LIVER

Biliary Granular Cell Tumor

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Granular cell tumors are rare, benign lesions most often located in the oral cavity, skin or subcutaneous tissue. Occurrence of this tumor in the biliary tree is extremely rare and has been reported mostly in young black women. Three patients are described presenting with biliary obstruction due to a granular cell tumor at the hepatic duct confluence. One patient is a 38-year-old white male with concomitant cutaneous granular cell tumors. The second patient is a 50-year-old white female who presented with cholestasis. The third patient is a 44-year-old, white female known with granular cell tumor localized in the esophagus. At preoperative examination, hilar granular cell tumors are difficult to differentiate from cholangiocarcinoma, sclerosing cholangitis or more common benign biliary tumors. Treatment consists of surgical excision after which prognosis is favorable.

Introduction

Granular cell tumors are benign lesions with characteristic histopathological and immunohistochemical features. These rare tumors are nonmetastasizing and have a predilection in the dermal and subcutaneous tissues, especially within the oral cavity, chest wall and extremities, but may present at any location. Only few reports exist of granular cell tumors arising in the biliary tree, mostly occurring in young black women with initial symptoms of abdominal pain, jaundice or both.[1] Clinically, biliary granular cell tumors may be diagnosed as any other benign or malignant bile duct tumor such as cholangiocarcinoma, sclerosing cholangitis or a benign biliary stricture. So far, 53 cases of biliary granular cell tumors have been reported in the literature. Most of these cases were not diagnosed until surgery. The prognosis after surgical excision is favorable. Herein, we present three cases of a granular cell tumor at the hepatic duct confluence, mimicking a Klatskin tumor.

Patients

Patient 1

A 37-year-old white male presented with an 18-month history of slowly progressive weight loss, right upper abdominal pain and eventually, an episode of obstructive jaundice. In the past this patient had undergone several excisions of cutaneous and muscular lesions, diagnosed as granular cell tumors. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) revealed a hilar lesion classified as a Bismuth type II stricture (fig. 1). Brush cytology was negative for a malignancy. Abdominal ultrasound showed a 1.0 cm solid tumor at the hepatic duct confluence extending into the right (1.0 cm) and left (1.5 cm) hepatic ducts.

Under the presumptive diagnosis of a Klatskin tumor type II, a diagnostic laparoscopy was performed in combination with laparoscopic ultrasonography, revealing no evidence of metastases. On subsequent laparotomy and exploration of the hilar lesion, no infiltration into the liver, portal vein or hepatic arteries was found. Local excision of the tumor was undertaken with construction of two hepaticojejunostomies on the right and left hepatic duct, respectively, using a Roux-Y jejunal loop. The postoperative course was complicated by a subhepatic abces which required surgical drainage. The patient is currently well more than 4 years after surgery; however, he underwent in the mean time, excision of two facial lesions which proved to be granular cell tumor.

Histopathological examination: The tumor consisted of a proliferation of cells lying individually or in groups, displaying a granular cytoplasm. The tumor infiltrated between collagenous vessels and was in close contact with surrounding nerve vessels. The tumor

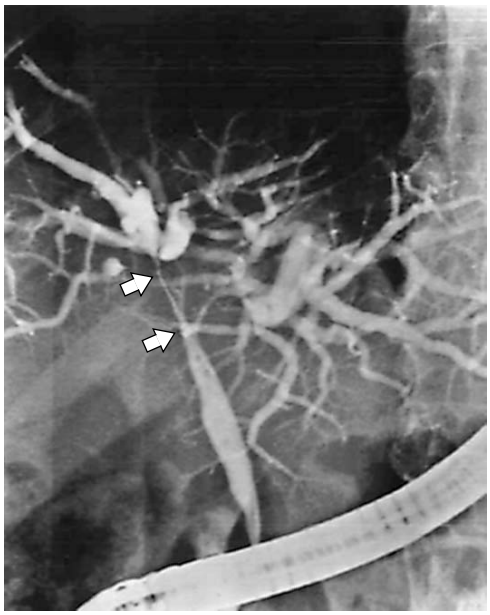

Fig. 1. Endoscopic retrograde cholangiopancreatography of patient 1 demonstrating a stricture at the level of the hepatic duct confluence (arrows).

Рис. 1. ЭРХПГ (клиническое наблюдение 1): стриктура на уровне конфлюенса печеночных протоков (показана стрелками).

