

# Granular Cell Tumor of the Biliary Tract

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**G**ranular cell tumor is an uncommon, largely benign neoplasm that most likely originates from a Schwann-like mesenchymal cell. Malignant transformation has been described, but is quite rare. Granular cell tumors are usually found in the subcutaneous tissue of the chest and upper extremities, tongue, and gastrointestinal tract.<sup>1</sup> When granular cell tumors develop in these externally or endoscopically accessible locations, histologic diagnosis is easily established based upon typical morphologic and staining characteristics after tissue biopsy or excision. In a structure such as the bile duct, accessibility is more difficult and, therefore, it delays diagnosis. Furthermore, the tumor mimics more common biliary stricturing conditions clinically and radiologically, and more readily causes obstruction, resulting in compromised hepatic function. Thus far, 76 cases of bile duct granular cell tumor have been reported in the English literature.

We present the case of a 16-year-old African-American female with a granular cell tumor in the extrahepatic bile duct that was initially suspected to be a choledochal cyst based upon clinical findings. The lesion led to significant liver failure requiring orthotopic liver transplant. In this case report, we also examine other reported cases of biliary granular cell tumor in terms of patient age, gender, race, presenting symptoms, and the precise locations of the tumor within the extrahepatic biliary system.

## Case Report

A 16-year-old, Jehovah's witness, African-American female presented with a 4-month history of increasing right upper quadrant abdominal pain, jaundice, fatigue, ascites, and hepatomegaly. The patient had an elevated total bilirubin level of 6.4 mg/dL (normal, 0.2–1.3 mg/dL), an elevated direct bilirubin level of 5.2 mg/dL (normal, 0–0.4 mg/dL), an elevated alkaline phosphatase level of 580 U/L

(normal, 30–125 U/L), an elevated gamma-glutamyl transpeptidase level of 1,171 U/L (normal, 14–51 U/L), an elevated serum glutamic oxaloacetic transaminase level of 173 U/L (normal, 3–44 U/L), and an elevated serum glutamic pyruvic transaminase level of 52 U/L (normal, 0–40 U/L). This profile was consistent with obstructive jaundice. The patient also had an elevated international normalized ratio of 1.86 and an elevated prothrombin time of 40 sec (normal, 23–33 sec). Initial work-up for possible causes of hepatomegaly and jaundice revealed a negative viral and autoimmune profile with the exception of a positive cytomegalovirus immunoglobulin (Ig)G antibody, Epstein-Barr virus IgG antibody, and varicella IgG antibody indicating past exposure. Ceruloplasmin and alpha-fetoprotein were within normal limits.

Abdominal ultrasound showed fusiform dilatation of the common bile duct with right and left intrahepatic ductal dilatation. Computed tomography scan showed a markedly enlarged liver and spleen with massive intra- and extrahepatic biliary dilatation (Figure 1). This pattern was radiologically suggestive of a choledochal cyst type IV.

At the time of presentation, the patient opted not to undergo a liver biopsy due to her anemia, coagulopathy, and religious beliefs preventing the use of blood products. Despite efforts to correct her anemia and nutritional issues, her symptoms and liver functions worsened significantly over the subsequent 8 months. Therefore, an orthotopic liver transplant was performed.

## Pathologic Findings

The explanted liver examined in the pathology laboratory was a 2,750-g, 28-cm × 24-cm × 9.8-cm liver with an attached 7.0-cm × 4.0-cm × 0.3-cm gallbladder (Figure 2). The surface of the liver was cholestatic, finely fibrotic, and nonbosselated. Serial sectioning of the liver showed diffuse cholestasis, fine fibrosis, and visibly enlarged portal areas with markedly dilated ducts. The distal common bile duct was concentrically thickened by a 1.5-cm × 1-cm × 1-cm tan yellow mass resulting in an extremely narrow lumen (Figure 3). The proximal bile duct was significantly dilated, corresponding to the

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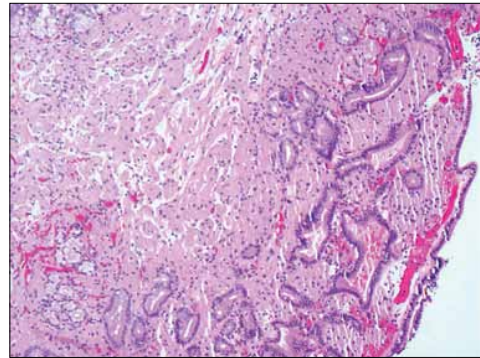
**Figure 1.** Postcontrast computed tomography scan showing massive intra- and extrahepatic biliary dilatation. The common bile duct (CBD) is displayed centrally.



