

# **KLATSKIN TUMOR AND ITS CORRELATION WITH BILIARY CALCULATIONS: A CASE REPORT**

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**Abstract:** **Goal:** Understand the diagnostic and therapeutic importance of cholangiocarcinomas, especially the Klatskin tumor, which, although it does not have a high incidence, is associated with a high lethality.

**Case report:** This is a descriptive study about a case treated by medical students. A female patient, 70 years old, diagnosed with Klatskin's tumor and calculi in the biliary tract was evaluated, showing the association between the two entities. Thus, understanding this relationship is effective for proper monitoring of this comorbidity, in order to improve the overall quality of life of affected patients.

**Final considerations:** The experience aimed at understanding Klatskin's tumor as an entity associated with several risk factors and high mortality, exposing these patients to possible conditions of vulnerability, such as malaise, jaundice, acholic stools and ascites. Therefore, early diagnosis is important for the establishment and recognition of possible risk factors and introduction of appropriate therapy. This way, the goal is to propose a good doctor-patient relationship and a detailed and individual look at these patients.

**Keywords:** Klatskin tumor, Cholangiocarcinoma, Choledocholithiasis, Gallstones

## INTRODUCTION

Cholangiocarcinoma (CCA) is a cancer that arises from the degeneration of the epithelium of the biliary tract, from the small intrahepatic bile ducts to the common bile duct (2). This neoplasm grows slowly and tends to spread longitudinally along the biliary tree, with neural, perineural and subepithelial invasion. Lymph node involvement, particularly of the portal and peripancreatic chains, can be observed in up to 46% of cases at the time of diagnosis. In turn, hematogenous dissemination is relatively rare and occurs more frequently in terminal cases (6). Bile

duct neoplasms are associated with a poor prognosis. Mortality is related to the local spread of the tumor and its consequences, such as obstructive jaundice, cholangitis and hepatocellular failure (8). Extrahepatic and perihilar ACC are the most common types, with 6-8% of ACCs being intrahepatic, 50-67% perihilar, and 27-42% distal extrahepatic (3).

It is a rare entity that represents less than 2% of all malignant tumors with an incidence between 1 and 2 new cases per 100,000 inhabitants per year. The average age of presentation is 50 years, with the majority of cases in the Western world diagnosed from the age of 65 years (1).

Some risk factors for cholangiocarcinomas have already been established, such as parasitic infections, primary sclerosing cholangitis, cholelithiasis, fibrocystic liver disease], toxins (rubber and chemical industries), chronic liver disease, Lynch syndrome and biliary papillomatosis (9). Other potential risk factors include inflammatory bowel disease, hepatitis B and C viruses, liver cirrhosis, diabetes mellitus, obesity, alcoholism, smoking, and genetic mutations (4). In addition to these, the possibility of prior cholecystectomy predisposing to the development of cholangiocarcinoma is discussed (5). However, chronic inflammation of the biliary tree or exposure to toxic agents concentrated in bile can lead to increased mitotic activity and damage to the DNA of biliary epithelial cells, with consequent malignant transformation. The DNA damage hypothesis is reinforced by the discovery of a series of mutations in oncogenes and tumor suppressor genes (8).

Based on its location, CCA is classified as intrahepatic, extrahepatic or perihilar (pCCA), also called Klatskin's tumor (TK), or distal (dCCA) (3). Regarding pCCAs, there is still a subdivision according to the Bismuth-Corlette classification into types I, II, III and

IV. Types I and II are limited to the common hepatic duct, while type III tumors involve the right (IIIa) or left (IIIb) hepatic ducts, and finally, type IV involves both hepatic ducts (1). In histology, they are generally adenocarcinomas and present with variable degrees of differentiation and phenotypes (4).

