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CASUISTIC PAPER

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Primary pure squamous cell carcinoma of the gall bladder – a case report of rare and aggressive entity with adverse prognosis

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ABSTRACT

Introduction. The most common malignancy of the biliary tract is gall bladder carcinoma and the main subtype according to the histological classification is Adenocarcinoma. Pure squamous cell carcinoma of the gall bladder is very rare entity accounting for only 1.1-3.7% of the gall bladder carcinomas. It is highly malignant with poor prognosis due to high proliferative rate and local invasiveness to the adjacent organs. The patients are usually diagnosed at an advanced stage with a bulky tumor owing to its aggressive behavior.

Aim. In this paper, we describe a female patient with primary pure squamous cell carcinoma of the gall bladder.

Description of the case. A 42-year old female patient presented with chief complaints of pain in abdomen associated with nausea and vomiting and gradually progressive jaundice since 02 months. Contrast Enhancing Computed Tomography (CECT) abdomen showed an enhancing mass lesion in gall bladder involving adjacent organs for which she underwent extended cholecystectomy with pancreaticoduodenectomy.

Conclusion. Diagnosis as well as the management of this exceptionally rare type of tumour is undoubtedly challenging because of non-specific clinical as well as imaging findings. This case report is an attempt to add to the literary evidence for better pathological as well as clinical understanding of this rare and aggressive entity thereby providing additional material for the early diagnosis as well as the development of effective targeted therapies which will certainly help in increasing the lifespan of these patients.

Keywords. adenocarcinoma, cholecystectomy, gall bladder, pure squamous cell carcinoma

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

The most common malignancy of the biliary tract is gall bladder carcinoma and the main subtype according to the histological classification is Adenocarcinoma (AC) followed by adenosquamous carcinoma (ASC) and squamous cell carcinoma(SCC).[1] There is considerable geographic as well as gender variation demonstrated by gall bladder carcinomas. The incidence is greater in Asian countries particularly India and Japan with a female preponderance of 3:1 partly because of higher incidence of gallstones in females and presents between 4th to 6th decade of life.[2] Delhi, the capital of India has the highest gallbladder cancer incidence rates for females (21.5 per 100,000).[3] Squamous differentiation can be encountered in about 7% of all the gall bladder adenocarcinomas. Those with squamous differentiation in less than 25% of the tumour are reported as focal squamous change; those with 25%-99% qualify as adenosquamous carcinoma.[4] Finding areas of squamous cell carcinoma in cases of otherwise usual adenocarcinoma of gall bladder is not a rare finding.[5] Pure squamous cell carcinoma without any glandular component is extremely uncommon. Pure squamous cell carcinoma of the gall bladder is very rare entity accounting for only 1.1-3.7% of the gall bladder carcinomas.[6] Squamous cell carcinoma of the gall bladder usually presents with an ill- defined clinical course. It is often diagnosed at an advanced stage and is characterized by extensive local spread and rarely distant metastasis. Though the exact mode of spread of these tumors is still not clear it has been observed that they spread widely by local infiltration and rarely metastasize to the regional lymph nodes or distant organs.[7] According to the report of Charbit et al. the growth rate of the squamous component is twice as fast as the adenocarcinomatous component. Hence the SCC is more aggressive, usually diagnosed when the tumor is large and locally advanced thereby having a poor prognosis in comparison to stage matched advanced gall bladder adenocarcinoma cases.[8]

Aim

In this paper, we describe a female patient with primary pure squamous cell carcinoma of the gall bladder.

Description of the case

A 42-year old female patient presented with chief complaints of pain in abdomen associated with nausea and vomiting and gradually progressive jaundice since 02 months. There was no history suggestive of gastric outlet obstruction. Her past medical history was non- contributory. Physical examination revealed deep icterus (bilirubin 14.8), a right hypochondrial hard lump and inferior border of liver is not separately palpable from mass. Laboratory tests revealed neutrophilic leukocytosis with total bilirubin 14.8 mg/dl. However, the values of liver enzyme test results were within normal limits. Contrast Enhancing Computed Tomography (CECT) abdomen was done showing an enhancing mass lesion in gall bladder involving duodenum and head of pancreas, multiple hepatoduodenal, periportal and retro pancreatic lymph nodes, involving right hepatic artery (fig.1.). She underwent extended cholecystectomy with pancreaticoduodenectomy with right hepatic artery ligation and the specimen sent to the Department of Pathology.