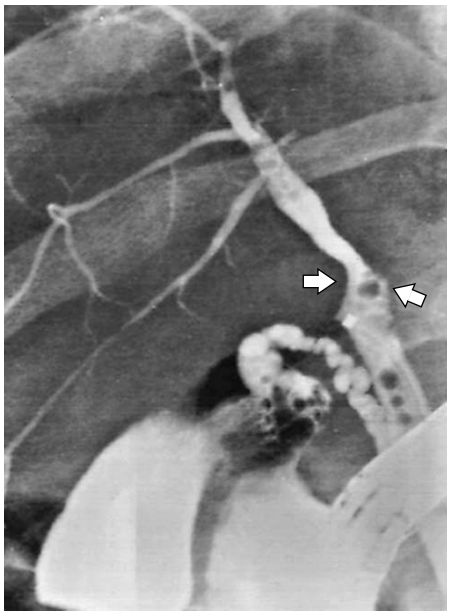

Fig. 2. Endoscopic retrograde cholangiopancreatography of patient 2 showing tumor impression at the hepatic duct confluence area (arrow head) and a complete stop at the origin of the main left hepatic duct (arrow).

Рис. 2. ЭРХПГ (клиническое наблюдение 2): сдавление опухолью области конфлюенса печеночных протоков (показано стрелкой) и полное отсутствие контрастирования желчного дерева выше уровня отхождения основного левого печеночного протока (показано стрелкой).

cells were microscopically similar to ganglion cells. The granules were periodic acid-Schiff positive and also S–100 immunoreactivity was positive. A diagnosis of granular cell tumor was made.

Patient 2

A 43-year-old white woman presented at our outpatient clinic with a 6-month history of fatigue, nausea, changed stools and weight loss. Laboratory examination showed signs of cholestasis. ERCP revealed a complete stop at the origin of the main left hepatic duct in combination with tumor impression at the hepatic confluence area with no dilatation of the right intrahepatic system (fig. 2). Brush cytology was negative for a malignancy. Abdominal ultrasound showed a solid, oval structure of 2×1 centimeters at the hepatic confluence with extension mainly in the left intrahepatic system. A stent was inserted into the left system at ERCP. There were no signs of tumor infiltration into the portal vein or hepatic arteries as assessed by duplex ultrasonography.

On the suspicion of a Klatskin tumor type II or III b, a laparotomy was performed. A hilar mass was encountered which extended into the left intrahepatic system. The liver, portal vein and hepatic arteries were all free of the growth. Deep hilar excision was carried out resulting in transection of the ducts of segments 4, 2, 3, 1 and the right common hepatic duct. These open ducts were combined into one hepaticojejunostomy for reconstruction of the biliary tract. The postoperative course was uneventful. The patient is currently well almost six years after surgery.

Histopathological examination: the tumor consisted of cells with granular cytoplasm and locally some eosinophilic granulocytes. Histopathology was compatible with a granular cell tumor, with resection margins free of tumor.

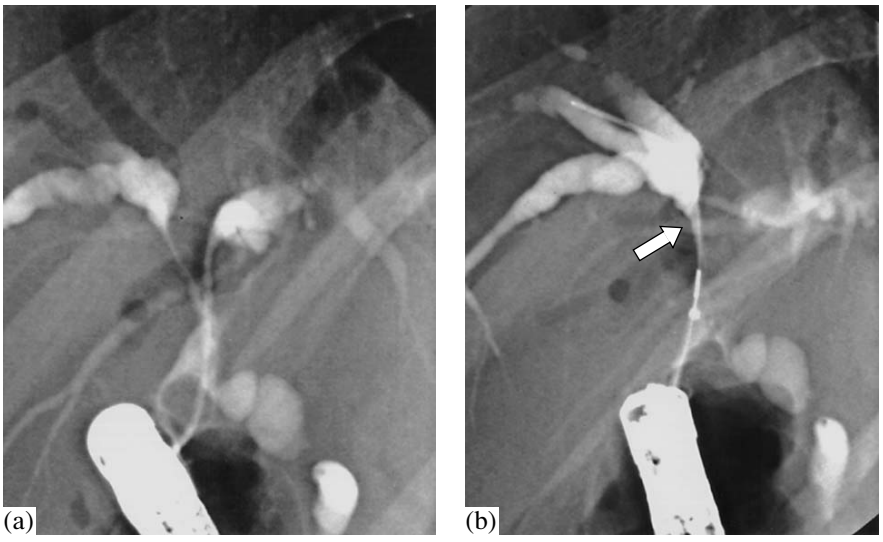

Fig. 3. Endoscopic retrograde cholangiopancreatography of patient 3 showing a tight, hilar stricture extending into the first segmental ducts of the right biliary system (arrow).