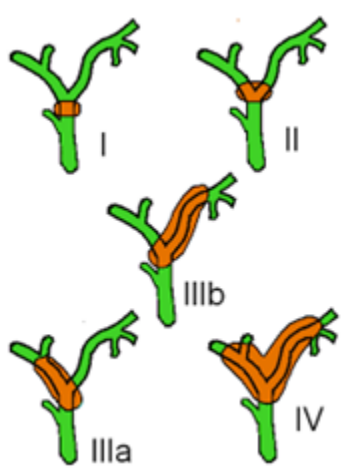


Figure 1 - Bismuth and Corlette classification for tumors of the confluence of the hepatic ducts. Type I – tumor below the confluence with free flow between the left and right channels. Type II – tumor obstructing the confluence, with no upper involvement of the main branches. Type IIIa – tumor obstructing the confluence and the right main branch. Type IIIb – tumor obstructing the confluence and the left main branch. Type IV – involvement of both main and secondary branches.

Serum tumor markers, specifically carcinoembryonic antigen (CEA) and CA19-9, are used for the diagnosis, treatment and monitoring of CCA, as well as tumor staging (5). However, usually the diagnosis of hilar cholangiocarcinoma is radiological. Based on imaging exams (computed tomography, magnetic resonance imaging or ultrasonography), the exact anatomical location of the lesion along the biliary tract can be established, in addition to concomitantly

evaluating the possibility of lymph node extension, vascular invasion or even the presence of metastases to distance (6).

Although most cholangiocarcinomas diagnosed in the West are sporadic, with no identification of the underlying cause, there is a spectrum of causes that have been invoked as predisposing to the development of cholangiocarcinoma, including diseases acquired by the presence of primary sclerosing cholangitis, cholelithiasis, hepatobiliary cyst diseases, diseases bile duct parasites, recurrent cholangitis, viral and toxic hepatitis (8).

The typical clinical picture presents intense and progressive jaundice as the most frequent sign at the time of diagnosis, which may be associated with other less frequent symptoms such as the abdominal pain in the right hypochondrium, weight loss, asthenia and pruritus (7), in addition to acholia, choluria, and slimming. When the lesion is located distally to the cystic junction with the main bile duct, the gallbladder is often enlarged and palpable – Courvoisier’s gallbladder (4).

The pCCA treatments consist of: surgical resection, orthotopic liver transplantation, portal vein embolization and palliatives (3).

## GOAL

Given the above and due to the rare incidence of this pathology in the population, the goal of this study is to report the case of a patient diagnosed with Klatskin’s tumor correlating with the presence of gallstones in the bile duct.

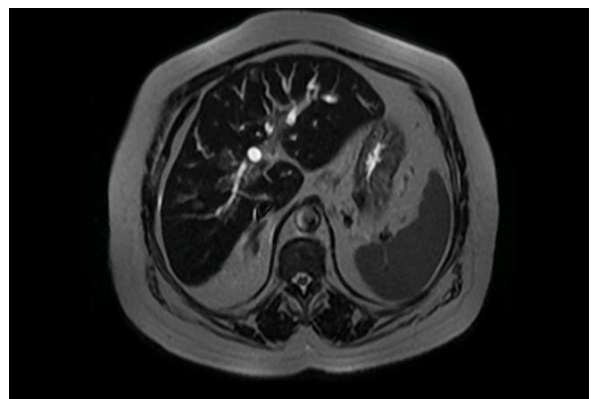
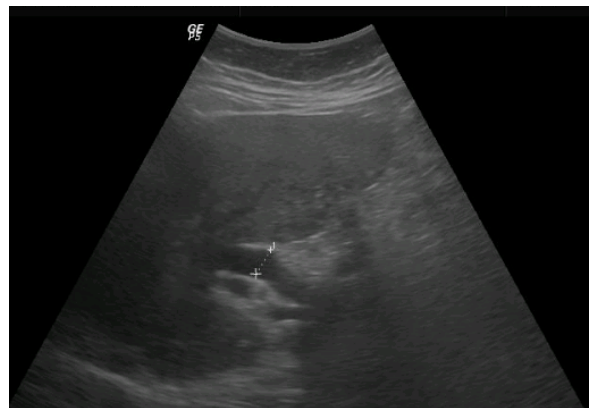
**Descriptors in English:** Klatskin Tumor, Cholangiocarcinoma, Choledocholithiasis, Gallstones

