

Small Cell Carcinoma of the Gall Bladder

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ABSTRACT

Small cell carcinoma of the gall bladder (SCCGB) is a rare condition, with only 53 prior cases reported in the world literature when our case was first diagnosed. Our patient was found to have limited stage disease and was treated with sequential laparoscopic cholecystectomy, etoposide/carboplatin chemotherapy followed by consolidating loco-regional radiation therapy. She is alive and well without evidence of disease more than 132 months since diagnosis. We describe here our experience in the diagnosis, staging workup, treatment, and surveillance of a case of SCCGB and review the published literature. Treated aggressively with currently available methods, patients with limited stage SCCGB can have an excellent prognosis. The authors' intent is to provide a reasonable plan of treatment for other physicians facing such an unusual patient.

CASE PRESENTATION

Our patient is a white woman who was 63 years old when she presented to the emergency department with chief complaints of extreme abdominal pain and emesis. Her social history was remarkable for smoking cessation 3 years earlier. An evaluation including ultrasonography showed her to have cholelithiasis and cholecystitis as well as a thickened area within the lumen of the gall bladder (Figures 1 and 2).

Laparoscopic cholecystectomy was performed the following day, after which she made an uneventful recovery. The significant pathologic findings were: a 7.1 x 4.5 x 2.6 cm tan-red, hemorrhagic mass lying primarily within the body of the gallbladder and extending into the infundibulum, cholecystitis, cholelithiasis, and a small perforation of the gall bladder. The histology is shown in Figure 3. The cystic duct was involved and the serosa had been perforated by the tumor. Lymphovascular invasion also was noted.

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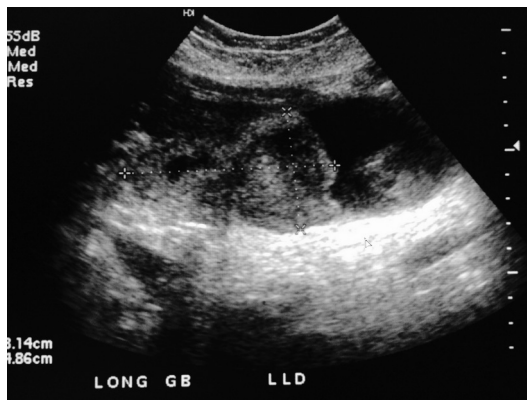
With regard to surgical margins, tumor was present on the serosal surface of the gall bladder, but the cystic duct margin was negative for tumor. Two gallstones were found within the gall bladder. On immunoperoxidase staining, the tumor cells were positive for synaptophysin, AE1-AE-3, cytokeratin CAM5.2, high molecular weight cytokeratin and cytokeratin 7. The tumor cells were negative for chromogranin, carcinoembryonic antigen, cytokeratin 20, epithelial membrane antigen (EMA) and vimentin.

In order to complete her tumor staging, a positron emission tomographic (PET) scan with fused computerized axial tomographic (CT) imaging was performed (Figures 4 and 5). Two lesions in the gastrophepatic ligament measuring 3.7 x 2.3 cm and 1.5 x 1.6 cm were noted. They had maximum standardized uptake values (SUV) of 17.2, while lesions posterior in the head of the pancreas had a maximum SUV of 14.2. These maximal SUV values strongly suggested a malignant etiology rather than an infectious or inflammatory process. There was no evidence of distant metastases.

Chemotherapy was initiated 30 days after the operation. It consisted of 4 courses of etoposide (100 mg/m² daily x 3) + carboplatin (area under the curve [AUC] x 6) beginning on day 1 of each 21-day cycle. Following completion of the chemotherapy, she received consolidation radiation therapy. The plan was designed to deliver 45 Gray units (Gy) while sparing appropriate volumes of kidney mass, liver, and spinal cord to keep the likelihood for normal tissue toxicities to a negligible level. This was very well accomplished. Forty percent of her right kidney received > 18 Gy; about 35% of the left kidney received > 18 Gy; 40% of her liver received > 30 Gy. Her clinical target volume received 45 Gy.