**Figure 2.** Gross photograph of the explanted liver showing fine fibrosis and cholestasis without any bosselations.



**Figure 3.** Gross photograph showing the concentrically thickened common bile duct with an extremely narrow lumen (center of the photograph).



**Figure 4.** Microphotograph of the bile duct showing monomorphic tumor cell infiltrate in the submucosa and the lamina propria of the mucosa (hematoxylin and eosin stain).

dilated common bile duct seen on abdominal ultrasound and computed tomography scan.

Upon microscopic examination, the mass from the distal bile duct showed a transmural diffuse neoplastic infiltrate (Figure 4). The infiltrate was composed of sheets and clusters of large, ovoid-to-round cells separated by thin fibrous connective tissue septa. The cells had abundant granular eosinophilic cytoplasm and small uniform hyperchromatic nuclei. There was minimal pleomorphism without any mitotic activity or necrosis. Morphologically, these findings were characteristic of granular cell tumor.

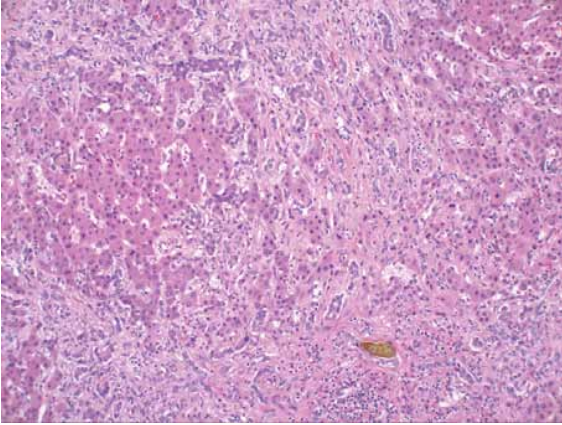
Microscopic examination of the liver showed characteristic changes of a secondary biliary cirrhosis with extensive bridging fibrosis extending from portal tract to portal tract, cholestasis, and cholangiolar proliferation (Figure 5).

**Ancillary Studies**

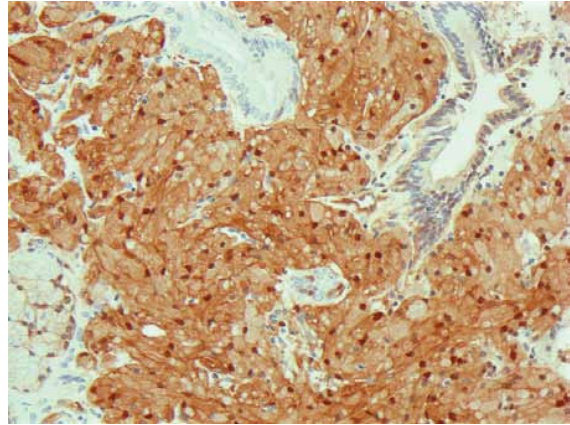
Unsurprisingly, the tumor was positive for periodic acid-Schiff stain pretreated by diastase digestion. The tumor cells were strongly positive for S-100 immunohistochemical stain (Figure 6). Electron microscopy revealed the presence of numerous intracytoplasmic lysosomes filled with lipid material, including microtubules thought to be related to myelin.<sup>2,3</sup> These ancillary studies confirmed the morphologic diagnosis of granular cell tumor.

**Discussion**

Granular cell tumor was first described in the oral cavity by Abrikosoff in 1926.<sup>4</sup> Abrikosoff initially called the lesion “granular cell myoblastoma” due to the belief that it originated from striated muscle.<sup>4</sup> The lesion was then noted to develop adjacent to peripheral nerves and,



**Figure 5.** Microphotograph of the liver showing extensive bridging fibrosis, cholangiolar proliferation, and cholestasis (hematoxylin and eosin stain).