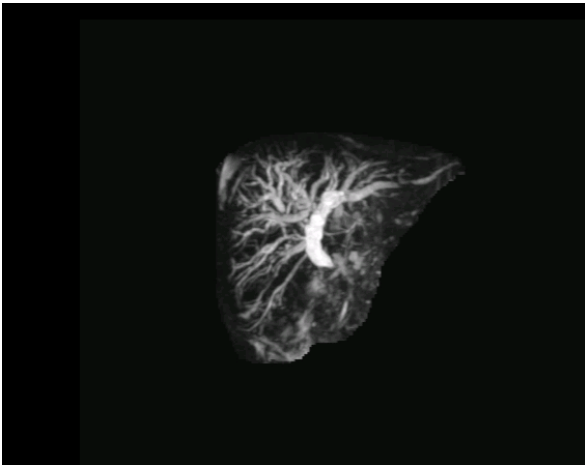
## CASE REPORT

Female patient, 70 years old, brown, married, born and raised in the state of São Paulo, retired, complaining of colic-like pain in the entire upper abdomen for 8 days,

which radiated to the back, associated with nausea and vomiting, ascites, choluria and acholic stools. The patient reported worsening abdominal pain two days ago, when she was referred to the Santa Casa de Misericórdia de Franca. She reported having no previous history of diagnosed cholelithiasis. She denied fever and weight loss. She reported a history of systemic arterial hypertension with irregular treatment, using Furosemide, Clonidine Hydrochloride, Spironolactone and Amlodipine; diabetes mellitus, using Metformin; dyslipidemia, using Bezafibrate and Simvastatin; chronic obstructive pulmonary disease, using formoterol fumarate with budesonide; and she had a history of stroke for 10 years, using AAS. She denied hospitalizations, only cesarean surgeries. Smoker with a smoking history of 40 years/pack. On physical examination at admission, she was in fair general condition, flushed, hydrated, acyanotic, jaundiced 4+/4+, afebrile, eupneic, active, lucid, and oriented in time and space. Cardiovascular system with rhythmic and normophonetic sounds in two stages, without murmurs, heart rate was 108 beats per minute, and blood pressure 140x100 mmHg. Respiratory system with vesicular murmur present bilaterally, without adventitious sounds. The abdomen was globular, flaccid, reduced bowel sounds, tympanic, painful on superficial and deep palpation in the right upper quadrant, with Courvoisier-Terrier and Murphy signs, without other visceromegaly; ends unchanged. In the laboratory tests at admission, the patient presented: Hb=12.8, Ht 38.2, Leukocytes 8,500/mm<sup>3</sup>, Platelets 470,000/mm<sup>3</sup>, Urea 56 mg/dL, Na 136 mEq/L, K 5 mEq/L, BT 24.7 mg/dL, BD 14.8 mg/dL, PT 14.2 sec, INR 1.31 TTPA 28 sec, amylase 70, creatinine 1.5, FA 660, GGT 80, PCR 62, TGO 195, TGP 158, and urine I with 19,600 leukocytes, with positive nitrite and bacteriuria.

In view of this situation, the diagnostic hypothesis of cholestatic syndrome with obstructive jaundice was raised, and among the possibilities, choledocholithiasis and periampullary neoplasia were considered. Abdominal tomography was performed, which showed dilation of intra and extra hepatic bile ducts. The patient was then hospitalized for diagnosis and follow-up of the case, and USG of the entire abdomen was requested, which showed low dilatation of the biliary tract, chronic calculous cholecystitis and chronic liver disease with a nodule of unknown etiology; Abdominal MRI showing suspicious hepatic nodules, dilatation of the biliary tree due to a stenosing lesion in the proximal common bile duct, cystic duct and infundibulum.