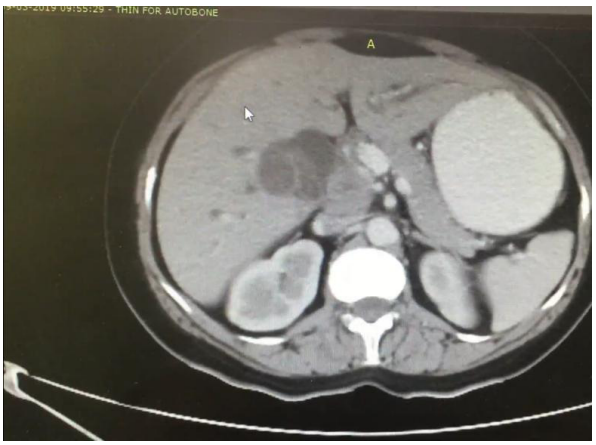
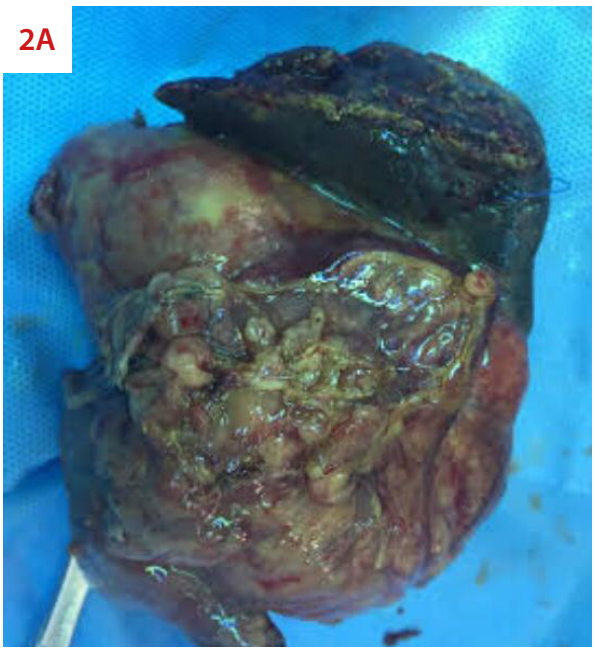


Fig. 1. CECT showing an enhancing large mass lesion in gall bladder

Grossly the specimen was submitted in two segments one labelled as radical cholecystectomy with liver wedge, distal stomach and proximal duodenum (fig.2A.) and second labelled pancreaticoduodenectomy specimen (fig.3A.). On cut opening the specimen it was observed that the entire gall bladder was tumorous with a large highly friable grey white infiltrative tumour creamy in consistency showing large areas of necrosis and haemorrhage. Grossly the tumor was seen invading the liver, pancreas and the adjacent duodenum, however the stomach attached appeared free of tumour (fig.2B,3B.). Multiple lymph nodes were dissected out from the specimen.

Microscopic examination showed mostly ulcerated gall bladder mucosa lined by columnar epithelium with an abrupt transition to an invasive tumor composed of masses and sheets of dysplastic squamous epithelium embedded in large pools of keratin (fig. 4.).

The tumour cells show moderate to marked nuclear pleomorphism with enlarged hyperchromatic nuclei, coarse chromatin, prominent nucleoli and moderate to abundant amount of eosinophilic cytoplasm. Extensive keratinization with presence of numerous prominent keratin pearls, dyskeratotic cells as well as intercellular bridges which are characteristic of squamous differentiation were quite evident in the sections. Dense fibrocollagenous stroma surrounding the tumour showed