**Figure 6.** Microphotograph of the S-100 immunohistochemical stain positivity of the tumor cells.

therefore, termed “granular cell neuroma.”<sup>5</sup> Later on, electron microscopy demonstrated that the lesion may actually be of Schwannian origin due to lysosomes containing myelin-like tubules and cytoplasmic processes surrounded by layers of basal lamina reminiscent of Schwann cells.<sup>3</sup> Immunohistochemistry revealed that the tumor was positive for S-100 and neuron-specific enolase and negative for desmin and smooth muscle actin, supporting the possibility of Schwannian origin.<sup>6</sup> Until the exact origin is identified, the tumor is best described as a granular cell tumor.

Typically, granular cell tumors present as solitary, yellow-tan, painless nodules less than 3 cm in their greatest dimension. They can develop at any age but are more prevalent among people in their 40s and 50s. There is also a slight female and African-American predominance.<sup>1</sup> Granular cell tumors most commonly develop in the dermis and subcutaneous tissue of the chest and upper extremities. After the skin and subcutis, the next most common site is the tongue, accounting for approximately 40% of cases.<sup>1</sup> These lesions are relatively rare in the gastrointestinal tract, accounting for 5–9% of reported cases.<sup>1</sup> Within the gastrointestinal tract, they are primarily found within the esophagus, followed by the colon, stomach, small intestine, and anal canal.<sup>7</sup> Less than 1% have been reported to develop within the biliary tree.

The first biliary case was described by Coggins in 1952 during the autopsy of a patient with alleged Laennec’s cirrhosis.<sup>8</sup> Since then, there have been 76 reported cases within the literature, which indicates the rarity of the disease in this location (Table 1).<sup>1</sup> Despite its rarity, granular cell tumor is the most common benign non-epithelial tumor of the extrahepatic biliary tract occurring more commonly in the bile duct than the gallbladder.<sup>9</sup> Within the biliary tree, 63% of the cases have occurred in

black women, at a median age of 32 years (range, 14–91 years).<sup>1</sup> Typically, most patients (95%) have presented with abdominal pain and/or jaundice (Table 2). Only 2 cases were found incidentally at autopsy or during an exploratory laparotomy while resecting colorectal cancer. Many patients were clinically suspected of having cholangiocarcinoma prior to surgery and, therefore, underwent extensive procedures such as a Whipple procedure. Other presentations included suspected metastatic melanoma, primary sclerosing cholangitis, and biliary strictures. Due to the rarity of the disease, patients are usually misdiagnosed with another entity such as a choledochal cyst, based upon similar characteristic radiologic findings of intra- and/or extrahepatic dilatation. However, many conditions obstructing this narrow lumen structure can create the clinical picture of a choledochal cyst. The differential diagnosis of such obstructive lesions includes cholangiocarcinoma, primary sclerosing cholangitis, biliary stricture, polyps, papillomas, adenomas, choledochal cysts, and, infrequently, granular cell tumors.<sup>1</sup>

Microscopically, these tumors are composed of polygonal cells with granular eosinophilic cytoplasm and small vesicular nuclei.<sup>1</sup> These granules within the cytoplasm react to periodic-acid Schiff and S-100 staining. They appear as clusters or sheets and infiltrate diffusely within the surrounding tissue separated by thin fibroconnective tissue septa. Typically, mitoses are rare, with no necrosis present. Reactive atypia of the overlying epithelium and metaplastic pyloric glands may occur, mimicking carcinoma.<sup>9</sup> Malignant granular cell tumors are quite rare but have been described within the subcutis and dermis showing rapid growth, a size greater than 4 cm, necrosis, pleomorphism, infiltrative edges (rather than pushing borders), and increased mitotic index.<sup>10–12</sup> Thus far, no malignant biliary granular cell tumors have been described.<sup>1</sup> Two

