



## Sarcomatoid Cholangiocarcinoma with Osteoclast-Like Giant Cells Developing within a Normal Liver: Report of a Case and Review of Literature

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### Abstract

**Background:** Sarcomatoid transformation of primary liver tumors is rare, more so that of sarcomatoid or spindle cell Intrahepatic Cholangiocarcinoma (ICCA) with an Osteoclast-like (OCL) giant cell component. We describe a new case developed in the context of normal background liver.

**Case Report:** A 53-year-old Caucasian male, with no previous liver pathology, presented with non-specific symptoms including vague abdominal pain, general malaise and abnormal Liver Function Tests (LFTs) with mixed cholestatic and hepatitis profile. Cross-sectional imaging demonstrated a large right side liver tumour and completion of staging did not reveal distant metastases. The tumour was technically resectable and the patient underwent a right hepatectomy with curative intent. Histology showed a cholangiocarcinoma with extensive sarcomatous changes and osteoclast-like type giant cells. Two months post-surgery, the patient developed hepatic recurrence and disseminated disease.

**Conclusion:** Sarcomatoid Cholangiocarcinoma (S-ICCA) has an extremely poor prognosis. Whilst tumor may be resectable at the time of presentation, the disease recurs or metastasizes soon afterwards, fact that suggests that alternate management strategies should be employed to improve prognosis.

**Keywords:** Cholangiosarcoma; Osteoclast-like giant cells; Sarcomatous transformation of sarcomatoid/spindle cell cholangiocarcinoma; Intrahepatic cholangiocarcinoma

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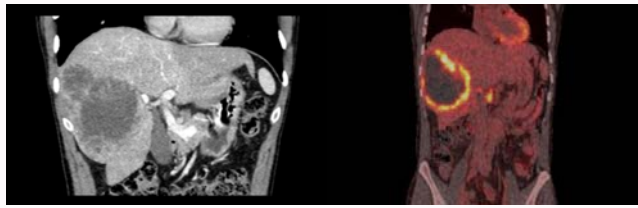
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### Introduction

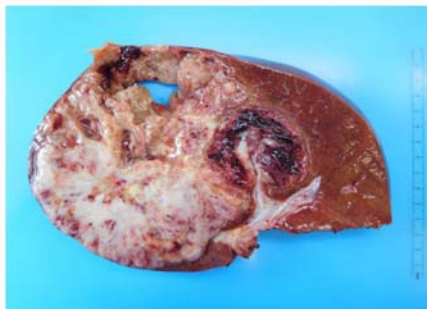
Cholangiocarcinoma (CCA) accounts for about 10% to 15% of all primary liver malignancies with a rising incidence [1,2]. One third of patients present with locally advanced, unresectable or metastatic disease [3,4]. ICCA sarcomatoid subtype is a rare histological subtype, occurring in approximately 4.5% of cases [5].

### Case Presentation

A 53 year old Caucasian male presented with a four-week history of vague abdominal pain, weight loss and general malaise. He was a non-smoker and consumed 6-8 units of alcohol a week. His background liver was normal. His identical twin brother had been treated for prostate cancer. Liver enzymes were abnormal at presentation; Gamma-Glutamyl Transferase (GGT) 350 IU/L, Alkaline Phosphatase (ALP) 300 IU/L, Aspartate Aminotransferase (AST) 76 IU/L and bilirubin was normal. Alfa fetoprotein and CEA were within normal limits at 3 ug/L and <2 ug/L respectively. Ca199 (carbohydrate antigen) was 4000 ug/L and Ca 125 was 92 U/ml. Computed Tomography (CT) demonstrated a large heterogeneous hypodense mass measuring approximately 15 cm in the right lobe of the liver with areas of extensive necrosis. Peripheral arterial enhancement was present but radiological features were not specific. As the lesion appeared resectable, further imaging in the form of a MRI (Magnetic Resonance Imaging) was not felt to be of aid. A biopsy was performed obtaining scant tumoral tissue with findings indicating a differential diagnosis between an undifferentiated primary liver carcinoma and a pleomorphic sarcoma. Obvious epithelial component was not identified but rare cells showed MUC1 expression favoring the diagnosis of a potential cholangiocarcinoma. Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) showed regional lymphadenopathy but no distant spread. At the time of laparotomy,



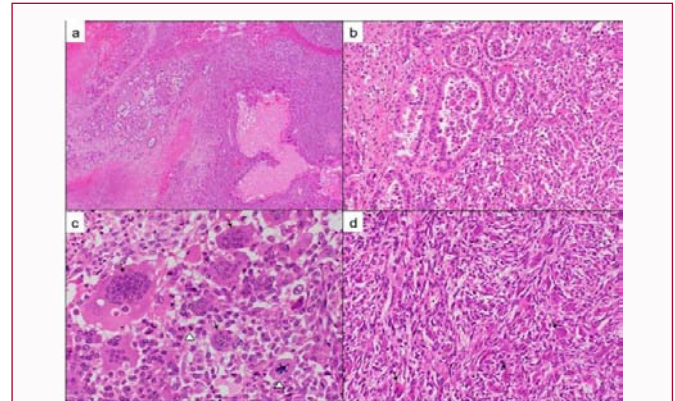
**Figure 1:** A) Preoperative CT scan B) PET scan.