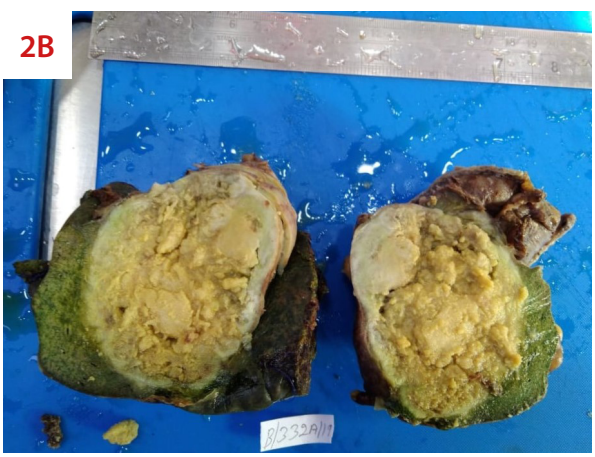
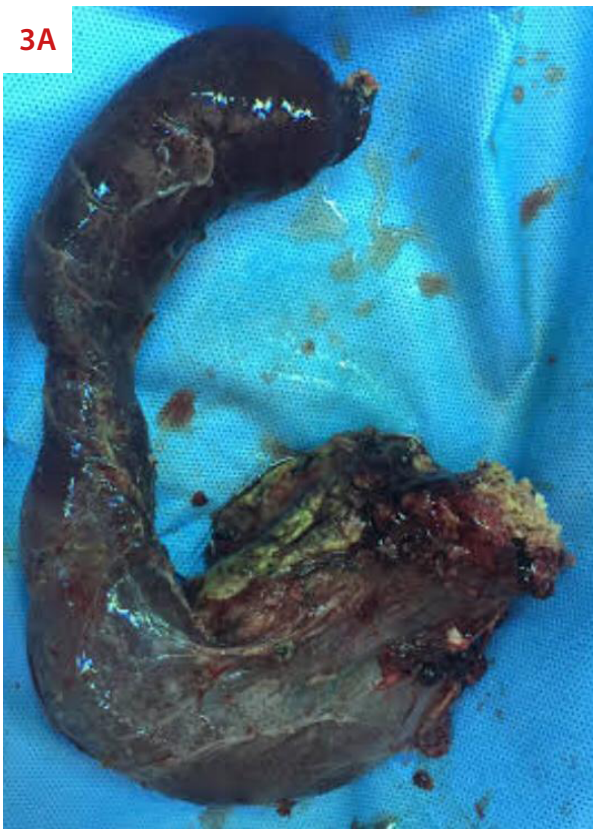


Fig. 2A. Gross specimen of gall bladder with liver wedge, **2B.** Cut surface of the specimen showing large grey white tumour infiltrating into the adjacent liver

marked desmoplastic reaction with lymphoplasmacytic infiltration, few neutrophils, eosinophils, many lymphoid aggregates and foreign body giant cell reaction. Atypical Mitotic figures seen with areas of necrosis. Foci of lymphovascular and perineural invasion identified. No invasive glandular element was identified in spite of multiple sectioning. The tumour was seen invading the liver, pancreas and duodenum, however the stomach was free of tumour. The liver vessels were free of tumour infiltration in the sections examined. The sections from all the surgical resection margins including the cystic duct were free of tumour. Out of total 11 lymph nodes identified 05 showed metastatic tumour deposits (fig. 5A, 5B, 5C, 5D, 5E, 5F.).

Final report was dispatched as Squamous cell carcinoma, G2: Moderately differentiated (TNM stage: PT-4N2M0). Postoperatively the patient developed sepsis and succumbed to death.



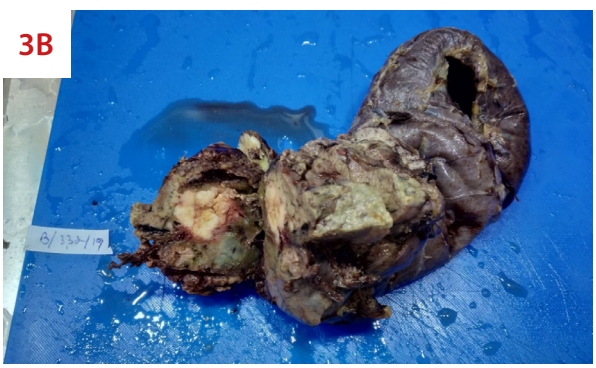


Fig. 3A. Pancreaticoduodenectomy specimen, **3B.** Cut surface of the specimen showing a grey white tumour infiltrating pancreas and duodenum