**Table 1.** Reported Cases of Biliary Granular Cell Tumors

Reference	Age (years)	Gender	Race	Symptoms	Location
This case report*	16	F	B	Jaundice/pain	CBD
Zaidi ( <i>J Coll Physicians Surg Pak.</i> 2007;17:572-573.)	39	F	–	Jaundice	CBD
Lochan ( <i>Surg Today.</i> 2006;36:934-936.)	51	F	–	Jaundice	CHD
Tonsi ( <i>Minerva Chir.</i> 2006;61:247-255.)	26	M	B	Jaundice/pain	CBD
Hoda ( <i>Acta Cytol.</i> 2005;49:199-203.)	24	F	B	Jaundice	CBD
	38	F	B	Jaundice	CHD
Altavilla ( <i>Ultrastruct Pathol.</i> 2004;28:171-176.)	39	M	W	Jaundice	CBD
Heuer ( <i>Z Gastroenterol.</i> 2004;42:323-325.)	26	F	–	Jaundice	CBD
Reynolds ( <i>J Ped Surg.</i> 2000;35:652-654.)	14	F	B	Fatigue	CBD
Karakozis ( <i>Surgery.</i> 2000;128:113-115.)	32	F	B	Pain	CD
	40	F	B	Pain	CBD
	63	F	B	Pain	CBD
Te Boekhorst ( <i>Dig Surg.</i> 2000;17:299-303.)	37	M	W	Jaundice/pain	CHD/HD
	43	F	W	Fatigue/ cholestasis	CHD/HD
Ogawa ( <i>J Jpn Surg Assoc.</i> 1999;60:183-187.)	83	F	A	Incidental finding	CD
Fairchild ( <i>Transplantation.</i> 1999;68:315-317.)*	34	F	–	Jaundice	CHD
Dusoleil ( <i>Gastroenterol Clin Biol.</i> 1999;23:993-994.)	35	M	W	Jaundice	CBD
Aubert ( <i>Gastroenterol Clin Biol.</i> 1999;23:1090-1093.)	22	F	W	Jaundice	CBD
	38	F	W	Jaundice	CBD
Butler ( <i>Am Surg.</i> 1998;64:1033-1036.)	31	F	B	Jaundice	CBD/CHD/CD
Ferri Romero ( <i>Rev Esp Enferm Dig.</i> 1994;85:217-219.)	44	M	W	–	CD
MacKenzie ( <i>Med Pediatr Oncol.</i> 1994;23:50-56.)	33	F	B	Jaundice/pain	CBD/CHD/CD
	53	F	B	Jaundice/pain	CBD
Foulner ( <i>Clin Radiol.</i> 1994;49:503-504.)	38	F	W	Pain	CD
Yang ( <i>South Med J.</i> 1993;86:478-479.)	32	F	B	Jaundice	CHD
Yazdanpanah ( <i>Gastroenterol Clin Biol.</i> 1993;17:607.)	33	M	W	–	CBD
Lewis ( <i>HPB Surg.</i> 1993;6:311-317.)	27	F	W	Jaundice/pain	CHD
Mulhollan ( <i>Am J Surg Pathol.</i> 1992;16:204-206.)	35	F	B	–	CHD
LaFreniere ( <i>J Surg Oncol.</i> 1991;46:60-66.)	32	F	B	Pain	CHD/CD
Eisen ( <i>Am J Surg Pathol.</i> 1991;15:460-465.)	24	F	B	Jaundice	CBD
	24	M	W	Jaundice	CBD
Sanchez ( <i>Am Surg.</i> 1991;57:446-450.)	29	F	B	Jaundice	CHD
Timberlake ( <i>Mil Med.</i> 1988;153:98-99.)	44	F	W	Pain	CD
Butterly ( <i>Surgery.</i> 1988;103:328-334.)	26	F	W	Pain	CHD
	37	F	B	Jaundice	CHD
Hobbiss ( <i>J R Coll Surg Edinb.</i> 1987;32:117-118.)	31	F	B	Pain	CD
Cheslyn-Curtis ( <i>Postgrad Med J.</i> 1986;62:96-103.)	38	F	W	Pain	CHD/CD
Kienzle ( <i>Dtsch Med Wochenschr.</i> 1986;111:197.)	33	F	–	Pain	CBD
Yamaguchi ( <i>Acta Pathol Jpn.</i> 1985;35:687-691.)	58	M	A	Pain	GB

(Table continues on following page)

