Adenoma–carcinoma sequence in intrahepatic cholangiocarcinoma

André Costa Pinho a,c,*, Renato Bessa Melo a,c, Manuel Oliveira a, Marinho Almeida a,c, Joanne Lopes b, Luís Graça a, J. Costa-Maia a

a Hepatobiliary-pancreatic Unit, General Surgery Department, Hospital S. João, Alameda Prof. Hernâni Monteiro 4200-319, Portugal
b Department of Pathology, Hospital S. João, Alameda Prof. Hernâni Monteiro 4200-319, Portugal
c Faculty of Medicine, University of Porto, Hospital S. João, Alameda Prof. Hernâni Monteiro 4200-319, Portugal

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ABSTRACT

INTRODUCTION: Cholangiocarcinoma is a rare tumor but recent data report a worldwide increase in incidence and mortality. There are several risk factors associated with cholangiocarcinoma, and chronic inflammation of biliary tree seems to be implied in the cholangiocarcinogenesis, but little is known about this process.

PRESENTATION OF CASE: We present a 56-year-old female with a bile duct adenoma incidentally discovered in the follow up of breast cancer that 18 months later progress to intrahepatic cholangiocarcinoma.

DISCUSSION: This is a rare presentation of intrahepatic cholangiocarcinoma that suggests the classic adenoma–carcinoma sequence in cholangiocarcinogenesis. Furthermore this case gives rise to some questions about the possible common ground on intrahepatic cholangiocarcinoma and breast cancer.

CONCLUSION: Cholangiocarcinogenesis is a complex multi-step mechanism and further investigations are needed to fully understand this process.

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1. Introduction

Cholangiocarcinoma is a rare tumor, originated from epithelial cells of biliary tree, which has become the second commonest primary hepatic tumor after hepatocellular carcinoma. Intrahepatic Cholangiocarcinoma (ICC) accounts for 5–20% of cases and differ in morphology, pathogenesis, risk factors, treatment and prognosis to Extrahepatic Cholangiocarcinoma (ECC).1

Recent epidemiologic studies report a worldwide increase on the incidence and mortality of ICC. In Portugal, from 1984 to 1996, there was an increase in mortality of 10.4% on males and 10.3% on females.2 Clinical presentation is usually late with low (under 20%) rates of surgical resectability.3 The 5-year survival rate is exceedingly rare in unresectable lesions, and remains low in resected tumors even with clear margins.

Established predisposing factors for cholangiocarcinomas mainly concern ECCs and are related to chronic inflammation of the biliary tract. Hepatitis C virus (HCV) infection represents a major risk factor for ICC.2 The mechanisms involved in cholangiocarcinogenesis are complex and highly variable. Neoplastic transformation of the cholangiocytes appears to be driven by chronic inflammation and bile stasis following a multistep process initiated by the release of growth promoting factors and cytokines.4 Malignant transformation of benign lesions such as Von Meyenburg Complexes (VMCs) and bile duct adenomas (BDAs) or adenofibromas have been described, leading to the hypothesis that those might be premalignant lesions.

2. Presentation of case

We present a 56-year-old female submitted to a right mastectomy. Pathology revealed a 10 mm ductal carcinoma in situ with positivity for estrogen and progesterone receptors. Two years later, a 31.8 mm nodule in liver segment V was observed in a scheduled abdominal ultrasound (US) and in a Magnetic Resonance Imaging (MRI) subsequently performed. The patient underwent a nodule biopsy, the pathological exam revealing bile duct adenoma (Fig. 1).

The patient remained asymptomatic, with no evidence of nodule growth or other changes in subsequent abdominal US performed, but 18 months later, MRI revealed a growth of the nodule to 38.3 mm (Fig. 2), with no evidence of extra-hepatic disease in several imagiological studies. Tumor markers remained within the normal range. A decision to resect was taken at our multidisciplinary Oncology clinic based on tumoral growth.

The patient underwent a right hepatectomy. The histological exam revealed an intrahepatic cholangiocarcinoma with an immuno-histochemical profile matching that of the bile duct adenoma diagnosed on the previous biopsy (Fig. 3).
3. Discussion

Cholangiocarcinogenesis is a multi-step process. Chronic inflammation of the biliary epithelium, associated to bile stasis, can lead to cellular genetic damage, activating cholangiocyte turn-over. Furthermore, chronic inflammation creates a local environment enriched in cytokines and growth factors (such as tumor growth factor-beta and interleukin-6) that promote cellular proliferation leading to hyperplasia and dysplasia. These genetic and epigenetic mutations eventually lead to cholangiocyte malignant transformation that results in dysregulation of apoptosis, enhanced proliferation, stromal proliferation and neoangiogenesis.

BDAs are almost always found incidentally as a solitary pericentimetric liver nodule. Pathologic diagnose may represent a challenge especially if the lesion is large or shows extensive atypia. Malignant transformation of benign lesions such as VMCs and BDAs or adenofibromas have been reported leading to the hypothesis that BDAs might be premalignant lesions.

In the case reported we present a rare presentation of ICC in a patient with a BDA incidentally discovered in the follow up of breast cancer, that 18 months later progressed to ICC. This case suggests the classic adenoma–carcinoma sequence, well known in colo-rectal cancer since Perry and Morson studies more than 30 years ago, but seldom documented in biliary carcinogenesis, although BDAs are risk factors for cholangiocarcinoma. We cannot, however, exclude the possibility of the cholangiocarcinoma diagnosis being missed in the previous biopsy. That being the case, we must stress the indolent evolution of a usually aggressive carcinoma.

Although never described, to our knowledge, the association of breast carcinoma and intrahepatic cholangiocarcinoma, we may speculate that there might be a common biological mechanism, namely hormonal. Several studies confirm the existence of estrogen receptors in intrahepatic cholangiocarcinoma and that 17-β estradiol promotes in vitro cellular proliferation of cholangiocarcinoma, which is blocked by tamoxifen. The lack of female preponderance in ICC and the much higher incidence of breast cancer suggest that other mechanisms prevail in cholangiocarcinogenesis.

4. Conclusion

Cholangiocarcinogenesis is a complex multi-step mechanism, and chronic inflammation of the bile tract and bile stasis appears to be the common pathological feature. Further investigations are needed to fully understand this process in order to discover novel tools for an early diagnosis and an efficacious specific therapy.

The case reported describes a patient with an incidentally discovered bile duct adenoma that months later progressed to intrahepatic cholangiocarcinoma. This is a rare presentation of this tumor and suggests the classic adenoma–carcinoma sequence in cholangiocarcinogenesis. Furthermore this case gives rise to some questions regarding hormonal influence in this complex process.
Conflict of interest statement

None.

Funding

None.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors’ contributions

André Costa Pinho was participated in the data collection, data analysis, and writing. Renato Bessa Melo, Manuel Oliveira, Marinho Almeida, Joanne Lopes, Luís Graça, and J. Costa Maia were participated in data analysis and writing.

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