

# Port Site Metastases in Squamous Cell Carcinoma of the Gallbladder

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**P**rimarily carcinoma of the gallbladder is rare and the prognosis is ominous except for those cases diagnosed incidentally following cholecystectomy. Squamous cell carcinoma of the gallbladder is an exceptionally rare and aggressive neoplasm of the gallbladder, accounting for up to 12.7% of the malignant neoplasms of this organ [1,2]. We present here a patient with squamous cell carcinoma of the gallbladder and review the literature.

## PATIENT DESCRIPTION

A 35 year old woman known to have hepatitis B was admitted with complaints of epigastric and right upper quadrant pain, nausea and vomiting. On examination, except for epigastric and right upper quadrant tenderness, the physical examination was otherwise normal. Laboratory tests revealed increased bilirubin levels and pathological liver functions. Abdominal ultrasound showed a distended gallbladder without stones but with sludge, and distended common and intrahepatic bile ducts. Acute cholecystitis was diagnosed and antibiotic treatment was initiated. The clinical picture slowly resolved, and the patient was discharged home and scheduled for a laparoscopic cholecystectomy 6 weeks later.

Five weeks later she returned with another bout of pain and, based on the clinical and ultrasonographic findings,

an endoscopic retrograde cholangiopancreatography was performed. A distended common bile duct was seen, but no stones were detected. A few days later she was discharged following resolution of her symptoms. The following day she was rehospitalized due to recurrent abdominal pain. An abdominal computed tomography scan showed a distended gallbladder and bilateral pleural effusions but was otherwise normal. Two days later the patient underwent laparoscopic cholecystectomy. The operation, during which there was spillage of bile from the gallbladder, was technically difficult. The patient had an uneventful postoperative course and was discharged on the 5th postoperative day.

On pathology, poorly differentiated squamous cell carcinoma of the gallbladder was diagnosed. Based on these findings, a reoperation was planned for radical excision of the tumor bed and lymphadenectomy. A preoperative chest and abdominal CT scan was normal, but secondary deposits were diagnosed on the abdominal CT, some of which were considered port site metastases. A diagnostic laparoscopy revealed grey friable tissue masses in the pelvis and on the peritoneum of the right abdominal wall at a distance from the trocar port site. Another firm mass was fixed to the cecum. Based on the accumulated data, surgery was deferred and the patient was referred for oncological treatment. However, the patient died 4 months later.

## COMMENT

Primary gallbladder carcinoma is the fifth most common cancer of the gastrointestinal tract and the most common malig-

nant tumor of the biliary tract. Generally diagnosed late in the course of the disease due to the non-specific symptoms and signs, it carries a poor prognosis with a 5 year survival rate varying between 0 and 10% [3,4]. Patients are usually diagnosed between their fourth and sixth decades of life. Females are two to three times more prone to develop the disease than men [3].

Gallstones are an important risk factor for gallbladder carcinoma and are found in 65–90% of patients with this type of carcinoma. The risk is in direct proportion to stone size. Most cancers originate in the fundus. Histologically, the majority of the cases are adenocarcinoma (80–95%), followed by undifferentiated anaplastic carcinoma (2–7%) and squamous cell carcinoma (1–6%). Sarcomas, lymphomas, and carcinoid and small cell tumors are rare. Rapid growth, early metastatic dissemination, and diffuse local and regional infiltration characterize the biological behavior of the lesion. This carcinoma tends to form large infiltrative masses invading the liver and adjacent organs (stomach, duodenum, transverse colon) by direct expansion [1]. Despite this local and regional infiltration, lymph node metastasis is not usually present, and seeding to the peritoneum is rare [2].