**Table 1.** (Continued) Reported Cases of Biliary Granular Cell Tumors

Reference	Age (years)	Gender	Race	Symptoms	Location
Yamashina ( <i>Am J Gastroenterol.</i> 1984;79:701-703.)	37	F	A	Pain	CD
Barber ( <i>J R Coll Surg Edinb.</i> 1984;29:56-57.)	38	F	–	Pain	CD
Chandrasoma ( <i>Cancer.</i> 1984;53:2178-2182.)	43	F	B	Jaundice	CBD
Orenstein ( <i>Am J Surg.</i> 1984;147:827-831.)	31	M	B	Pain	CD
	91	F	B	Jaundice	CBD
Balart ( <i>Am J Gastroenterol.</i> 1983;78:297-300.)	56	F	B	Jaundice/pain	CBD
Aisner ( <i>Arch Pathol Lab Med.</i> 1982;106:470-471.)	41	F	B	Pain	GB/CD/CBD
Penalba ( <i>Ann Chir.</i> 1982;36:723-726.)	22	F	B	Jaundice	CBD
Dewar ( <i>Gut.</i> 1981;22:70-76.)	28	F	W	Jaundice	CBD
Manstein ( <i>Dig Dis Sci.</i> 1981;26:938-942.)	31	F	B	Jaundice	CBD
Mauro ( <i>J Can Assoc Radiol.</i> 1981;32:254-256.)	38	F	B	Jaundice	CHD/CD
Bocquet ( <i>Arch Anat Cytol Pathol.</i> 1980;28:360-364.)	21	F	B	Jaundice	CBD
Jain ( <i>Am J Gastroenterol.</i> 1979;71:401-407.)	46	F	B	Pain	CBD
Assor ( <i>Am J Surg.</i> 1979;137:673-675.)	31	F	B	Pain	CD
	33	F	B	Jaundice	CBD
	37	F	B	Pain	CBD
Farris ( <i>Arch Pathol Lab Med.</i> 1979;103:510-512.)	23	F	B	Jaundice/pain	CD
	31	F	B	Pain	CBD
Zvargulis ( <i>Am J Dis Child.</i> 1978;132:68-70.)	11	M	B	Jaundice	CBD
Raia ( <i>AMB.</i> 1978;24:379-380.)	30	M	W	Jaundice	CBD
Ishii ( <i>Am J Gastroenterol.</i> 1977;68:38-44.)	39	F	A	Pain	CBD
Savage ( <i>Postgrad Med J.</i> 1977;53:574-577.)	30	F	W	Jaundice	CBD
Reul ( <i>Am J Surg.</i> 1975;129:583-587.)	39	F	B	Pain	CD
Kittredge ( <i>Am J Radiol.</i> 1975;125:35-46.)	41	F	B	Jaundice/pain	CHD/CD
Dursi ( <i>Rev Surg.</i> 1975;32:305-310.)	30	F	B	Jaundice	CBD
Whisnant ( <i>Am J Dig Dis.</i> 1974;19:471-476.)	15	M	B	Jaundice	CBD
LiVolsi ( <i>Arch Pathol.</i> 1973;95:13-17.)	30	F	B	Jaundice	HD
	40	F	W	Pain	CD
Abt ( <i>Mt Sinai J Med.</i> 1971;38:457-461.)	44	F	B	Pain	CD
Christiansen ( <i>Arch Pathol.</i> 1970;90:423-432.)	34	F	W	Pain	CD
Whitmore ( <i>Am J Dig Dis.</i> 1969;14:516-520.)	37	F	B	Jaundice	CBD
	61	F	B	Autopsy	CBD
McKay ( <i>Can J Surg.</i> 1968;11:44-51.)	34	F	–	Pain	CD
Goldman ( <i>JAMA.</i> 1967;200:1185-1186.)	14	F	B	Pain	CD
Serpe ( <i>Am J Dig Dis.</i> 1960;5:824-826.)	34	F	B	Pain	CD
Duncan ( <i>Ann Surg.</i> 1957;145:271-274.)	30	F	B	Jaundice	CBD
Fialho ( <i>Rev Bras Med.</i> 1952;9:616-618.)	21	F	B	Pain	CD
Coggins ( <i>Arch Pathol.</i> 1952;54:398-402.)	25	F	B	Jaundice	CBD

A=Asian; B=black; CBD=common bile duct; CD=cystic duct; CHD=common hepatic duct; F=female; GB=gallbladder; HD=hepatic duct; M=male; W=white.

\*Transplanted cases.

