

**Title:**

**Intraductal papillary neoplasia of the bile duct with malignancy: A differentiated entity of cholangiocarcinoma with a better prognosis, a review of three new cases**

**Authors:**

Baltasar Pérez Saborido, Martín Bailón Cuadrado, Mario Rodríguez López, Enrique Asensio Díaz, Beatriz Madrigal Rubiales, Asterio Barrera Rebollo

DOI: 10.17235/reed.2017.4835/2016

Link: [PubMed \(Epub ahead of print\)](#)

Please cite this article as:

Pérez Saborido Baltasar, Bailón Cuadrado Martín, Rodríguez López Mario, Asensio Díaz Enrique, Madrigal Rubiales Beatriz, Barrera Rebollo Asterio. Intraductal papillary neoplasia of the bile duct with malignancy: A differentiated entity of cholangiocarcinoma with a better prognosis, a review of three new cases. Rev Esp Enferm Dig 2017. doi: 10.17235/reed.2017.4835/2016.

Enero 2017 • Volumen 109 • Número 1 • Páginas 1-86 CODE: REED3N ISSN: 1137-068

Revista Española de **Enfermedades Digestivas**  
THE SPANISH JOURNAL OF GASTROENTEROLOGY  
Factor de Impacto (2016) JCR: 9.455 (Q4) SCIE: 0.34 (Q2)

Acceso al texto completo en: [www.reed.es](http://www.reed.es) y [www.singed.es](http://www.singed.es)

ORGANO OFICIAL DE:  
SOCIEDAD ESPAÑOLA DE PATOLOGÍA DIGESTIVA, SOCIEDAD ESPAÑOLA DE ENDOSCOPIA DIGESTIVA Y ASOCIACIÓN ESPAÑOLA DE ECOGRAFÍA DIGESTIVA

<b>Editorial</b>	Lesión de Bileftume: diagnóstico por gastroscopia E. Navarro-García, M. N. Barco-Frutos, M. del Pozo y J. C. Domercq Muñoz	65
<b>Trabajos Originales</b>	Notes Clínicas Cáncer color rectal en adultos: ¿case report and review of the literature focusing in the presentation of refractory constipation? W. de Almeida-Noronha, V. L. Ribeiro-Cabral and S. L. Lemos	67
	3 Hemangioendoteliooma gástrico. Una localización infrecuente de tumor vascular I. Alonso-Abad, J. M. García-González, L. Aguirre-Díaz, A. M. Quintana-Rivera y A. Calvo-Rodríguez	69
	40 Hemocidiosis por amebiasis postoperatoria C. Pérez-Carpas, A. Estrella-Sánchez, M. A. Ramos-Capitán, J. Arroyave-Rodríguez y C. García-Díez	70
	Endoscopia virtual de intestino largo: ¿case report? M. Rodríguez-López, E. Asensio-Díaz, M. Rodríguez-López y C. Domercq Muñoz	73
	26 Mucor micosis: un caso de colon ascendente A. Torres-Palmer, M. B. Ramos-Vázquez, J. C. Domercq-Ramos, J. Castro-Laborda and S. L. Carballido	76
	33 Cartas al Editor Neoplasia neuroendocrina intestinal, un tumor poco habitual M. de la Hoz, J. García-Fernández y M. C. Núñez-Rodríguez	79
<b>Revisión</b>	Presentación intestinal de infección por <i>Mycobacterium parvum</i> (M. parvum) en un paciente con inmunodeficiencia adquirida V. Torres-Vega, D. M. Aguirre y J. A. Álvarez	80
<b>Insights en Patología Digestiva</b>	49 Perforación intestinal: ¿síndrome de intestino delgado o perforación de divertículo? Y. Seo, H. Zhu and D. Liu	81
	40 Análisis de los factores de riesgo en el diagnóstico diferencial de abdomen agudo C. Sánchez-Jiménez, L. González-Nieto y J. A. Jódar-Panadero	81
	41 Perforación múltiple de divertículos de intestino delgado en un paciente con síndrome de Ulceras Quíjano E. Hernández-López, A. Borge-García y E. Palencia-Lizaso	83
	42 Aspecto anatómico como manifestación patomorfológica de un adenoma actínico gástrico J. Álvarez-Otero, J. Fernández-Sánchez y J. de la Fuente-Aguado	83
	43 All that glitters is not gold: A different cause for an "ulcerative colitis" A. Pineda, M. Sola, F. Vila-Roca and G. Navarro	85
	44 Revisiones 2016	85