An Endoscopic Retrograde Cholangiopancreatography was then requested, which revealed low obstruction of the bile duct suggestive of cholangiocarcinoma, a plastic prosthesis was placed in the bile duct, in addition to brushing for biopsy and drainage of the duct. In addition, tumor markers were also requested, with results of CA19.9 of 527.4, CEA 177 and Alpha Fetoprotein of 5.1. The patient was then referred for outpatient oncological follow-up.

## DISCUSSION

Cholangiocarcinomas are rare gastrointestinal neoplasms that have a low incidence, ranging from 0.01 to 0.8%. (10) Because they are biliary tract carcinomas, they have an embryonic origin that differ from liver cells, which is why they are classified as primary liver tumors and account for between 5 and 30% of liver carcinomas. (11) Klatskin tumors are perihilar cholangiocarcinomas originating from the bifurcation of the main hepatic duct. Most cases are of unknown etiology, however there are some main risk factors: primary sclerosing cholangitis, chronic choledocholithiasis, cirrhosis, sclerosing cholangitis, ulcerative colitis. Cholelithiasis is found in approximately 30% of patients with cholangiocarcinomas, and although this is an expected value in the elderly population, the

most affected by this tumor, there may be a relationship between these diseases that is still not very well established. (10) (12)

Gallstones can be formed by cholesterol, bilirubin, mixed or calcium bilirubinate, which are more prevalent in Asians. In developed countries, 80% of stones are cholesterol and the rest are bilirubin or calcium bilirubinate. Cholesterol stones undergo bile saturation, acceleration of nucleation and gallbladder hypomotility to be formed. Cholesterol needs bile acids and phospholipids to stay in solution as it is insoluble in water. As cholesterol increases, it accumulates in the form of vesicles that together activate the formation of cholesterol crystals, with the saturation of bile by cholesterol being the main factor responsible for the formation of calculi. The initial step for formation is nucleation and what favors this process is mucin, a glycoprotein that is produced in the gallbladder when there is bile supersaturation. The vesicle wall absorbs excess cholesterol causing vesicular hypomotility that allows microcrystals to remain longer inside the vesicle and aggregate to form calculi. Bilirubin stones come from hepatobiliary pathologies, hemolytic anemia or problems with erythropoiesis. (13)

The etiology of the Klatskin tumor is uncertain and in most cases its appearance is sporadic, however there are works that suggest that carcinogens induce the neoplastic differentiation of pluripotent and hepatic cells close to the portal triad, which from pre-neoplastic lesions would give rise to cholangiocarcinomas. There are gene mutations in the neoplastic biliary epithelium that support this theory. There are correlations between inflammation of the biliary tree or exposure of toxic agents in the bile to an increase in mitotic activity and consequent damage to the DNA of the cells of the biliary epithelium, leading to a malignant transformation. Studies indicate that 100% of

the samples of cholangiocarcinoma collected were positive for proliferating cell nuclear antigen (PCNA), in 37-94% abnormal expressions of the p53 suppressor gene were found and in 21-100% abnormal expressions of the protooncogene were identified. K-ras. Furthermore, these last two mutations were also found in the pancreatic juice and bile of patients with cholangiocarcinoma.

Another risk factor for cholangiocarcinoma is primary sclerosing cholangitis, whose inflammatory process leads to the development of fibrosis and stenosis both in intrahepatic and extrahepatic life, in addition to the fact that approximately 40 - 50% of these patients also have ulcerative colitis, polycystic liver disease, parasitic diseases by *Clonorchis sinensis* and *Opisthorchis viverrini*, responsible for generating inflammation and transformation of the epithelium. The symptoms of the Klatskin tumor are quite nonspecific, and can be found in other diseases that occur with obstruction of the biliary tract, namely: pain in the right hypochondrium, acholia, choluria and jaundice, which may not be present initially if there is no complete biliary obstruction. Faced with a classic clinical picture of obstructive jaundice, as presented by the patient, the physician's clinical reasoning must seek the main etiological diagnoses that may be the cause of this cholestatic syndrome, so that the appropriate complementary tests are requested to assist in the diagnostic investigation. Among the main etiologies of this syndrome, we can highlight: Choledocholithiasis, pancreatic head adenocarcinoma, duodenal papilla tumor and cholangiocarcinoma; These etiologies, which were suggested as possible causes of the condition reported in this study. (15)