**Table 2.** Reported Cases of Biliary Granular Cell Tumors Summarized by Age, Gender, Race, Clinical Symptoms, and Location

		Number of cases	Percent
Age (years)	<20	5	6.5%
	20–29	15	19.5%
	30–39	39	50.6%
	40–49	10	13.0%
	≥50	8	10.4%
Gender	Male	12	15.6%
	Female	65	84.4%
Race	Black	47	61.0%
	White	19	24.7%
	Asian	4	5.2%
	Unknown	7	9.1%
Clinical symptoms	Jaundice	33	42.8%
	Jaundice and pain	9	11.7%
	Pain	28	36.4%
	Fatigue	2	2.6%
	Incidental	2	2.6%
	Unknown/not listed	3	3.9%
Location	CBD	38	49.4%
	CD	19	24.6%
	CHD	9	11.7%
	HD	1	1.3%
	GB	1	1.3%
	Multiple sites	9	11.7%

CBD=common bile duct; CD=cystic duct; CHD=common hepatic duct; GB=gallbladder; HD=hepatic duct.

cases have shown local recurrence but were likely secondary to incomplete removal.<sup>13,14</sup>

Within the biliary tree, these lesions can cause obstruction by concentric narrowing of the bile duct. As with all causes of biliary obstruction, over time, the long-term effect will be secondary biliary cirrhosis, if left untreated.<sup>15</sup> Rarely, the secondary biliary cirrhosis may cause liver failure requiring transplantation, as in our patient. In the literature, only 1 other case of transplantation has been described of a granular cell tumor of the bile duct causing severe secondary biliary cirrhosis with liver failure due to a lack of suspicion and correct diagnosis in a timely manner.<sup>15</sup>

Typically, the accepted treatment for granular cell tumors in this location is surgical excision with tumor-free margins followed by hepaticojejunostomy.<sup>1</sup> Treatment with percutaneous or endoscopic stents is only used for temporary decompression.<sup>1</sup> If complete excision is obtained, the patient typically has good tumor-free long-term survival, as with our patient 21 months postsurgery. However, these patients do require long-term follow-up care for possible local recurrence and the potential for severe secondary effects requiring transplantation.<sup>15</sup>

### Summary

Granular cell tumors of the biliary tree are rare benign lesions typically occurring in young African-American women initially presenting with abdominal pain and jaundice. The lesions are often clinically misdiagnosed as a more common disorder such as choledochal cyst, but physicians should be aware that the lesions may be granular cell tumors. Timely intervention with limited local excision in such cases may prevent secondary long-term damage to liver function and the need for transplantation.

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# Review

## Abrikosoff's Tumor and the Hepatobiliary System: A Curiosa Revisited

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In 1926, Abrikosoff described a mesenchymal cell neoplasm that he referred to as a granular cell myoblastoma.<sup>1</sup> Since then, this entity has fallen within the domain of dermatologists, otolaryngologists, and histopathologists with an interest in these areas. These lesions are histologically characterized by a collection of polygonal eosinophilic cells with a low nuclear-cytoplasmic ratio and prominent cytosolic granules. The cells can also be fusiform and may be arranged in compact nests or in a more diffuse pattern.<sup>2</sup> Mitotic activity is generally low, and granular cell tumors are, for the most part, benign lesions; they show local invasion only occasionally, and metastatic spread is found very rarely.<sup>3,4</sup> By electron microscopy, the tumor cells contain large lysosomes and myelin bodies.<sup>2</sup> These features, along with the immunohistochemical demonstration of S-100 protein expression, have led many experts to consider the lesions to be of neural origin, although, as discussed below, their histogenesis remains an enigma. The lesions have fascinated histopathologists in part due to their propensity to mimic other neoplasms and infiltrative processes and in part because they frequently induce a hyperplastic or pseudoepitheliomatous response in overlying epithelium. This is particularly an issue in lesions arising in the oral cavity but has also been described in lesions found elsewhere, including the urinary tract. Granular cell tumors may occasionally be multifocal, and some are associated with a genetic predisposition; recent research has suggested that they may form part of the so-called LEOPARD syndrome, which is associated with a dominant-negative mutation at exon 12 in the *PTPN11* gene.<sup>5</sup> Congenital granular cell tumors have been reported, principally in the oral cavity.<sup>6</sup>