The symptoms overlap those of cholecystitis until the disease invades surrounding structures. Pain and jaundice, an indicator of poor prognosis, are the most characteristic clinical features. Carcinoma may be suspected in elderly patients with a long history of chronic cholecystitis and gallstones who have experienced a recent change in symptoms and have severe pain. Over one-half of the patients with gallbladder carcinoma have such a his-

tory [3,4]. Anemia, chemical jaundice and an elevation of serum alkaline phosphatase are usually seen in laboratory data. Increased tumor marker levels such as CEA and CA19-9 should raise the suspicion of malignancy [3]. Ultrasound is the most useful method of diagnostic workup for gallbladder carcinoma, and with color Doppler it is possible to differentiate between biliary sludge and carcinoma. CT scanning can accurately detect gallbladder abnormalities and the extent of the disease. The main purpose of CT is to diagnose the extent of tumor growth and establish whether there is direct infiltration into adjacent organs, vessels and lymph nodes, or distant metastases. Magnetic resonance cholangiopancreatography can supply even more detailed information than ultrasound or CT. Angiography, rarely used, can show the extent of tumor growth, thus providing information about resectability. Laparoscopic gallbladder biopsy should be avoided in patients with suspected lesions and those potentially curable as it may cause tumor dissemination [4].

The curative therapy for gallbladder carcinoma is surgical resection. Unfortunately, most patients have unresectable disease at diagnosis. Treatment with radical or extended cholecystectomy is possible in only 10–30% of patients [4]. Carcinoma of the gallbladder is discovered during cholecystectomy for benign disease in 1–2% of cases [4]. The presence of gallbladder carcinoma should be suspected if the cholecystectomy is technically difficult. All gallbladders removed for stone disease must be opened and examined for suspicious lesions before the abdomen is closed. In patients in whom carcinoma is discovered by histological examination following laparoscopic cholecystectomy, the port site should be excised because of the possibility of port site disease dissemination. If carcinoma is suspected during laparoscopic cholecystectomy, the operation should be converted to open surgery [4]. For early stages of the disease (without invasion to the muscle layer – Tis and T1a), simple cholecystectomy is adequate, with a 5 year survival rate of 85–100%. For more

advanced disease (tumor invasion of the muscularis or perimuscular layer without extension beyond the serosa – T1b or T2), a radical cholecystectomy, offering a 5 year survival rate of 80–90%, should be performed. Surgery should be attempted only if it is possible to achieve complete resection and not for debulking purposes. Surgical resection is contraindicated in the presence of multiple liver metastases, ascites, multiple peritoneal metastases, distant metastases, extensive involvement of the hepatoduodenal ligament, encasement/occlusion of the major vessels, and poor performance status. Patients with advanced unresectable carcinoma of the gallbladder and obstructive jaundice may need palliative treatment in the form of a bilioenteric bypass or endoscopic/percutaneous stenting to relieve the jaundice. Non-operative stenting is the preferred approach. A major problem with advanced carcinoma is pain, which may require palliative management [4].

The results of radiotherapy in patients with gallbladder carcinoma are disappointing. External radiotherapy may be used for palliative management of advanced gallbladder carcinoma. However, tumor control is rarely achieved by radiotherapy

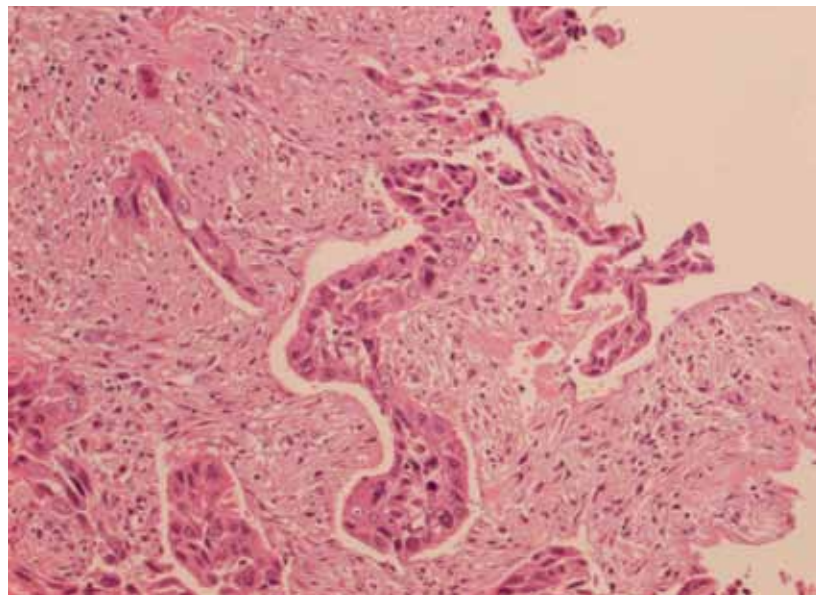
alone because of the relative radio-resistance of the tumor [4]. The chemotherapy combination of cisplatin plus gemcitabine for advanced biliary cancer is the best treatment option [3].