Рис. 3. ЭРХПГ (клиническое наблюдение 3): протяженная гилюсная структура, захватывающая проток I сегмента печени (показана стрелкой).

Table 1. Reported cases of biliary granular cell tumors

Reference	Age	Sex	Race	Symptoms	Location
This report	37	M	W	Jaundice/pain	CHD/HD
This report	43	F	W	Fatigue/cholest.	CHD/HD
This report	44	F	W	Pain/cholest.	CHD/HD
MacKenzie (*Med Pedi Oncol 1994; 23:50–56*)	33	F	B	Jaundice/pain	CBD/CHD/CD
MacKenzie (*Med Pedi Oncol 1994; 23:50–56*)	53	F	B	Jaundice/pain	CBD
Foulner (*Clin Radiol 1994; 49:503–504*)	38	F	W	Pain	CD
Mulhollan (*Am J Surg Pathol 1992; 16:204–206*)	35	F	B	–	CHD
Lewis (*HPB Surgery 1992; 6:311–317*)	27	F	W	Jaundice/pain	HJ
Eisen (*Am J Surg Pathol 1991; 15:460–465*)	24	M	W	Jaundice CBD	
Eisen (*Am J Surg Pathol 1991; 15:460–465*)	24	F	B	Jaundice CBD	
Sanchez (*Am Surgeon 1991; 57:446–450*)	29	F	B	Jaundice CHD	
Timberlake (*Mil Med 1988; 153:98–99*)	44	F	W	Pain	CD
Butterly (*Surgery 1988; 103:328–334*)	37	F	B	Jaundice CHD	
Butterly (*Surgery 1988; 103:328–334*)	26	F	W	Pain	CHD
Hobbiss (*J R Coll Surg Edinb 1987; 32:117–118*)	31	F	B	Pain	CD
Cheslyn-Curtis (*Postgrad Med J 1986; 62:96–103*)	38	F	W	Pain	CD/CHD
Kienzle (*Dtsch Med Wochenschr 1986; 111:197*)	33	F	–	Pain	CBD
Yamaguchi (*Acta Pathol Jpn 1985; 35:687–691*)	58	M	O	Pain	GB
Yamashina (*Am J Gastroenterol 1984; 79:701–703*)	37	F	O	Pain	CD
Barber (*J R Coll Surg Edinb 1984; 29:56–57*)	38	F	–	Pain	CD
Chandrasoma (*Cancer 1984; 53:2178–2182*)	43	F	B	JaundiceCBD	
Orenstein (*Am J Surg 1984; 147:827–831*)	31	M	B	Pain	CD
Orenstein (*Am J Surg 1984; 147:827–831*)	91	F	B	JaundiceCBD	
Balart (*Am J Gastroenterol 1983; 78:297–300*)	56	F	B	Jaundice/pain	CBD
Aisner (*Arch Pathol Lab Med 1982; 106:470–471*)	41	F	B	Pain	GB/CD/CBD
Penalba (*Ann Chir 1982; 36:723–726*)	22	F	B	JaundiceCBD	
Dewar (*Gut 1981; 22:70–76*)	28	F	W	JaundiceCBD	
Manstein (*Dig Dis Sci 1981; 26:938–942*)	31	F	B	JaundiceCBD	
Mauro (*J Can Assoc Radiol 1981; 32:254–256*)	38	F	B	Jaundice CHD/CD	
Bocquet (*Arch Anat Cytol Pathol 1980; 28:360–364*)	21	F	B	Jaundice CBD	
Jain (*Am J Gastroenterol 1979; 71:401–407*)	46	F	B	Pain	CBD
Assor (*Am J Surg 1979; 137:673–675*)	33	F	B	Jaundice CBD	
Assor (*Am J Surg 1979; 137:673–675*)	37	F	B	Pain	CBD
Assor (*Am J Surg 1979; 137.673–675*)	31	F	B	Pain	CD
Farris (*Arch Pathol Lab Med 1979; 103:510–512*)	31	F	B	Pain	CBD
Farris (*Arch Pathol Lab Med 1979; 103:510–512*)	23	F	B	Jaundice/pain	CD
Zvargulis (*Am J Dis Child 1978; 132:68–70*)	11	M	B	Jaundice CBD	
Raia (*AMB 1978; 24:379–380*)	30	M	W	Jaundice CBD	
Ishii (*Am J Gastroenterol 1977; 68:38–44*)	39	F	O	Pain	CBD

Table 1. (Contd.)