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Granular cell tumors have been described at various sites along the gastrointestinal tract, most notably in the esophagus, but also in the duodenum, stomach, and colon.<sup>7-9</sup> The case reported by Patel and Jakate<sup>10</sup> serves to remind physicians that these tumors can also be seen occasionally in the hepatobiliary system. Their case report includes a very helpful, up-to-date summary of the world literature of such lesions in the biliary tree. These lesions are most commonly seen around the extrahepatic common bile duct, though some are described (including 1 from our own center) at the hilum of the liver and in the pancreas.<sup>11-16</sup> To our knowledge, intrahepatic granular cell tumors have not hitherto been described.

The case report by Patel and Jakate<sup>10</sup> aims to place this lesion into context. Since the first description in the biliary tree in 1952, there have been fewer than 80 such cases reported in the world literature.<sup>11</sup> Granular cell tumors remain, therefore, quite low on the list of differential diagnoses in patients with obstructive lesions in the extrahepatic biliary system. Nevertheless, this lesion does have a peculiar epidemiologic characteristic, in that it is a tumor principally seen in young female African-American patients (with more than three quarters of patients under 40 years of age). Most of these tumors clinically manifest with obstructive jaundice, which is caused by compression of the common bile duct (or, less commonly, the ducts at the hilum) by the mass effect of the surrounding granular cell tumor. Although reactive change may occur in the biliary epithelium overlying a peribiliary granular cell tumor, exuberant pseudoepitheliomatous change does not appear to be a feature and likely does not contribute significantly to the biliary obstruction. Treatment is usually surgical excision with hepaticojejunostomy.

In the case reported by Patel and Jakate,<sup>10</sup> the lesion gave rise to chronic cholestasis and a secondary biliary fibrosis leading to hepatic failure with synthetic dysfunction necessitating orthotopic liver transplantation. This case highlights several of the difficulties of establishing a preoperative diagnosis of granular cell tumor involving the biliary system, largely due to the difficulty of access because of anatomical reasons (which was further complicated by consent issues regarding a biopsy before the transplant). Hoda and associates<sup>17</sup> discussed the diagnosis of biliary granular cell tumor via endoscopic brush cytology in 2 cases. In only 1 of these cases, however, was a firm preoperative diagnosis made using this approach; given the predominantly subepithelial nature of this lesion, the sensitivity of such a diagnostic modality is likely to be low.

The histogenesis of granular cell tumors remains of interest. Although the lesion was originally coined "granular cell myoblastoma," there is no evidence of muscle differentiation.<sup>18</sup> Ultrastructurally, the cells exhibit

features of Schwann cells and, accordingly, are S-100 antigen-positive. These lesions are commonly seen at sites of abundant nerves, and some exhibit a complex hybrid appearance with concomitant features of a perineurioma.<sup>19</sup> Other neural antigens are also present in granular cell tumors, including calretinin, a calcium-binding protein structurally related to S-100 protein, as well as nestin, p75/NGFR, and PGP 9.5.<sup>20-23</sup> Recent immunohistochemical studies, however, have shown that there are also non-neural antigens present. CD 68 immunoreactivity likely reflects the high lysosomal content, rather than any indication of monocyte/macrophage derivation. Of particular note was the demonstration by Murakata and Ishak<sup>21</sup> of inhibin alpha immunoreactivity in all 17 of the hepatobiliary granular cell tumors in their series. This protein is classically expressed in sex cord stromal tumors, placental/gestational trophoblastic lesions, and adrenocortical neoplasms. Several researchers have suggested that granular cell tumors represent a non-neoplastic process reflecting a degenerative change in cells of neural origin as a reactive phenomenon<sup>22</sup>; expression of inhibin alpha makes this unlikely. Although granular cell tumors show some morphologic resemblance to so-called PEComas (tumors showing perivascular epithelioid cell differentiation),<sup>24</sup> the former lack the close association with blood vessels, exhibit less diverse microscopic features, and do not express HMB45 or Melan A.

Irrespective of its origin, granular cell tumor can involve the hepatobiliary system. It remains an uncommon lesion but one that can, as Patel and Jakate<sup>10</sup> and others<sup>25</sup> have demonstrated, lead to significant biliary obstruction and hepatic failure.

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