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| **TITLE** | **ADENOSQUAMOUS CARCINOMA OF THE GALLBLADDER WITH OSTEOBLAST FORMATION AND INVOLVEMENT OF THE BILE DUCT** |
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| **KEYWORDS** | Keywords: Adenosquamous carcinoma, gallbladder. |
| **DIAGNOSIS** | Gallbladder carcinoma with osteoblast formation |
| **SUMMARY** | We describe an adenosquamous carcinoma of the gallbladder in a 40 year old male presenting with obstructive jaundice secondary to a bile duct stricture. The bile duct adjacent to the gallbladder was involved solely with adenocarcinoma and this was confirmed with immunohistochemistry using antibodies to ca 19.9. ca 125 and CEA. We postulate that only the adenocarcinoma component of the primary tumour invaded the epithelium of the adjacent bile duct. This led to the progression and involvement of the adjacent bile duct epithelium by the adenocarcinoma component only.<br><br>INTRODUCTION<br><br>Although carcinomas arising in the gallbladder are the fifth most common gastrointestinal malignancies, the majority of these tumours are adenocarcinomas. Unusual malignant epithelial tumours of the gallbladder include: signet ring cell carcinoma, cribriform adenocarcinoma, clear cell and small cell carcinomas [1]. Primary adenosquamous carcinoma of the gallbladder is an extremely uncommon neoplasm and accounts for one to two percent of all malignancies of the gallbladder [5,7]. There are several reports of adenosquamous carcinoma of the gallbladder [7]. The MRI findings of adenosquamous carcinoma has been described [9]. The morphological and immuno-histochemical findings have also been reported [8]. Adenosquamous carcinoma of the gallbladder with spindle cell features has been described by Suster et al [8].<br><br>In this report we describe a case of adenosquamous carcinoma of the gallbladder with involvement of the adjacent bile duct by the adenocarcinoma component of the tumour and the formation of osteoblast with osteoid in the wall of the gallbladder. The immunochemical pattern of this neoplasm in the wall of the gallbladder and in the cystic bile duct, is described. |
| **CASE REPORT** | A 40 year old male presented with symptoms of obstruction of the bile duct. The ERCP revealed stricture of the higher bile duct and the biliary brushing cytology revealed adenocarcinoma cells. Radiological investigation suggested the diagnosis of malignant stricture. Preoperative assessment was carried out and surgical resection was feasible. |
| **PATHOLOGY** | The surgical specimen consisted of a gallbladder and main hepatic duct with the upper portion of the common bile duct. The gallbladder measured 9.5 cms. in length, was dilated and measured 8 cms. across (Fig. 1). The wall of the gallbladder showed irregular thickening with two tumour areas measuring 1.5 cms. and 1.0 cms. There was another tumour area in the posterior wall measuring 2 cms. in maximum diameter. An irregular area of the neck of the gallbladder represented possible tumour involvement. The entire mucosal surface was irregular and thickened. There was no evidence of stones.<br><br>The bile duct measured of 5.5 cms. with tumour involving the full length of the specimen (Fig.2). The wall of the bile duct was thickened measuring up to 0.5 cms. in thickness and the lumen was stenosed measuring up to 0.1 cm. in diameter. The tumour appeared to involve both proximal and distal margins of excision macroscopically.<br><br>Immunohistochemistry:<br><br>Sections for immunohistochemistry were prepared at 4 µm and were stained with cytokeratin (CK)7, CK8, CK18, CK19, CA 125, CA 19.9, CEA, Cam 5.2, CD15, MIBI and P53. The sections were deparaffinised in xylene and hydrated in graded alcohol, through to distilled water. Heat medicated epitope retrieval was performed in the sections to be stained for 23 minutes in a microwave oven at 560w. Immunostaining was performed on a Tech Mate 500 plus automated stainer (Dako) using a labelled Streptavidin Biotin (LSAB) technique with Chem Mate reagents. These included a serum buffer to block the non-specific binding of |

reagents to tissue components, a biotinylated multi-lenk secondary antibody, hydrogen peroxidase to block endogenous peroxidase, streptavidin peroxidase to combine with the biotinylated secondary antibody and 3,3* – diaminobenzidine tetrahydrochloride 5% (DAB) to vidualise the sites of peroxidase reactivity.

