Sarcoma of the gallbladder is infrequent. Among the 8,534 autopsies performed at the Cook County Hospital from Jan. 1, 1929, to July 1, 1936, there were found 31 primary malignant tumors of the gallbladder, 28 of which were carcinomas, 1 a melanoblastoma, and 2 sarcomas.

Sarcoma of the gallbladder was accurately described by Landsteiner (1) in 1904. In the literature prior to that year he found 6 cases, reported by Ingalls, Riedel, Klinger, Boutwell and Ford, Destrée, and Siebert. The first three of these cases, however, were not considered as definite primary sarcomas of the gallbladder, and in the remaining three cases the observations were incomplete.

A full report of a fusocellular sarcoma of the gallbladder was given by Griffon and Ségal (2) in 1897, and of a polymorphocellular sarcoma by Newiadomsky in 1900. This latter case and those of Bayer, Parlavecchio, Iwasaki, Hotes, Schoenlank, and Becker are cited by Jaffé (3). Other reports are those of Wieting and Hamdi (4), Cathcart (5), Carson and Smith (6), Rohdenberg (7), Magoun and Renshaw (8), Brendolan (9), Brunschwig (10), Bignami (11), and Büttner (12).

**Case I:** A white male, sixty-two years of age, a carpenter, was admitted, complaining of a dull, burning pain in the right upper quadrant of the abdomen, of three weeks' duration. Although constant, the pain was eased by the ingestion of soft food, by daily bowel movements, and by the application of heat. Loss in weight and abdominal distention had also been noticed. In the week prior to admission there had been a loss of appetite.

The patient was moderately nourished but asthenic. The temperature, pulse, and respiration were normal. The blood pressure was 148/100. Chest findings were normal. The abdomen was distended by fluid. Rectal examination was negative. On the basis of these findings a tentative clinical diagnosis of carcinoma of the gastro-intestinal tract with metastases to the liver was made. The patient was too ill, however, for complete diagnostic studies. He died two weeks after admission.

**Autopsy** (Dr. Jaffé): The skin was of a grayish brown color. On opening the abdominal cavity it was found to contain about three liters of a thin, dark red fluid. The liver was at the level of the xiphoid process and right costal margin. The greater omentum was discolored a deep purple red, markedly thickened, firm, nodular, and adherent to the anterior abdominal wall. The peritoneum in the region of the right upper quadrant was covered with grayish white nodules measuring up to 4 mm. in diameter. The gastrohepatic and gastroduodenal ligaments were infiltrated by similar tissue.

The gallbladder was 10 cm. in length and surrounded by firm, nodular, purplish-gray masses. In the region of the fundus the wall was thin; in the mid-portion it was 8 mm. thick and was firm in consistency and grayish-white in color. In this region the lumen was considerably narrowed and filled with a thick, dark green, mucoid bile, which contained facetted, grayish-green stones from 2 to 18 mm. in diameter. The mucosa was smooth, light
pleomorphic-cell sarcoma of the gallbladder

Purplish-gray to yellowish-gray, but in the region of the constriction it was purplish-red and finely granular. The liver adjacent to the gallbladder contained purplish-gray nodes up to 5 cm. in diameter; smaller nodes were observed in both lobes, up to 8 mm. in diameter. The transverse colon and the mesocolon were firmly adherent to the inferior aspect of the liver and gallbladder. The adhesions were formed by firm, dark purple-gray lobular masses.

Metastases to the gastrohepatic and hepatoduodenal ligaments and to the peripancreatic and mesenteric lymph nodes were also found.

Microscopic Examination: Sections of the primary tumor and metastases were stained with hemalum eosin, Heidenhain’s iron hematoxylin, Mallory’s phosphotungstic acid hematoxylin modified after La Manna (13), and the Van Gieson method.

In both the primary tumor and the metastases there were numerous large pleomorphic cells, many of which were multinucleated (Fig. 1). The nuclei were round to oval in shape, with dense, deeply staining chromatin granules and distinct nucleoli. The cell outlines were often indistinct, and an occasional cell was of stellate shape. In addition to the pleomorphic cells there were elongated, spindle-shaped cells with irregular, hyperchromatic nuclei, which lay parallel to each other and were separated by fine strands of a fibrillar ground substance. The tumor cells for the most part were supported by fine strands of a fibrillar connective tissue, except in smaller areas in which the intercellular ground substance was more abundant. Throughout the tumor were thin-walled, moderately dilated capillaries.

With the Mallory phosphotungstic acid hematoxylin stain occasional cells with central nuclei were seen, the cytoplasm of which contained fine, bluish stained granules. In the periphery of the cell these granules were arranged in transverse lines, while toward the center they were irregularly distributed. Focal areas of necrosis with leukocytic infiltration and hemorrhage were seen throughout the tumor.