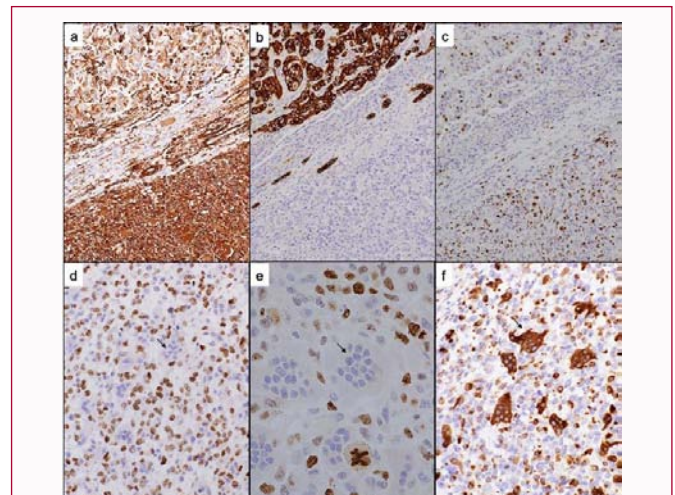
**Figure 2:** Tumour macroscopy. The right hepatectomy weight was 2668 grams. A representative section of the tumour, perpendicular to the transaction margin, shows a large tumour mass (170 mm in greatest dimension), with heterogeneous appearance. Whitish firm areas alternate with pseudocystic areas of necrosis and hemorrhagic areas. The liver capsule was intact and the resection was complete.

he was noted to have hilar and loco regional lymphadenopathy. He underwent a modified extended right hepatectomy with hilar and peripancreatic lymphadenectomy. Post-operatively, his only complication was a non-compromising pulmonary embolus on day seven and he was discharged home fifteen days after surgery on treatment dose of low molecular weight heparin. Macroscopic examination showed a 17 cm (seventeen centimeters) tumour, well demarcated with firm white areas and extensive friable and necrotic as well as hemorrhagic areas. The liver capsule and transaction margins were uninvolved (Figure 1). Sampling of the different areas of the tumor showed heterogeneous histological findings, with areas of adenocarcinoma with focal mucin production, consistent with mass-forming Intrahepatic Cholangiocarcinoma (ICC) intermixed with predominant sarcomatoid areas. Sarcomatoid areas were composed of polygonal anaplastic cells, few of them multinucleated, and spindle cells arranged in a vague storiform pattern. The most striking feature was the presence of abundant osteoclast-like giant-cell component at the sarcomatoid areas. Focal high-grade dysplasia and immature squamous metaplasia was present in large bile duct. Extensive microvascular invasion was present involving peritumoral sublobular hepatic veins. Lymphovascular invasion at portal areas and perineural invasion were also present.

Immunoprofile confirmed the epithelial nature of the malignancy. Clear cut adenocarcinoma areas showed diffuse strong expression for cytokeratins AE1/AE3, CK8/18, CK7, CK19 and EMA. CA19.9 was focally positive. The atypical cells at the sarcomatoid areas showed diffuse strong Vimentin expression and very rare positivity for CK8/18. Other epithelial and mesenchymal markers (desmin and smooth muscle act in for muscular differentiation, S100 for nerve derived tumors, CD31 and CD34 for endothelia, CD68 for histiocytic differentiation and cKIT) were negative. OCL like cells expressed CD68 and common leukocyte antigen, in keeping with macrophagic origin. Ki67 proliferative index was high at the sarcomatoid areas,



**Figure 3:** Representative microscopy of the tumour. Areas of conventional cholangiocarcinoma with glandular structures (left area) and solid fusocellular component (right area) of figures a and b. Osteoclastic-like giant cells (arrows) intermixed with polygonal atypical cells, some of them with mitotic figures (white arrowheads). c. Areas of fusiform cell component in a storiform pattern with some osteoclastic-like giant cells (arrows). d. Hematoxylin-eosin.



**Figure 4:** Immunostaining. The superior panel (a,b,c) shows the transition zone between adenocarcinoma (upper left area) and sarcomatoid component (lower right corner). Vimentin is diffusely expressed at the sarcomatoid component; a. Cytokeratin 7 is restricted at the glandular component; b. Ki67 proliferative activity. The inferior panel (d,e,f) shows absence of p53 expression; d. and absence of Ki67 proliferative activity; e. of the osteoclastic-like giant cells (arrows). These cells are positive for CD68.

intermediate at the glandular areas and negative at the OCL cells. Strong diffuse p53 expression present at the sarcomatoid component.