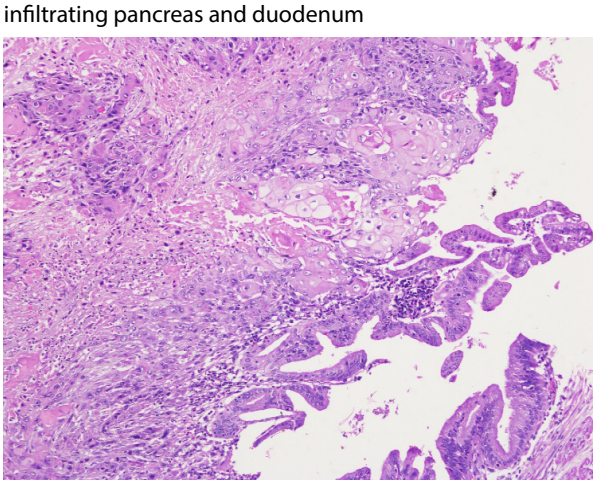


Fig. 4. Gall bladder columnar lining epithelium with an abrupt transition to invasive squamous cell carcinoma (H&E stain, 10x)

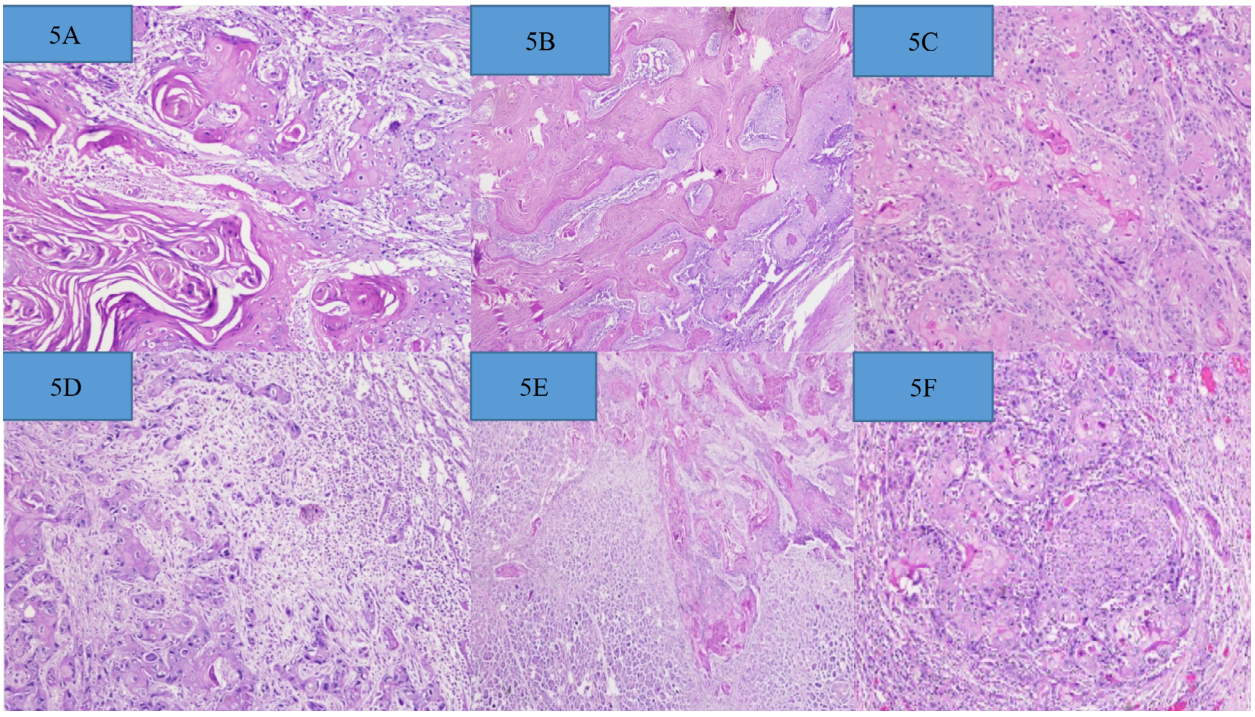


Fig. 5. Histopathological findings: **5A-5B.** Sheets of dysplastic squamous epithelium with large pools of extra cellular keratin. Many prominent keratin pearls noted (40x), **5C.** The tumour cells showing moderate to marked nuclear pleomorphism with enlarged hyperchromatic nuclei, coarse chromatin, prominent nucleoli and moderate to abundant amount of eosinophilic cytoplasm (40x), **5D.** The tumour invades into the liver parenchyma (10x), **5E.** The tumour invades into the adjacent pancreatic parenchyma (10×), **5F.** Foci of perineural invasion identified (40×) (H&E stain).