The wall of the gallbladder in the uninvolved portion was slightly thickened, especially in the subserosa, and the structure of the mucosa was fairly well preserved. In the subserosa just beneath the muscularis, and especially about the blood capillaries, were small accumulations of round cells (Fig. 2). In the region of the tumor the pleomorphic cells

Fig. 1. Case I (P. M. 1091, '35): Primary Tumor of Gallbladder Wall, Showing Pleomorphism of Tumor Cells

Heidenhain iron hematoxylin. × 200.
described above replaced the mucosa, separated the muscle fibers of the muscularis, and became more abundant in the serosa. The tumor tissue extended deeply into the liver parenchyma, sparing the larger vessels but completely replacing the liver cells. Mitotic figures were numerous and atypical.

**Anatomic Diagnosis:** Pleomorphic-cell sarcoma of the gallbladder with invasion of the right lobe of the liver and extensive metastases to the liver, the gastrohepatic and hepatoduodenal ligaments, the peripancreatic tissue, the greater omentum, the peritoneum, the mesentery, and the mesocolon; cholelithiasis.

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**FIG. 2. CASE I (P. M. 1091, '35): WALL OF GALLBLADDER SHOWING INVOLVEMENT OF THE SUBSEROUS (A)**

The mucosa and muscularis in this section are spared, but show small areas of round-cell infiltration about the small blood vessels (B). Hemalum and eosin. × 80.

**CASE II:** A white female, fifty years of age, was admitted with swelling over the right side of the abdomen, which had been present for the past three weeks. This had given no trouble until three days previous to admission, when the patient began to vomit either immediately following meals or after a lapse of several hours. The day prior to admission she began to complain of dull pain in the region of the swelling, radiating to the flanks.

The patient was well nourished and did not appear acutely ill. Her temperature was 99.6°F, pulse 88, respiration 20, and blood pressure 138/74. The thyroid was slightly enlarged and a few coarse râles were heard over both lung bases posteriorly. The heart borders were within normal limits, the heart tones regular and of good quality.
The abdomen was soft, except for an area of slight resistance in the right upper quadrant. Here there was a firm, palpable, nodular mass projecting from beneath the right costal margin. This mass moved with respiration and extended to the umbilicus. A diagnosis was made of primary carcinoma of the gallbladder or liver.

In further laboratory studies it was twice found impossible to visualize the gallbladder. X-ray examination of the lungs showed extensive hematogenous metastases. Traces of blood were found in the stools. While in the ward, the patient continued to become weaker, and the mass extended rapidly below the level of the umbilicus. Anorexia and vomiting persisted until death, one month after admission and about two months after the onset of the symptoms.

**Autopsy** (Dr. Jaffé): A slight icteric tinge was observed in the sclerae and conjunctivae. On opening the abdominal cavity, the liver was found to extend 17 cm. below the xiphoid process and 13 cm. below the right costal arch. The greater omentum was loosely adherent to the liver and contained soft, deep purple-gray nodes up to 10 cm. in diameter. The transverse colon was displaced downward and to the left.

The gallbladder was greatly enlarged (Fig. 3), measuring $12 \times 11.5 \times 10.5$ cm. A lobular mass completely replaced the wall of the mid-portion, while the fundus and neck were spared. The tumor measured 30 mm. in its greatest thickness, was very soft, friable, and of a dirty grayish-brown to purplish-brown in color. The lumen of the gallbladder contained dirty brown material and numerous faceted dark brown stones up to 20 mm. in diameter.

The right lobe of the liver was considerably deformed by nodes measuring up to 12 cm. in diameter. On sectioning, these nodes were found to be medullary, well circumscribed, and deep purple-red in color. In the left lobe smaller nodes up to 2.5 cm. in diameter were seen. The intervening liver parenchyma was light grayish-brown, and the markings were obscured.

Extensive metastases were observed in the lungs, the heart, the walls of the pulmonary veins, the thyroid, the pancreas, the right suprarenals, the kidneys, and the peribiliary and peripancreatic lymph nodes.

**Microscopic Examination:** The gallbladder tumor seemed to take its origin from the mid-portion of the wall, extending chiefly towards the liver. It was very pleomorphic. In places, spindle-shaped cells predominated, forming interlacing bundles. Elsewhere the cells
were large, oval, polygonal or band-shaped, with ample cytoplasm that revealed an occasional fine fibrillation. The nuclei of these large cells were very bizarre in shape, indented, segmented, lobulated, and rich in coarse chromatin granules. Many cells were multinucleated. Both the spindle-cell and pleomorphic cell tissue were surrounded by and invaded strands of connective tissue. Large areas of necrosis enclosed deposits of golden-yellow bile pigment and cholesterol crystals.

With the Mallory phosphotungstic acid hematoxylin stain the pleomorphic multinucleated cells had a deeply staining granular cytoplasm, whereas the pleomorphic, mononucleated cells showed a pale-staining vacuolated cytoplasm. Van Gieson stain disclosed a scanty stroma of connective tissue.

The microscopic study of the liver metastases showed many multinucleated cells with a granular or vacuolated cytoplasm. The polymorphism was striking, many of the nuclei showing atypical mitosis. In the metastases to the lung the cells displayed a decided tendency to assume a spindle shape and to form interlacing bundles (Fig. 4). Oblong cells were quite prominent and appeared to have a more deeply staining granular cytoplasm. Their nuclei were slightly elongated. There was no evidence of striations in the cytoplasm of these cells.