The dosage of total bilirubin and its fractions, in addition to liver enzymes (oxalacetic transaminase and pyruvic transaminase) and canalicular enzymes (alkaline phosphatase

and gammaglutamyltransferase) are normally the first laboratory tests requested, as occurred in the case of the patient reported, however, because they are nonspecific tests, help little in determining the etiology. The dosage of serum tumor markers, such as carcinoembryonic antigen (CEA), CA50 and CA19-9, direct the diagnostic reasoning towards neoplastic causes, such as cholangiocarcinoma, which leads to elevations in the serum levels of these three markers, however, it is not possible to make a diagnosis, as several other neoplasms alter these markers. (16, 17, 18)

Given the above, it is necessary to complement the investigation with imaging tests, such as ultrasonography, computed tomography and magnetic resonance imaging, which can show the dilation of the intrahepatic bile ducts, which is common in these neoplasms. In addition, such exams allow the realization of the Bismuth-Corlette classification and help in the staging of the lesions, according to the TNM method. (27 and 28)

However, these tests are not always able to determine the exact location and extent of involvement of the biliary tract caused by the growth of these tumors. Thus, it is useful to perform endoscopic retrograde cholangiopancreatography, which, in addition to determining this location and extent, also allows the decompression of the affected pathway and the collection of biological material for pathological analysis, through brushing, which can then confirm the neoplasm. Endoscopic fine needle aspiration biopsy (EE-FNAB) can be associated with the analysis of brushing material obtained by ERCP, increasing the accuracy of the diagnosis. (25 and 26)

Once diagnosed and staged, the best therapeutic plan for the tumor must be selected, with the following available: Surgical resection, which is potentially curative;

Orthotopic liver transplantation, reserved primarily for patients who lack healthy liver tissue, such as those with primary sclerosing cholangitis or advanced cirrhosis; Portal vein embolization in the hepatic lobe affected by the neoplasm, which triggers the proliferation of hepatic cells in the healthy lobe; And palliative approaches, whether surgical, endoscopic, percutaneous or chemotherapy. (22)

## CONCLUSION

Klatskin's tumor is characterized as a rare hilar cholangiocarcinoma, whose clinical picture is the presence of progressive jaundice, abdominal pain predominant in the right hypochondrium and severe weight loss, which may be associated with other symptoms of cholestatic syndrome, such as the fecal choluria and acholia. Given its rarity, however, high lethality, its early recognition for adequate therapeutic management becomes essential. Therefore, in view of such relatively common and benign clinical findings in most patients, in elderly patients and, above all, with complaints of exacerbated weight loss in a short period of time, it is crucial and mandatory to rule out cases of malignancy. make use of abdominal imaging tests and laboratory dosage of tumor markers.

With regard to the etiology of the tumor, this is still uncertain. Despite the presence of gallstones being related and present in most cases, further studies are needed for etiological elucidation. In the case report described in this article, the patient presented with cholestatic syndrome, in which chronic calculous cholecystitis was evidenced on abdominal ultrasound. It is known that this was responsible for causing obstruction in the bile ducts and, this way, promoted the obstructive symptoms of jaundice, choluria and fecal acholia. The hypothesis was also created that this chronic inflammation caused

by gallstones could be a possible risk factor. This proves how essential it is to identify the risk factors associated with the development of cholangiocarcinomas, with the implementation of preventive measures being of fundamental importance when available. Finally, as a result of the high mortality caused by the tumor, the importance of early diagnosis and treatment is reinforced for the natural evolution of the disease, notably with regard to a favorable prognosis. Treatment, when possible, must be curative. However, even if palliative, its main goal is to improve the quality of life of the patient, providing well-being, autonomy, control of symptoms and, if possible, increased life expectancy.

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