Two months following surgery, prior to commencement of chemotherapy, a FDG-PET scan revealed advanced disease with disseminated metastases involving lung, liver, peritoneum and bones. He was commenced on Cisplatin and Gemcitabine chemotherapy and underwent five sessions of radiotherapy targeting vertebral metastatic disease. However, his overall condition deteriorated with skin deposits along the surgical incision. Chemotherapy was discontinued and he succumbed two months later. His identical twin brother underwent a computed tomography which did not reveal any abdominal pathology and has normal liver function tests.

## Discussion

Only 36 cases of sarcomatous ICCA have been described in English literature to date [6,7]. The case reported here is the fifth one described on Caucasian patient [8]. While a slight male predominance

has been reported [7,8] there are not known risk factors and patients often present with non-specific symptoms such as abdominal discomfort and general malaise. These tumors are also commonly found incidentally on imaging. Liver biochemistry profile and tumour markers can be corroborative but nonspecific. Radiological features are not typical for common primary liver malignancies (adenocarcinoma) such as HCC or CCA. The majority appears poorly enhancing hypovascular tumors with a thin rim or as non-enhancing tumors [9]. These appearances are attributed to extensive tumour necrosis contributing to overall loss of classical radiological features of hepatic malignancies [9]. Median survival of patients with sarcomatous ICCA who do not have surgery is reported to be four months; and eleven months for patients who undergo resection [10]. However, surgical resection followed by adjuvant chemotherapy seemed to have improved survival on a single patient with peritoneal disease at the time of commencement of chemotherapy [11]. The patient was alive 29 months following presentation and reported being well at the time of report of the case [11]. The osteoclast-like type giant cells component is an uncommon finding in primary liver tumors (hepatocellular carcinoma or cholangiocarcinoma). To our knowledge only fifteen cases have been described in literature to date [7,11-25]. Eleven of those were sarcomatous HCCs which developed on background of established liver cirrhosis, or liver disease with a cofactor such as viral hepatitis or excess alcohol consumption [12-22]. Two further cases [23,25] occurred in patients with a background of recurrent hepatolithiasis and no information is available for the background liver pathology in two more cases [11,24]. Our case is the fourth one described in English literature of a sarcomatous transformation of cholangiocarcinoma with osteoclast-like type giant cells and the first one of this specific type of tumour developing within a normal background liver parenchyma.

In the context of primary liver tumors the most commonly described presence of osteoclast-like giant cells is within sarcomatous HCCs [12-26]. Multinucleated malignant cells may be present in carcinomas, in particular in poorly differentiated and undifferentiated carcinomas, but these cells differ from OCL cells in terms of morphology and immunoprofile. OCL contain a higher number of nuclei which in contrast with the malignant cells are bland and non-proliferative as demonstrated with negative Ki67 expression. These cells show histiocytic lineage likely indicating a peculiar reaction of the stroma. Established liver disease is known to be a risk factor for primary liver tumors such as HCC and ICCA but also may play a role in the developing of sarcomatous transformation in primary hepatocellular malignancies. Of note, in the case reported here, this histopathologically rare tumour variant arose within a normal liver background without co-existing factors for liver disease. These tumors are usually resectable at presentation, favoring surgery as the most common initial approach. However, recurrence and dissemination can occur within weeks. Adjuvant chemotherapy has contributed in one case in which 2 year survival was achieved implying that histological characteristics of the tumour may play a role in disease course [11]. However, in our case, such an approach was not successful as the tumour was proved to be very aggressive with early postoperative recurrence and distant spread. The role of chemotherapy does not appear to be clear in the management of these tumors. Overall the benefit of adjuvant chemotherapy aiming to control the disease is not well established in these patients. Understanding the genetic background of ICCA might help with future development of gene targeted treatments [27,28]. In our case

the identical twin brother did not develop the disease indicative more of a mutational process on the pathogenesis of the tumour rather than genetic predisposition. To our knowledge, this is the first case of sarcomatoid cholangiocarcinoma with osteoclast-like giant cells developing in background of normal liver.

## Conclusion

Sarcomatoid cholangiocarcinoma is very rare entity amongst primary liver cancers. Osteoclastic like cell component among these tumors is even more rare. Its role on the biological behavior of the tumor is uncertain. Pathogenesis of these tumors is poorly understood and its rarity has precluded the development of oncological treatment. Surgical resection is common practice, however, alternative approaches combining adjuvant and/or neoadjuvant chemotherapy and may improve the overall survival rate of the affected patients. Background liver pathology and risk factors for liver disease seem to play a role as most cases described were in patients with liver cirrhosis. Genetic analysis of such tumors may effectively guide treatment.

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