The patient experienced expected side effects of nausea and fatigue. However, her nausea was not effectively controlled with aggressive antiemetics until the daily dose was reduced to 1.25 Gy. After that, her tolerance was excellent and she completed therapy without significant impact on her weight or oral intake.

Figure 1. Parasagittal View of the Gall Bladder



Ultrasound image shows cholelithiasis and a significant size intraluminal mass, which ultimately proved to be small cell carcinoma upon histologic evaluation.

Figure 2. Transverse Ultrasound of the Gall Bladder Showing the Intraluminal Mass



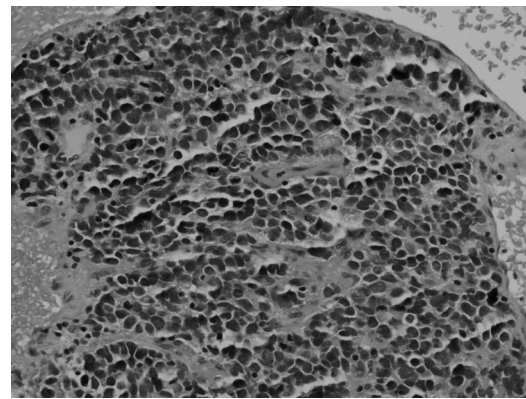
At the conclusion of therapy, she had no uncontrolled toxicities, no significant pain, and was taking oral nourishment and fluids well. She did not require readmission to the hospital for symptom management. She was followed with physical examination, complete blood count, and comprehensive metabolic profile every 3 months for the first 2 years, and every 6 months for the next 3 years, then annually. CT scanning was repeated at those same intervals. Her surveillance computerized axial tomographic scans have remained normal. She remains alive and asymptomatic more than 132 months from diagnosis.

DISCUSSION

Small cell carcinoma of the gall bladder (SCCGB) is rare. A search of the English medical literature showed only 53 reported cases.¹ The prognosis is poorer than that of differentiated carcinomas of the gall bladder. It tends to affect an older patient population occurring at a median age of 65 years, with a female preponderance of 76%.² It is frequently associated with cholelithiasis. Metastasis to lymph nodes occurs in 88%, liver 88%, lung 23%, and peritoneum 19%.² The 5 patients treated with surgery and chemotherapy by Moskal et al² had a median survival of 13 months. This represents an improvement over historical reports. Those with pure small cell tumors had a median survival of 9 months, while those with mixed tumors had a median survival of only 4.5 months.²

Pathologic characteristics may include large size at diagnosis, extensive necrosis, and propensity for submucosal growth. Histologically, these tumors are composed predominately of small round cells usually mixed with spindle cells, both of which have hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm. The growth pattern is usually diffuse. However, focal nesting or festoon patterns can be seen. Most of these tumors show neuroendocrine differentiation by immunohistochemistry

Figure 3. Gall Bladder Wall



Photomicrograph specimen showing small cell carcinoma which, perforated the serosa (hematoxylin-eosin, original magnification x200). The cystic duct margin was negative for tumor. Lymphovascular invasion was present. The cells demonstrated positivity for synaptophysin, AE1-AE3, cytokeratin CAM5.2, high molecular weight cytokeratin and cytokeratin 7. It was negative for chromogranin, carcinoembryonic antigen, cytokeratin 20, EMA and vimentin.

such as synaptophysin, chromogranin, or neuron-specific enolase. Immunoperoxidase stains showed focal carcinoembryonic antigen in 3 of 11 tumors studied by Albores-Saavedra et al.³ Molecular changes have been identified as well. On electron microscopy, neurosecretory granules are sometimes present.⁴ Significantly, frequent occurrences of p53 (75%), p16INK4a (33%), and K-RAS codon (17%) mutations have been identified.^{4,5}

Our experience demonstrated that this disease can exhibit FDG hyper-avidity on PET scanning (Figures 4 and 5).