Reference	Age	Sex	Race	Symptoms	Location
Savage (*Postgrad Med J 1977; 53:574–577*)	30	F	W	Jaundice CBD	
Reul (*Am J Surg 1975; 129:583–587*)	39	F	B	Pain	CD
Kittredge (*Am J Radiol 1975; 125:35–46*)	41	F	B	Jaundice/pain	CHD/CD
Dursi (*Rev Surg 1975; 32:305–310*)	30	F	B	Jaundice CBD	
Whisnant (*Am J Dig Dis 1974; 19:471–476*)	15	M	B	Jaundice CBD	
LiVolsi (*Arch Pathol 1973; 95:13–17*)	40	F	W	Pain	CD
LiVolsi (*Arch Pathol 1973; 95:13–17*)	30	F	B	Jaundice HD	
Abt (*Mt. Sinai J Med NY 1971; 38:457–461*)	44	F	B	Pain	CD
Christiansen (*Arch Pathol 1970; 90:423–432*)	34	F	W	Pain	CD
Whitmore (*Am J Dig Dis 1969; 14:516–520*)	37	F	B	Jaundice CBD	
Whitmore (*Am J Dig Dis 1969; 14:516–52*)	61	F	B	Autopsy finding	CBD
McKay (*Can J Surg 1968; 11:44–51*)	34	F	–	Pain	CD
Goldman (*JAMA 1967; 200:1185–1186*)	14	F	B	Pain	CD
Serpe (*Am J Dig Dis 1960; 5:824–826*)	34	F	B	Pain	CD
Duncan (*Ann Surg 1957; 145:271–274*)	30	F	B	Jaundice CBD	
Fialho (*Rev Bras Med 1952; 9:616–618*)	21	F	B	Pain	CD
Coggins (*Arch Pathol 1952; 54:398–402*)	25	F	B	Jaundice CBD	

CD = cystic duct; GB = gallbladder; CHD = common hepatic duct; HD = hepatic ducts (excluding CHD); CD/CHD = tumor at the confluence of CD and CHD; CBD = common bile duct; W = white; B = black; O = oriental; M = male; F = female.

Patient 3

A 44-year-old, white female patient was referred to our institution for management of a tumor in the liver hilum. Seventeen years previously, she had undergone a (open) cholecystectomy for cholelithiasis. In addition, a choledochoduodenostomy was created because during surgery, the common hepatic duct appeared to be thickened. Biopsies of the proximal hepatic duct wall at that time, showed fibrosis and muscular hyperplasia. Ever since that operation she had intermittent complaints of upper abdominal pain. Recently, the upper abdominal pain attacks had increased and were accompanied by signs of cholangitis. ERCP revealed a patent choledochoduodenostomy with 1cm proximal to the anastomosis, a tight stricture extending into the right and left hepatic ducts. To the right, the stricture seemed to involve the first segmental ducts of the biliary tree. Stents were inserted for drainage of the biliary system. Brush cytology examinations showed inflammatory changes of the epithelium without suspicion of a malignancy. CT scan showed a mass lesion at the liver hilum. No invasion of the portal vein or hepatic arteries was detected. A presumptive diagnosis of a hilar stenosis was made whilst a proximal bile duct cancer (Klatskin tumor) could not be ruled out.

Of particular note is that 5 years after the previous cholecystectomy and choledochoduodenostomy, the patient was found to have multiple, submucosal lesions on oesophageal endoscopy, diagnosed as granular cell tumor on histopathological evaluation of biopsies. Interval endocopies and endo-sonographies showed no progression of the oesophageal lesions.

At surgical exporation of the liver hilum, a sclerotic lesion was found at the hepatic duct confluence which extended proximally into the right biliary system. Biopsy of the lesion revealed granular cell tumor. Local excision was performed with construction of a hepatico-jejunostomy on the right and left hepatic duct, using a Roux-Y jejunal loop. The post-operative course was uneventful and the patient is doing well, six months after the operation.

Histopathological examination: Sections of the bile duct showed a submucosal proliferation of clustered cells with granular cytoplasm. The granules in the cytoplasm stained strongly positive with periodic acid-Schiff. S-100 immunoreactivity was also strongly positive. The histopathological diagnosis was granular cell tumor.