ARAN [www.gruposinra.com](http://www.gruposinra.com)

*This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.*

ACCEPTED

NC 4835 inglés

**Intraductal papillary neoplasia of the bile duct with malignancy: A differentiated entity of cholangiocarcinoma with a better prognosis, a review of three new cases**

Baltasar Pérez-Saborido<sup>1</sup>, Martín Bailón-Cuadrado<sup>1</sup>, Mario Rodríguez-López<sup>1</sup>, Beatriz Madrigal-Rubiales<sup>2</sup> and Asterio Barrera-Rebollo<sup>1</sup>

<sup>1</sup>HBP Surgery Unit. General and Digestive Surgery Department. Hospital Universitario Río Hortega. Valladolid, Spain. <sup>2</sup>Pathology Department. Hospital Universitario Río Hortega. Valladolid, Spain. <sup>3</sup>Endoscopy Department. Hospital Universitario Río Hortega. Valladolid, Spain

**Received:** 12/01/2017

**Accepted:** 3/04/2017

**Correspondence:** Baltasar Pérez Saborido. BPH Surgery Unit. Service of General Surgery and Digestive Diseases. Hospital Universitario del Río Hortega. C/ Dulzaina, 2. 47013 Valladolid, Spain  
e-mail: perezsb@hotmail.com

**SUMMARY**

**Introduction:** Intraductal papillary neoplasms of the bile duct have been recognized as a differentiated entity to other biliary tumors since 2001. They are characterized by intraductal growth, with or without mucus production, and have malignant potential, although they have a better prognosis than other types of cholangiocarcinoma.

**Material and methods:** From January 2010 to August 2015, we included three patients with a confirmed diagnosis of bile duct intraductal papillary neoplasia with malignancy that were treated at our center. Two cases were male and one female with a mean age of 67.3 years.

**Results:** All three patients presented malignancy at the time of diagnosis. One patient was asymptomatic and the diagnosis was reported in the hepatectomy specimen after a liver transplant due to autoimmune hepatitis. The other two patients presented with

cholestasis and acute cholangitis and the diagnosis was made based on imaging tests (computed tomography [CT] and magnetic resonance imaging [MRI]) and endoscopic retrograde cholangiopancreatography (ERCP) with brushing and a biopsy. The treatment in both cases was surgical with a left hepatectomy, and resection of the left bile duct and segment I. They did not receive adjuvant treatment. None of the cases had recurrence of the disease.

**Discussion:** Malignant intraductal papillary neoplasias of the biliary tract represent a different entity of cholangiocarcinoma with a better prognosis. Its diagnosis is based on imaging tests and histology by ERCP. The treatment is surgical, achieving a high rate of success with a low relapse rate.

**Key words:** Intraductal papillary biliary neoplasia. Cholangiocarcinoma.

## INTRODUCTION

Intraductal papillary neoplasms of the bile duct have been recognized as a differentiated entity of other types of biliary tumors since the first description by Chen et al. in 2001 associated with hepatolithiasis (1). This term was finally introduced by the World Health Organization in 2010. They are characterized by an intraductal papillary growth and a better prognosis than the common cholangiocarcinoma (2). Some studies have reported a similar behavior to the intraductal pancreatic mucinous neoplasias although with some differentiated features. Up to 40-80% of cases may present with invasive carcinoma, either tubular carcinoma or mucinous adenocarcinoma, suggesting that it is a disease with a high potential for malignancy (3-7).

It is difficult to obtain a preoperative diagnosis due to its low incidence and the absence of specific symptoms (8). Aggressive surgical treatment is required due to its better prognosis compared to cholangiocarcinoma (9).

We reviewed the literature and present three cases recently treated at our General Surgery Department, all of them with malignancy at the time of diagnosis. Two patients were managed by performing a hepatic resection, and the third one was an incidental finding after a liver transplant.