Discussion

Primary pure squamous cell carcinomas of the gall bladder are rarely reported thus leading to sparse meaningful and sometimes underestimated diverse literature. Rapid growth, wide infiltration, dissemination and metastasis are the characteristics of primary pure squamous cell carcinoma of the gall bladder.

Due to the paucity of studies in the literature the knowledge on etiology, pathogenesis, clinicopathological characteristics as well as prognosis of this rare entity remains scarce. The gall bladder originates from foregut and hence most of the gall bladder carcinomas are heterogeneous during neoplastic transformation making pure SCC of gall bladder a rare entity. The etiopathogenesis of SCC of gall bladder is still not very well defined or understood, though several theories have been proposed. The source of origin is the obvious question as there is no squamous epithelium in a normal gall bladder. The origin of squamous cell carcinoma of gall bladder is theorized either from a squamous metaplasia of an existing adenocarcinoma or from a metaplasia – dysplasia-carcinoma sequence. One of the theory states that the squamous cell carcinoma arises from the pre-existing squamous metaplasia of the gall bladder. While another and more plausible theory suggests that it originates from the squamous differentiation of the neoplastic cells of adenocarcinoma via expression of mixed phenotypes within a single tumour.[9,10] Apart from the metaplasia-dysplasia – carcinoma sequence other presumptive causative possibilities suggested are chronic cholecystitis, cholelithiasis and parasitic infestation.[6,11] There are genetic changes also that have been identified along with mutations that consist of decreased expression of 23nm and overexpression of c-erb B2 gene product.[12] Dong et al deduced that CD109 may promote the proliferation of Gall bladder squamous cell carcinoma) GBSCC by suppressing the TGF-β signal component.[13] Another recent study has reported the mutation of ERBB and PTEN in GBSCC.[14]

Squamous cell carcinoma often appears necrotic grossly. They also tend to have significant amount of inflammation which may lead to misdiagnosis of cholecystitis at the time of clinical presentation. The gall bladder tumors can be identified by radiological imaging and abdominal ultrasound followed by CT scan is the initial diagnostic procedure of choice for biliary diseases but since the tumor lacks specific diagnostic test the confirmed diagnosis is always made by histopathological as well as immunohistochemical tests. Gall bladder tumors can be considered in elderly patients with radiological evidence of diffuse gall bladder wall thickening and intraluminal masses.[9] The definite diagnosis of gall bladder carcinoma is confirmed only by histological examination of the resected mass.[15] The char-

acteristic feature of pure squamous cell carcinoma is prominent keratinization in the form of keratin pearls without any evidence of malignant invasive glandular differentiation. Squamous differentiation can be represented in various patterns ranging from prominent keratinization to poorly differentiated with a pavement pattern, abundant eosinophilic cytoplasm, individual cell keratinization or intercellular junctions as the only evidence.[6]

Conclusion

For proper understanding of the behavior and thereby deciding the mode of treatment of both the common as well as unusual types of gall bladder carcinomas thorough knowledge of the various types of the gall bladder cancer and their precursors is needed. Most of the patients present with nonspecific findings like abdominal pain, discomfort and weight loss. The characteristics of GBSCC are rapid growth, metastasis, with wide infiltration and dissemination. Only few literary descriptions and studies majority of which are case reports regarding the clinical and biological behavior are available because of the rarity of this entity. The diagnosis and management of this rare entity is quite challenging and the management guidelines are also not very clearly well defined. Incriminated to be a worst malignancy advanced radical surgery is the treatment of choice of squamous cell carcinoma of the gall bladder in which the resection of the involved organs is done where the lesion tends to remain localized without any metastasis or peritoneal deposits. However, radical surgical resection with no remaining lesion can be potentially curative if identified early offering a better prognosis as well as survival as the extent of the tumor at the time of diagnosis is the most important parameter in determining the survival. Multimodal therapy with surgical resection, chemotherapy and radiotherapy has shown to increase survival in some studies. However, till date there are no consensus and randomized trial data to evaluate as well to assess the benefit of adjuvant therapy. Due to the low incidence of the disease and no universally accepted treatment protocol, further studies are needed to emphasize the treatment. The better understanding of the tumor biology of the various types of gall bladder cancers including both common as well as unusual type and their precursors can certainly aid in understanding the behavior will definitely help in treatment as well as the development of effective targeted therapies which will certainly help in increasing the lifespan of these patients.

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