The metastases to the kidney, heart, and lungs were composed predominantly of spindle-shaped cells which showed a distinct relation to the intercellular fibrillar substance. This finding was most striking in the sections stained by the Van Gieson technic and was most marked in the lungs.

Anatomic Diagnosis: Pleomorphic-cell sarcoma of the mid-portion of the gallbladder with extensive metastases to the kidney, heart, and lungs, the pulmonary hilus, peribiliary and peripancreatic lymph nodes, the pulmonary veins, adrenals, thyroid gland, mesentery, peritoneum, and greater omentum; cholelithiasis.

The two cases described represent the most frequent variety of sarcoma of the gallbladder wall, namely, the spindle-cell sarcoma derived from the
stroma and containing large polymorphic cells, many of which are multinucleated. A less frequent type of sarcoma of the gallbladder is the myosarcoma. Landsteiner (1) described two cases of myosarcoma, one of which was associated with a squamous-cell carcinoma (14). Lymphosarcoma of the gallbladder has been reported by Magoun and Renshaw (8) and Rohdenberg (7), a melanoblastoma by Wieting and Hamdi (4), a myxochondrosarcoma by Bayer (cited by Jaffé) and an endothelioma by Becker (cited by Jaffé). Karlmark (15) collected 31 cases of sarcoma of the gallbladder and 5 cases of endothelioma of the gallbladder. Gallstones were present in 22 of the cases of sarcoma of the gallbladder wall and in all 5 cases of endothelioma. Büttner (12) has since added 4 more cases.

As to the etiological factors involved in the origin of sarcoma of the gallbladder, great stress is placed by many authors, including Magoun and Renshaw (8), Musser (16), and others, upon the presence of stones in the lumen or the organ. Hotes and Schoenlank (quoted by Jaffé) and Büttner (12), on the other hand, support Aschoff in the view that such a relationship is merely hypothesis and cannot be definitely proved.

In the autopsy material of the Cook County Hospital 21 of the 28 cases of primary carcinoma of the gallbladder were found to be associated with one or more stones in the lumen. Two of the cases were discovered incidentally post mortem, and in both of these the gallbladder contained stones. The two cases of sarcoma of the gallbladder from the Cook County Hospital series, reported in this paper, were associated with stones. The single melanoblastoma was without stones. Practically the same ratio of stones to malignant tumors of the gallbladder is reported by Magoun and Renshaw (8), who quote similar figures from other sources. Ewing (17) believes that two forms of sarcoma may arise in the wall of the gallbladder, one from smooth muscle fibers and the other from connective tissue and blood vessels, both being due to the presence of stones or inflammation of the gallbladder wall.

Approximately 72 per cent of the cases of sarcoma of the gallbladder recorded in the literature were associated with cholelithiasis. Inflammatory changes in the wall of the gallbladder in cases of sarcoma have been described by Carson and Smith, Schoenlank, Parlavecchio, Bayer, Bignami, and Büttner, and since chronic inflammatory cell proliferation may ultimately terminate in sarcoma, the possibility that sarcoma of the gallbladder may develop from chronic inflammatory changes cannot be denied a priori. Sarcomatous transformation of chronic inflammatory granulation tissues was well illustrated by a case of fibrosarcoma following a chronic osteomyelitis of many years' duration which recently came under the author's observation.

In view of the infrequent reports of myosarcoma of the gallbladder, the possibility of its having been overlooked, because of the difficulty of staining muscle fibrils, was considered. With this point in mind, great care was taken in staining the sections with Mallory's phosphotungstic acid hematoxylin, after the modification of La Manna (13). By this method striations, if present, are usually brought out very clearly. In neither of the two cases reported was it possible to show myofibrils, but with the Van Gieson stain a relation between the tumor cell and the intercellular connective tissue fibrils was often demonstrated.
Sarcoma of the gallbladder usually occurs in the later decades of life. The earliest age reported is thirty-eight years (Carson and Smith, 6; Thöle, quoted by Karlmark). The oldest patient was seventy-seven (Karlmark, 15). The majority of cases occurred between the fifth and seventh decades.

The disease is more frequent in women than in men in a ratio of about six to one, according to Büttner. Carson and Smith believe that sarcoma of the gallbladder occurs much more frequently than is reported in the literature, since a gross diagnosis of carcinoma of the gallbladder is often made without a biopsy for confirmation.

The treatment in the late stages of this disease is discouraging. Magoun and Renshaw believe that treatment should be instituted when the patient presents signs of either cholecystitis or cholelithiasis. They have shown that of over 7,000 surgically removed gallbladders, 84 were the site of tumors.

**SUMMARY AND CONCLUSIONS**

Two cases of pleomorphic-cell sarcoma of the gallbladder have been reported. In both cases there were generalized metastases. The presence of gallstones or, more particularly, of chronic inflammatory changes in the wall of the gallbladder may be considered a possible etiologic factor.

**BIBLIOGRAPHY**