The slides were counterstained with haematoxylin and mounted in DPX mounting medium. Negative controls were included by substituting the primary antibody for antibody diluent.

Microscopy

Tissues from the free wall of the body of the gallbladder showed areas of keratinising squamous cell carcinoma and areas of a poorly differentiated adenocarcinoma (Fig 3.). In a few areas the two components were mixed but in many areas there was complete separation of these two components with partial to full thickness involvement of the wall. Sections from the neck of the gallbladder revealed areas of adenosquamous carcinoma. There was also a small area of spindle cell growth with osteoblast and osteoid formation (Fig. 4) involving the margin of excision and the attached wall (the liver bed of the gallbladder). Sections from the remaining gallbladder wall revealed areas of squamous carcinoma in situ and high grade dysplasia of the grandular epithelium. Sections taken from the bile duct revealed adenocarcinoma involving the full thickness of the wall and the surrounding soft tissue. There was extensive perineural and vascular invasion. Both proximal and distal margins of the section were involved by adenocarcinoma.

Immunochemistry

The adenocarcinoma component of this tumour stained positively with the following markers CEA, CAM 5.2, CA 125, CA 19.9 and Alpha 1 antitripsin. Both components of squamous and adenocarcinoma were positive for CA 19.9, CA 125, CK7, CK18 and CK19 (Fig. 5). Tumour cells stained negatively by CD56, CK20, CD 15 and alpha feto protein. Both components of the tumour showed high MIB1 (Fig 6.) and P53 indices. The morphological and immunochemical findings were those of primary adenosquamous carcinoma with focal osteoid formation and involvement of the bile duct by the adenocarcinoma component. The epithelium of the gallbladder showed carcinoma in situ of squamous type and high grade glandular neoplasia.

## DISCUSSION

Some authors have reported cancers of the gallbladder invading the bile duct and bile duct carcinoma invading the gallbladder [2]. In this case report the primary tumour arose in the gallbladder with evidence of dysplasia and carcinoma in situ. This has been reported by other authors [3]. There was an area showing osteoid transformation. Osteoblast and osteoid formation and osteoclast like giant cells have been described in tumour arising in the gallbladder [4,5].

The higher positive rate of immunostaining for proliferative markers and p53 and MIB1 of the adenocarcinoma component of this tumour in comparison with the squamous carcinoma component indicates that the adenocarcinoma component had a greater proliferative activity and this probably led to the dissemination of the adenocarcinoma component into the adjacent bile duct system.

The histogenesis of adenosquamous carcinoma has been postulated by Neishi Hara et al [6]. These authors suggested that the squamous carcinoma component of the adenosquamous carcinoma of the gallbladder arises by a step wise molecular progression of a pre-existing adenocarcinoma.

Watacombe et al [10] suggested that there are three distinct pathways in gallbladder carcinogenesis that is: demonocarcinoma develop from a predominant P53, demonocarcinoma with anomalous union from K-ras mutation and P53 mutation and carcinoma in adenoma from K-ras, P53 and probably APC gene-related. The finding of squamous carcinoma in situ and severe glandular dysplasia in our case suggests that malignant transformation occurred from these premalignant lesions to invasive carcinoma.

The histogenesis of osteoid formation is not known, but some authors have reported factors implicated in the formation of osteoblast and osteoclast including parathyroid hormone and prostaglandin E2.

The prognosis of adenosquamous carcinoma of the gallbladder has been reported by Neshihara et al [5]. These authors suggest that the prognosis of adenosquamous carcinoma of the gallbladder is worse than pure adenocarcinoma. The median survival for adenosquamous carcinoma is 10 months in comparison to 99 months for well differentiated adenocarcinoma for TNM 2-4 stages.

