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Acinar Cell Carcinoma of the Pancreas

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ABSTRACT Acinar cell carcinoma of the pancreas is a rare tumor which is defined as a carcinoma that exhibits pancreatic enzyme production by neoplastic cells. This review includes recent developments in our understanding of the epidemiology and pathogenesis of ACC, imaging and pathological diagnosis and approaches to treatment with reference to the literature.

KEY WORDS: carcinoma, acinar cell, pancreas.

Introduction

Acinar cell carcinoma (ACC) of the pancreas is a rare tumor. It is defined as a carcinoma exhibiting pancreatic enzyme production by neoplastic cells[1]. ACC is now more frequently documented in the literature, and is being recognized more often. But many aspects remain unclear because only a few large-scale clinical studies on ACC in multi-institutions have been conducted.

Epidemiology

ACC is an uncommon malignancy with a reported incidence of 1%~2% among exocrine tumors of the pancreas[2,3]. The largest number cases to date have been comprised by Kitagami et al.[4] who reported that 115 patients (77 males and 38 females) with ACC displayed a mean age of 59.6 years (a range of 30~85 years). Other previous reports indicate that the tumors tended to occur in older patients, between the fifth and seventh decade, with a male predominance of 2:1 over females[5-9]. A small number of cases to date have been reported in children[5,6,9-11.] with a 3-month-old patient[10] being the youngest documented case. Taken together, there is a wide age with a male predominance.

Pathogenesis

The specific molecular alterations that characterize ACC have remained obscure[9,12,13]. Studies of ACC to date have demonstrated the lack or rarity of genetic alterations commonly present in ductal adenocarcinomas. Although ACC is rare in humans, it can readily be induced in experimental animals[14-17]. These animal models of pancreatic tumorigenesis provide reproducible cancers with which to study the pathogenesis, biological behavior, and possible treatments of ACC.

Clinical manifestations

The presenting symptoms generally are nonspecific, including ab-

dominal and back pain, nausea, postprandial vomiting, bloating, diarrhea, weight loss related to the local tumor growth or metastases[4-7, 11,18-21]. Other rare symptoms include hypoglycemia[22], Cushing's Syndrome[23] and morbid obesity[24]. Ectopic ACCs presenting as submucosal tumors of the stomach also have been reported[25,26]. Some of the most common signs at presentation were a palpable abdominal mass, elevated liver enzymes, jaundice, and anemia[7,20].

In most cases, the enzymes produced by ACC are not biologically active, but occasionally a dramatic clinical syndrome results from the secretion of functioning lipase[18]. This syndrome of diffuse fat necrosis, due to systemic release of tumor-elaborated lipase, commonly manifests as peripheral polyarthropathy and painful, erythematous subcutaneous nodules[6,19,20]. It is not known why only some ACCs liberate sufficient lipase to induce the syndrome or why the fat necrosis is predominantly subcutaneous[18,22]. To our knowledge, besides ACC of the pancreas, there has not been any other malignancy associated with the production of lipase which appears to be a tumor specific antigen for ACC of the pancreas.

Laboratory data

The serum tumor markers are within normal limits in most of the patients[7]. None of the common tumor markers have been consistently demonstrated in ACC[6,11,19], but elevated serum concentrations of α-fetoprotein, carcinoembryonic antigen , and CA19-9 have occasionally been reported[4,11,21,22,27-32]. The relationship of tumor markers with the diagnosis and evaluation of ACC needs to be studied further[4,31-33].

Elevated serum concentrations of lipase or amylase levels, bilirubin level, and the peripheral eosinophilia level have been reported[20,30]. In the future, more investigations of the exocrine function in relation to cancer stages and prognosis should be undertaken[11,18].

Imaging diagnosis

Recent advances in diagnostic imaging have been made[4], but as Matsuyama et al.[28] and Kitagami et al.[4] still indicate, confirming the diagnosis of ACC preoperatively is difficult. If criteria for detecting the differences between ACC and other tumors on some images were to be established, the diagnostic skill for ACC would improve dramatically.

Ultrasound diagnosis

With US, a well-defined, predominantly hypoechoic mass has been described [34].