## **PATIENTS AND METHOD**

We included three patients with a confirmed diagnosis of intraductal biliary neoplasia after histopathological analysis of the specimen that were surgically treated in our General Surgical Department from January 2010 to August 2015. We analyzed their clinical presentation, diagnostic method, treatment and long-term follow-up.

### **Case report 1**

A 64-year-old male presented with pain in the right hypochondrium of a few weeks duration with no other associated symptoms. Blood tests revealed slightly elevated GGT (70 U/l) as well as a CA 19.9 analysis of 170 U/ml. Abdominal ultrasonography showed dilation of the left bile duct but the main bile duct was normal. A MRI-cholangiogram was performed in which a dilation of the left biliary tree with a polypoid lesion at the origin of the left hepatic duct was seen; there were no other findings (Fig. 1C). Before a treatment strategy was defined, an ERCP showed a dilation of the left bile duct due to the existence of a polypoid lesion at the origin of the left hepatic duct. This was biopsied and a plastic prosthesis was inserted. The biopsy confirmed the diagnosis of papillary neoplasia with high grade dysplasia. Surgical treatment was proposed and a cholecystectomy was performed with an anatomical left hepatectomy with resection of segment I and excision of the left biliary tree until it was confluent with the right. The frozen biopsy sample of the bile section border showed no involvement. The postoperative period was uneventful. The final histology confirmed the diagnosis of intraductal papillary neoplasia with a papillary and invasive cholangiocarcinoma focus, without lymphatic extension. Complementary treatment was not performed and after five years of follow-up the patient is free of disease.

### **Case report 2**

We present the case of a 78-year-old man who was admitted to the Emergency Department due to pain in the right hypochondrium as well as fever and cutaneous and mucosa jaundice. Blood tests revealed increased GGT and total bilirubin levels with a CA 19.9 analysis of 1,973 U/ml. As in case 1, ultrasound showed a dilation of the

left bile duct. However, cholangio-MRI showed a large dilation of the left biliary tree and the presence of villous material and mucin (Fig. 1A and B). ERCP demonstrated mucin leakage and villous occupation of the left biliary tree, a biopsy was obtained and a plastic prosthesis was placed (Fig. 2). The histological analysis reported an intraductal papillary neoplasia with high grade dysplasia. The patient also underwent surgical treatment with a left hepatectomy and resection of segment I and the left bile duct, cholecystectomy and lymphadenectomy of the hepatic hilum. There was no involvement of the border of the biliary resection shown by an intraoperative biopsy. The definitive histological study confirmed the diagnosis of cholangiocarcinoma with an isolated and focal microinfiltrant component in the distal branch of the hepatic segment III with the production of mucus (Fig. 3). Adjuvant treatment was not performed and the patient has no disease recurrence after four years of follow-up.

### **Case report 3**

A 60 year old female diagnosed with autoimmune hepatitis with decompensation and portal hypertension was also assessed for liver transplantation. Ultrasound revealed a tortuous dilation of the left bile duct. The CT scan showed the aforementioned dilation of the left bile duct and the presence of a rounded 2 cm image reported as possible hepatocarcinoma. With a diagnosis of end stage liver disease and hepatocarcinoma, she was included in the waiting list for transplantation. After a month, a cadaveric liver transplant was performed using the piggy-back preservation technique. There were no complications during the transplant and postoperative period. Histological analysis of the specimen showed an invasive intraductal papillary cholangiocarcinoma with an extensive papillomatosis of the biliary tract, in addition to a macronodular liver cirrhosis compatible with an autoimmune origin. She did not receive adjuvant therapy but the immunosuppressive treatment was adapted with mTOR inhibitors. The patient has no signs of tumor recurrence at the present time.

### **DISCUSSION**

Intraductal papillary neoplasms of the biliary tract associated with hepatolithiasis were first described in 2001 by Chen et al. (1). They are considered as an entity with a

similar behavior to a pancreatic intraductal mucinous neoplasm (4). Their incidence is not well established. However, Barton et al. reported finding these lesions in 23 out of 223 patients analyzed in their series of hepatectomies performed due to cholangiocarcinoma and other cystic, bile and hepatic lesions (7% of the biliary tumors) (4).