Discussion

The first description of a granular cell tumor in the skin was by Abrikossoff in 1926.[2] A similar tumor located in the biliary tree was first described by Coggins in 1952.[3] Since that time, 53 biliary granular cell tumors were reviewed in the literature (table 1 and 2). Abrikossoff believed that these tumors originated in

striated muscles and therefore classified them as myoblastomas.[2] Since then, there has been great controversy concerning the origin of these tumors. Light microscopy, electron microscopy and immunohistochemical staining suggested a close relation of these tumors with peripheral nerves. The now widely accepted theory is that granular cell tumors arise from Schwann cells.[4–9] The cases described in the literature so far (n = 53) showed that 62% (n = 33) of these biliary granular cell tumors occurred in black women with a median age of 31 years (range 14–91 years). The initial symptoms of a biliary granular cell tumor are most often abdominal pain, jaundice or a combination of these two.

Biliary granular cell tumors with concomitant other locations in the same patient are very rare. This has been described in only five cases (6%) in the literature, of which three were located in the skin or subcutaneous tissue.[10–12] In the other 2 cases, the concomitant extrabiliary granular cell tumor was located in the stomach wall.[11, 13] Interestingly, two patients described in this report had extra-biliary manifestations of granular cell tumor, in the skin and oesophagus, respectively. The differential diagnosis of any obstructive lesion in the region of the hepatic duct confluence includes cholangiocarcinoma, sclerosing cholangitis or the more common benign biliary tumors, such as papillomas or adenomas, and should also include a biliary granular cell tumor. A malignant lesion cannot be ruled out on the basis of the usual diagnostic examinations as demonstrated by the three patients described in this report, who were operated on the suspicion of a proximal bile duct cancer (Klatskin tumor). In our total series of patients who underwent resection under the presumptive diagnosis of a Klatskin tumor, 15% turned out to have a benign lesion on histopathological examination of the specimen.[14]

Treatment of biliary granular cell tumor with stents, either percutaneous or endoscopic, other than for temporary biliary decompression, is inappropriate in this curable disease. In other types of benign biliary strictures, endoscopic treatment was associated with a significantly higher complication and mortality rate in comparison with local resection of the tumor.[15–17] The treatment of choice, therefore, is excision of the tumor with tumor-free margins, followed by construction of a hepaticojejunostomy.

Macroscopically these granular cell tumors appear yellow-white and are usually less than 3 centimeters. Microscopically these tumors consist of polygonal granular eosinophilic cells. These granules react strongly with periodic acid-Schiff staining. Furthermore, they have centrally located small vesicular nuclei. The granular cells often lie in clusters or sheets and infiltrate diffusely within the surrounding nerves and soft tissue. Mitoses are scant and there are no areas of necrosis. A granular cell tumor can be malignant, but this is very rare and has only been described in the skin.[18, 19] This malignant type tends to be larger than 3 cm, shows many mitoses, necrosis and the cells are smaller in size. Until now, no malignant, granular cell tumor has been described in the biliary system. Thus far, 2 cases of local recurrence have been reported, but they were probably due to incomplete resection of the tumor.[12, 20]

In summary, granular cell tumors are benign lesions that occasionally occur in the biliary tree. These tumors often present in young black women with initial symptoms of abdominal pain, jaundice or both. These tumors are indistinguishable from cholangiocarcinoma, sclerosing cholangitis or the more common benign biliary tumors, on preoperative imaging studies. Excision with tumor free margins is the only appropriate treatment and is associated with a good prognosis.

Table 2. Cases of biliary granular cell tumors summarized from the literature according to age, sex, race, symptoms and location

		Number	%
Age, years	< 20	3	5
	20–29	11	20
	30–39	28	51
	40–49	8	15
	>50	5	9
Sex	F	48	87
	M	7	13
Race	Black	38	69
	White	13	24
	Oriental	3	5
	Unknown	1	2
Symptoms	Jaundice	21	38
	Pain	24	43
	Jaundice + Pain	7	13
	Fatigue + Cholestase	1	2
	Unknown	2	4
Location	CBD	25	45
	CD	16	29
	CHD	5	9
	CD/CHD	3	5
	HD/CHD	2	4
	HD	1	2
	CBD/CHD/CD	1	2
	GB	1	2
	GB/CD/CBD	1	2

CD = cystic duct; GB = gallbladder; CHD = common hepatic duct; HD = hepatic ducts (excluding CHD); CD/CHD = tumor at the confluence of CD and CHD; CBD = common bile duct; M = male; F = female.

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