The stage of disease at presentation is the most important determinant of prognosis. Factors predicting poor prognosis include high grade, low tumor acid mucopolysaccharide, and increased serum lactate dehydrogenase [4].

Very little is known about squamous cell carcinoma of the gallbladder, and as mentioned above, these tumors account for up to 12.7% of all gallbladder cancers [1,2]. The diagnosis is based on histological identification of cords, trabeculae or sheets of infiltrating neoplastic cells [2] [Figure]. A few theories regarding the origin of squamous cell carcinoma have been suggested. The most accepted is that squamous cell carcinomas arise from squamous metaplasia, probably as a consequence of chronic irritation [2].

Adenosquamous carcinoma of the gallbladder infiltrates extensively and metastasizes early and widely, while the behavior of pure squamous cell carcinoma is disputable. Some authors suggest that it is highly invasive and metastasizes early,

Histology slide shows cords and trabeculae of a squamous cell carcinoma of the gallbladder



while others claim that it grows locally with no visceral and no, or rare, lymph node metastases [2]. The course of the disease in our patient was very aggressive with wide-spread metastatic deposits throughout the abdominal cavity.

An important issue is that of port site metastases. Various studies have reported port site metastases in conjunction with laparoscopic surgery. These occurred in cases of gallbladder cancer as well as colonic cancer [5]. To the best of our knowledge, this is the first report of dis-

seminated and port site metastases in a case of squamous cell carcinoma of the gallbladder.

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**Capsule**

**In situ identification of bipotent stem cells in the mammary gland**

The mammary epithelium undergoes profound morphogenetic changes during development. Architecturally, it comprises two primary lineages, the inner luminal and outer myoepithelial cell layers. Two opposing concepts on the nature of mammary stem cells (MaSCs) in the postnatal gland have emerged. One model, based on classical transplantation assays, postulates that bipotent MaSCs have a key role in coordinating ductal epithelial expansion and maintenance in the adult gland, whereas the second model proposes that only unipotent MaSCs identified by lineage tracing contribute to these processes. Through clonal

cell-fate mapping studies using a stochastic multicolor *cre* reporter combined with a new three-dimensional imaging strategy, Rios et al. provide evidence for the existence of bipotent MaSCs as well as distinct long-lived progenitor cells. The cellular dynamics at different developmental stages support a model in which both stem and progenitor cells drive morphogenesis during puberty, whereas bipotent MaSCs coordinate ductal homeostasis and remodeling of the mouse adult gland.

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**Capsule**

**The immune system suffers in space at least in flies**

A concern regarding manned long-term space missions is that changes in gravitational force compromise the human immune system, but the underlying cellular and molecular reasons have not been clear. Taylor et al. studied innate immunity in *Drosophila melanogaster* that traveled aboard Space Shuttle Discovery in 2006. Flies reared in space were compared to flies that underwent development on Earth. Upon the return of the space-reared flies to Earth, both groups of flies were subjected to bacterial (*Escherichia coli*) or fungal (*Beauveria bassiana*) infections, and their gene expression profiles were examined. Genes associated with Toll receptor-mediated immune responses to fungal infection were acti-

vated only in the Earth flies. The expression of specific antimicrobial peptides also failed in the space flies. Other mechanisms, such as the Imd signaling pathway response to bacterial infection, were not affected in space flies. The space flies exhibited increased expression of heat shock response genes, a subset of stress response genes that are activated to manage aberrant protein folding. The authors suggest that microgravity may alter the folding and stability of proteins, which triggers the deployment of heat shock proteins that, in turn, may interfere with the Toll receptor signaling pathway.

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**“The things we admire in men, kindness and generosity, openness, honesty, understanding and feeling are the concomitants of failure in our system. And those traits we detest, sharpness, greed, acquisitiveness, meanness, egotism and self-interest are the traits of success. And while men admire the quality of the first they love the produce of the second”**

John Steinbeck (1902-1968), American novelist and Nobel laureate for literature. His most famous works are the Pulitzer Prize-winning novel *The Grapes of Wrath* (1939), *East of Eden* (1952) and the novella *Of Mice and Men*