These lesions have a high potential for malignancy; in some series the rate exceeds 80% and this malignization is usually in the form of invasive carcinomas (4,10). In our series, the incidence of malignancy was 100% as all three patients had malignant lesions at the time of diagnosis. Choi et al. differentiate the potential for malignancy according to the location of the lesion as follows: 94% in lesions of the main bile duct, 64.3% in hilar and 79.2% in intrahepatic lesions (11). However, the malignant potential is not associated to the production of mucus. Mucus production is variable. The series by Barton et al. reported a rate of 74% (4) and this study showed a 100% rate. A relationship between MUC1 and MUC5AC and the potential for malignancy has been described. The most frequent histological type is papillary proliferation with mucin production. MUC2 expression is found more frequently in mucin producing lesions and MUC1 expression is found more frequently in non-mucinous lesions. (6)

Despite the high risk of cancer progression, this entity appears to have a better prognosis than classical papillary cholangiocarcinoma. It is difficult to differentiate these two entities and there is still a lot of controversy with regard to this issue. However, the intraductal papillary neoplasias are differentiated from the papillary cholangiocarcinoma based on mucus production, morphology of the papillary cells and at the immunohistochemical level. This has been demonstrated by Fujikura et al. in a series of 52 patients (25 intraductal papillary neoplasms and 27 intraductal cholangiocarcinomas), although it is not clear whether the prognosis depends on these favorable histological findings or the fact that they are usually diagnosed at an earlier stage (2).

The clinical presentation is usually non-specific. Symptoms include right hypochondrium pain and sometimes episodes of jaundice and cholangitis (4). The largest series to date, published by Choi et al., who reviewed 55 cases, reported a cholestasis rate of only 9% (11). However, in our study it was present in two of the

three cases. Lee et al. found that jaundice was more frequent in patients with mucus production in their series of 58 patients (10). An intermediate incidence rate of 38% cholestasis was reported by Barton et al. (4).

Lee et al. reported an increase in CA 19.9 levels in 40% of patients, and especially in those with mucus producing lesions (10). Two patients in our series had elevated levels (CA 19.9 = 1,947 U/ml) and in particular, the patient with a large mucus content. Definitive diagnosis in symptomatic cases is based on imaging tests, defined by the presence of mucus within the biliary tract or by intraluminal lesions on both CT and C-MRI scans (8). This was described in the study by Lee et al., where intraluminal lesions were present in 32 of 55 patients (11). The most common finding on imaging is dilation of the biliary tract with no capability to detect intraductal lesions (10). In a series of 37 patients from the Nagoya University, a biliary mass considered to be malignant was detected in 36 of 37 patients. In addition, a CT scan can identify biliary infiltration. The most frequent findings are hypodense enhancement in the late arterial phase and intense delayed enhancement, which are indicative of proliferation of fibrovascular tissue, although this should be confirmed by ERCP and a histological analysis (4). This was the diagnostic process in the two symptomatic patients of our series. It would be ideal to perform a cholangioscopy, which can provide an accurate map of the papillomatous involvement of the biliary tract and aid in reducing relapses (10).

Aggressive surgical treatment should be considered for intraductal biliary neoplasia due to the good prognosis (9). Hepatectomy is also performed, however, there is no consensus as to whether a complete resection of the extrahepatic bile duct should be performed or not. According to published series, this resection does not provide any benefit in terms of survival or disease-free survival. In our series, none of the patients underwent a resection of the biliary tract as it was not affected and at the time of follow-up there was no recurrence at this location. Choi et al. reported a relapse rate of 23% in cases with main biliary tract involvement and 16% in intrahepatic cases. However, no recurrence occurred in hilar cases (11).

As in our series, adjuvant treatment was not used as patient prognosis is good and long-term survival was achieved. In cases with bilateral involvement or with terminal liver disease that precludes a partial resection, liver transplantation has been shown to

obtain good survival rates, as seen in our third patient. However, we must consider this as an incidental finding as the transplant was not performed due to the biliary intraductal papillary neoplasia discovered in the resected liver specimen. In these cases, resection of the extrahepatic biliary duct does not seem to be justified either as extension beyond the duct bifurcation is rare. It is preferable to perform a common bile duct to duct anastomosis than a hepatic-jejunostomy in order to maintain the bile duct for a subsequent diagnosis of a relapse (12).