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| **LEGENDS** | Figure 1: A macroscopic appearance of the dilated gallbladder with two areas arrowhead showing diffuse tumour formation.<br><br>Figure 2: Hepatic bile duct and part of common duct of the gallbladder infiltrated by carcinoma.<br><br>Figure 3: Haemotoxylin and Eosin (H & E) stained section for the adenosquamous carcinoma showing the two components of the tumour.<br><br>Figure 4: Areas of osteoblast and osteoid formation (H & E).<br><br>Figure 5: Immunohistochemistry staining for cytokeratin 7.<br><br>Figure 6: Immunohistochemistry staining for MIB1. |


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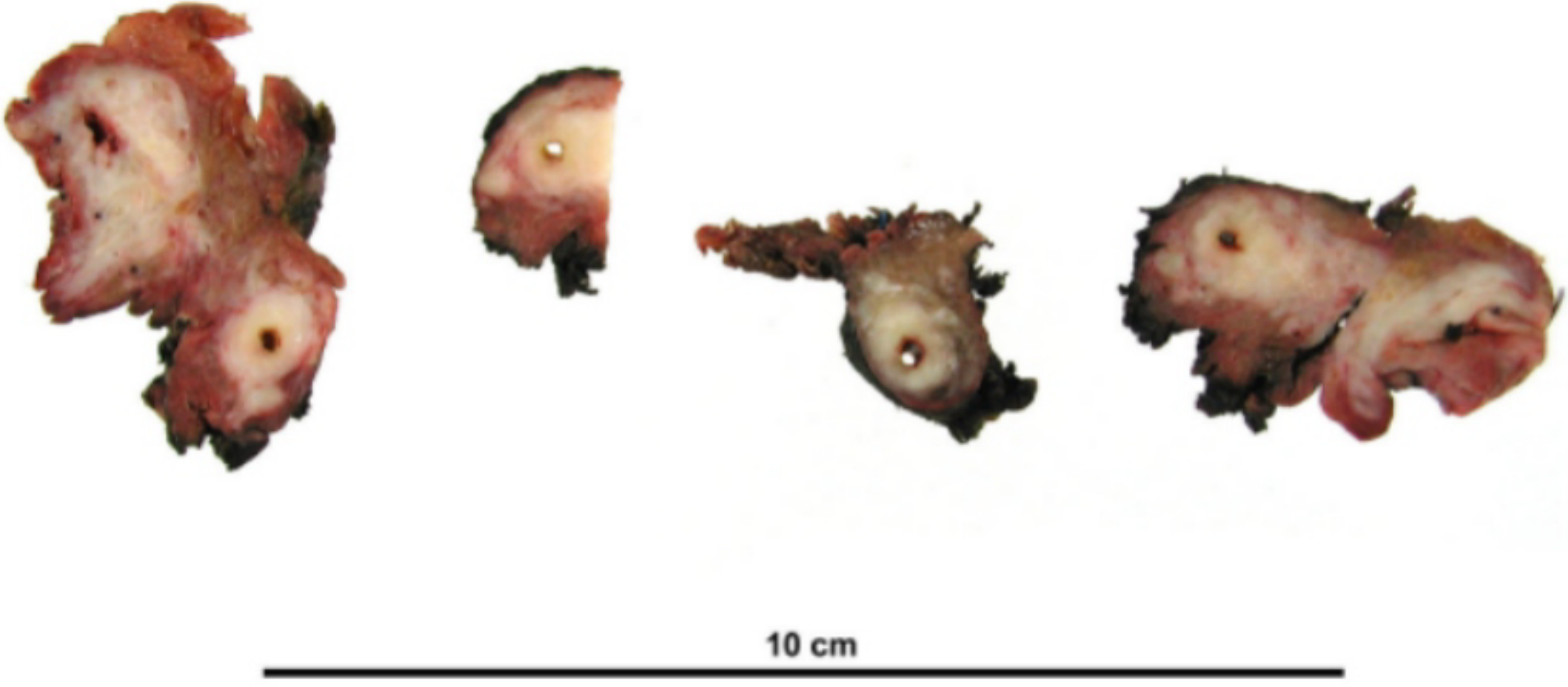
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