946) described a case of cystic disease of the liver which would be more appropriately classified as a multilocular cystadenoma. In this instance, the whole of the left lobe of the liver in a 39-year-old male was replaced by a mass consisting of multiple cysts varying from 8 cm. in diameter to microscopic size. All were lined by bile duct type epithelium and from the photomicrograph the lining appears rather irregular and a little infolded. There is no description of the cyst contents or of the cellularity of the stroma. Burch and Jones (1952) reported the removal of a large trilocular tumour from the inferior surface of the liver of a 54-year-old woman. Two of the loculi contained thick, viscid, dark green fluid. The epithelium was flattened and devoid of papillary projections. Geist (1955) also fails to distinguish between retention and proliferative cysts, including in his review of solitary liver cysts the above case and that of Evans (1921-2), which was originally reported as a cystic adenoma and clearly shows both multilocularity and papillary epithelial infolding. The second case, which he himself reports, also appears to be a cystadenoma. The cyst measured $19 \times 10$ cm. and was multilocular, the loculi being lined by somewhat infolded bile duct type epithelium. Recent reports of true neoplastic cystadenomata include those of Edmondson (1958), Williams (1961), and Corrin (1962). Their incidence is thus higher than a cursory inspection of the literature would suggest.

Solitary non-parasitic hepatic cysts involve the right lobe of the liver about twice as often as the left. The lesion may arise at any age though the majority of patients have been in the fourth and fifth decades,
and there is a pronounced sex difference, females being affected more often than males, the ratio in the collected series being approximately 4:1. Whether the same is true of proliferative cystadenomata is uncertain as insufficient cases have yet been reported. The present case, however, conforms with the above pattern in all respects.

Warvi (1944) recognizes two types of bile duct adenoma, the rare solid or ‘tubular’ type and the commoner cystadenoma or ‘vesicular’ type, which he describes as similar histologically to the cystadenoma of any other gland such as ovary or pancreas. On these grounds, Corrin’s (1962) case, with areas of solid cords of polygonal cells surrounding small tubular lumina in addition to the complex papillary parts, appears to be an example of cystic change occurring in a tubular adenoma: a true cystic adenoma. It differs histologically from some of the cases he cites and from the present case, which are of pseudomucinous cystadenoma-like pattern. Cystadenomata vary in appearance depending on the degree of proliferative activity of their neoplastic epithelium; this is well typified by ovarian and also by pancreatic cysts, and indeed a very real difficulty is frequently encountered in endeavouring to assess the future behaviour of proliferating mucinous cystadenomata. In the present case the epithelial changes with giant cells, nuclear polymorphism and hyperchromasia, multilayering and increased mitotic activity with abnormal forms, indicate undoubted cytological malignancy. Coupled with close packing of glands and obliteration of the intervening stroma in places, the weight of evidence in favour of the diagnosis of malignant transformation of a cystadenoma is difficult to refute. As the malignant change is confined to one polyp and is in its centre, quite well removed from the capsule, it may be that the outlook is not unfavourable, but, as there is no standard of comparison, the prognosis must remain speculative.

A unique feature of the present case is the extensive goblet cell change in the tumour epithelium. Where the pale mucin-ous type of cell occurs, goblet cells are not seen but they abound in the tall eosino-phile epithelium in which papillary processes are common. Goblet cells are a normal feature of the common bile duct of some animals (Cameron and Hou, 1962) and have been reported in the extrahepatic bile ducts in man (Macklin and Macklin, 1932). They occur not infrequently in the gall bladder in association with chronic inflammation (Nicholson, 1923), though they are not normally seen in that organ. Christie (1954) described the occurrence of argentaffin cells in chronically inflamed gall bladders in addition to goblet cells. In the present case, numbers of cells giving positive staining reactions both by the Masson-Fontana and diazo techniques can be found in the epithelium adjacent to the basement membrane. They occur only occasionally in the mucinous epithelium but are quite frequent in the proliferative tall papillary epithelium. In the area of malignant change neither goblet cells nor argentaffin cells could be demonstrated, presumably due to epithelial de-differentiation. There is no relationship in this tumour between goblet and argentaffin cells as the latter have a very irregular pattern of distribution and are not found with increased frequency in areas where goblet cells are most numerous. Christie (1954) found that the occurrence of argentaffin cells was not related to the activity of the inflammatory process and concluded that they were likely to appear in intestinal epithelium wherever it might arise, though their presence in such epithelia was not invariable; he was unable to offer any explanation of their function. The liver and bile ducts are of endodermal origin so that this type of metaplastic change, although not previously recorded in a cystadenoma, is quite acceptable. Its presence clearly illustrates the endodermal origin of the tumour epithelium and so affords further evidence of the primary nature of the tumour in which the malignant change has arisen. The factor or factors responsible for the initiation and maintenance of the metaplasia are unknown. Infection following the original biopsy cannot have played any part, since both goblet and argentaffin cells were present in the original material.

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