Long-term survival is variable; 5-year survival rates of 38% have been described in cases of invasive carcinoma (greater than the 10-20% described in the hilar or intrahepatic cholangiocarcinoma series). Choi et al. reported overall survival rates of 77.6% at three years and 62.5% in cases of invasive carcinoma (11). Lee et al. reported an 81% rate of disease-free survival at five years in surgically treated patients (10). Our patient had a long disease-free survival.

## REFERENCES

1. Chen TC, Nakanuma Y, Zen Y, et al. Intraductal papillary neoplasia of the liver associated with hepatolithiasis. *Hepatol* 2001;34:651-8. DOI: 10.1053/jhep.2001.28199
2. Fujikura K, Fukumoto T, Ajiki T, et al. Comparative clinicopathological study of biliary intraductal papillary neoplasms and papillary cholangiocarcinomas. *Histopathol* 2016;69:950-61. DOI: 10.1111/his.13037
3. Schlitter AM, Born D, Bettstetter M, et al. Intraductal papillary neoplasms of the bile duct: Stepwise progression to carcinoma involves common molecular pathways. *Mod Pathol* 2014;27:73-86. DOI: 10.1038/modpathol.2013.112
4. Barton JG, Barrett D, Maricevich M, et al. Intraductal papillary mucinous neoplasm of the biliary tract: A real disease? *HPB (Oxford)* 2009;11:684-91.
5. Nakanuma Y, Sato Y, Harada K, et al. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. *World J Hepatol* 2010;2:419-27. DOI: 10.4254/wjh.v2.i12.419
6. Ohtsuka M, Kimura F, Shimizu H, et al. Similarities and differences between intraductal papillary tumors of the bile duct with and without macroscopically visible mucin secretion. *Am J Surg Pathol* 2011;35:512-21. DOI:



10.1097/PAS.0b013e3182103f36

7. Rocha FG, Lee H, Katabi N, et al. Intraductal papillary neoplasm of the bile duct: A biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? *Hepatol* 2012;56:1352-60.
8. Minagawa N, Sato N, Mori Y, et al. A comparison between intraductal papillary neoplasms of the biliary tract (BT-IPMNs) and intraductal papillary mucinous neoplasms of the pancreas (P-IPMNs) reveals distinct clinical manifestations and outcomes. *Eur J Surg Oncol* 2013;39:554-8. DOI: 10.1016/j.ejso.2013.02.016
9. Wan XS, Xu YY, Qian JY, et al. Intraductal papillary neoplasm of the bile duct. *World J Gastroenterol* 2013;19:8595-604. DOI: 10.3748/wjg.v19.i46.8595
10. Lee SS, Kim MH, Lee SK, et al. Clinicopathologic review of 58 patients with biliary papillomatosis. *Cancer* 2004;100:783-93. DOI: 10.1002/cncr.20031
11. Choi SC, Lee JK, Jung JH, et al. The clinicopathological features of biliary intraductal papillary neoplasms according to the location of tumors. *J Gastroenterol Hepatol* 2010;25:725-30. DOI: 10.1111/j.1440-1746.2009.06104.x
12. Charre L, Boillot O, Goffette P, et al. Long-term survival after isolated liver transplantation for intrahepatic biliary papillomatosis. *Transpl Int* 2006;19:249-52. DOI: 10.1111/j.1432-2277.2005.00253.x

Fig. 1. A and B. MRI image showing dilation of the left bile duct with cystic images and occupation. C. MRI image showing the left bile duct dilation and stenosis in the left hepatic duct origin.

Fig. 2. ERCP image with amputation of left hepatic duct (arrow) and the outlet of mucus at the level of the ampulla of Vater (symbol).

Accepted Article

Fig. 3. Histopathology study showing macroscopic sections of the left hepatic lobe with dilation of the bile tract with mucus inside. Hematoxylin/eosin microscopic sections demonstrate intraductal papillary proliferation with some focal malignancy.

Accepted Article