As recently as the year 2000, Mithal et al reported a case in

Figure 4. PET Scan of Gall Bladder Bed Showing Area of Intense Uptake

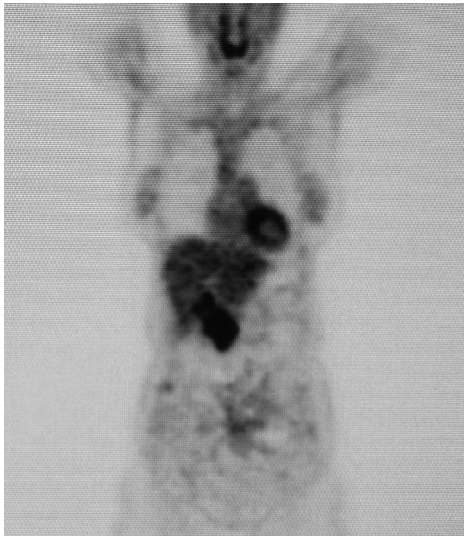


Figure 5. PET Scan of Gall Bladder



The multiple areas of 2,3-fluorodeoxyglucose avidity were interpreted to be areas of likely gastrohepatic ligament involvement by the carcinoma. That finding coupled with the absence of distant spread on the PET scan led to the conclusion that the patient had limited stage disease.

Table. Summary of Chemotherapy and Radiation Therapy Regimens Employed, Responses, and Survival

Reference	No. Cases	No. LTD/No. EXT	Responders/ Total No. Treated	Type of Chemotherapy and Radiation Therapy (RT)	Survival (months)
Fujii et al ¹					
Case	1	0/1	1/1	cis-DDP + VP-16 no RT	12+
Review	35	12/23	2/19	no chemotherapy specified	7/13
Albores-Saavedra et al ³	19	1/18	2/19	CAV + nitrososurea, no RT	7, 13
Lane et al ⁷	1	0/1	1/1	carbo + VP-16, 45 Gy in 25 fractions	11
Okamoto et al ⁸	1	0/1	1/1	cis-DDP + gem, no RT	7
Bahadur et al ⁹	2	0/2	1/1	cis-DDP + VP-16, no RT	5, 9
Pavithran et al ¹⁰	1	0/1	1/1	5FU + cis-DDP→docetaxel + carbo, No RT	13
Ron et al ¹¹	1	0/1	1/1	cis-DDP + VP-16, no RT	6+

Abbreviations: LTD, limited stage disease; EXT, extensive stage disease; cis-DDP, cis-Platinum; CAV, cyclophosphamide, doxorubicin (Adriamycin), vincristine; carbo, carboplatinum; gem, gemcitabine; VP-16, Etoposide; 5FU, 5-fluorouracil; Gy, Gray.

a 25-year-old woman.⁶ They asserted that chemotherapy is not known to improve survival. Our patient has shown a totally different possibility. Her therapy was based upon principles of treatment promoted by the National Comprehensive Cancer Network guidelines. We chose to apply consolidating radiation therapy after the course of chemotherapy out of concerns for increased hepatotoxicity from simultaneous application of these modalities. It appears that, just as in the treatment of small cell carcinoma of the lung, only patients with limited stage disease are capable of complete remission and long-term survival.

A summary of the different chemotherapy regimens and radiation therapy employed is shown in the Table. The most commonly used regimens employed a platinum derivative plus

VP-16. This is currently typical treatment of small cell carcinoma of the lung. The stage of disease was not apparent in the other patients. The addition of local, consolidating radiation therapy after completion of the chemotherapy may be a discriminating difference between our patient and others reported. Had extensive stage disease been present at the time of diagnosis, then we would not have applied radiation therapy with curative intent. Based upon our experience, a patient with SCCGB should undergo rigorous staging to include PET/CT scanning. If localized or even loco-regional disease allows a designation of limited stage disease, we recommend sequential chemotherapy with VP-16 and carboplatin followed by loco-regional radiation therapy with curative intent. This approach can offer hope to

these rare patients. Since so little literature exists regarding this disease, our report is offered in the spirit of providing guidance and cautious optimism to physicians faced with the dilemma of treating such an unusual patient.

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