CT diagnosis

Although ACC is a rare pancreatic tumor, recognition of the CT features may help radiologists to suggest the diagnosis in some cases. A CT scan is important in the diagnosis of ACC, not only for tumor staging, but because CT can reveal tumor features useful in distinguishing ACC from other pancreatic neoplasms.

Tatli et al.[20] reported that with CT scans, the tumor is almost always well demarcated and most show a well-defined, partial or complete capsule. The masses are frequently exophytic. The internal architecture is usually heterogeneous in attenuation. Most tumors show a central hypoattenuating area, often large, which represents tumoral necrosis. Calcification is present in one-third to half of the cases, and may be visible on plain radiographs. These calcifications may be punctate or chunky and may be peripheral or central within the tumor. Although intratumoral hemorrhage may be a prominent pathologic feature, hemorrhage may not be observed with CT. Chiou et al.[7] reported that internal calcification occasionally is present, but intratumoral hemorrhage is rare.

The degree of tumor enhancement lies between that of a ductal adenocarcinoma and pancreatc islet cell tumor, and the enhancement pattern can be washout or persistent enhancement in the PV phase. The tumor usually enhances, but less than normal pancreas. Smaller tumors tend to show a homogeneous enhancement pattern, while larger tumors generally exhibit enhancement of the peripheral, solid portion of the mass[7,20], and contain cystic areas due to necrosis when large[20]. In an isolated case reported by Mustert et al.[35], the appearance of an ACC on dual-phase helical CT was hyperdense in the arterial phase, and mimicked a neuroendocrine neoplasm. Therefore, they suggest that ACC can occasionally appear as a hyperdense mass, and should be included in the differential diagnosis of enhancing pancreatic neoplasms on a dual phase CT.

MR diagnosis

Little information concerning MR imaging appearance of ACC is available in the literature. Tatli et al.[20] describe one ACC as homogeneous and slightly hypointense on T1-weighted images, and hyperintense on T2-weighted images relative to the normal pancreas. Enhancement of this mass was homogeneous and less than that of the surrounding parenchyma. Another ACC was well marginated with a central area of mixed signal intensity on T1-weighted images, and a high signal intensity on T2-weighted images. The central focus correlated pathologically with necrosis. Sahani et al.[36] reported on an isolated case of functioning acinar cell pancreatic carcinoma using mangafodipir trisodium (Mn-DPDP)-enhanced MRI.

Both CT and MR imaging can demonstrate associated enlarged regional lymph nodes, invasion of adjacent organs, venous encasement, and venous tumor thrombus. Both are useful for preoperative tumor staging[7,20].

Radiograph diagnosis

ACC can cause hyperlipasemia, which may lead to diffuse subcutaneous nodules and polyarthropathy. Arthropathy is caused by periarticular fat necrosis and involves peripheral joints such as the ankles, knees, wrists, and small joints of the hands and feet. Radiographs of the osseous lesions typically show multiple lytic areas that might be mistaken for metastases involving both cancellous and cortical bones[34].

Radiologic differential diagnosis

The radiologic differential diagnosis of ACC includes ductal adenocarcinoma, neuroendocrine tumor, solid and pseudopapillary tumor, pancreatoblastoma, mucinous cystic neoplasm, and pseudocyst[20,37-43]. It is important to differentiate these neoplasms because treatment and prognosis differs significantly for these various entities. Dual-phase CT can increase the conspicuity of pancreatic neoplasms and may show enhancement patterns that could help narrow the differential diagnosis[37,38].

Pathological diagnosis

The 3 main components of the pancreas are ducts (4%), acinar cells (82%), and islet cells (14%). Although acinar cells occupy most of the normal pancreas, ACC accounts for only about 1% of all pancreatic neoplasms[44]. ACC is far less common than either ductal adenocarcinoma, which comprises more than 90% of total pancreatic neoplasms, or islet cell tumors[39,45,46]. Pathologically, ACCs recapitulate the acinar component of the pancreas. Although acinar differentiation is defined as the production of pancreatic enzymes by tumor cells (documented by electron microscopic analysis or immunohistochemistry), ACCs also have distinctive histologic features. A definite diagnosis of ACC can be established on the basis of immunohistochemical and electron microscopic results[6].

Tumor location

ACC occurs throughout the pancreas with no preferential location[5,47]. But other studies[6,7,11] reported that nearly half of the ACC occurred in the head of the pancreas.

Gross features

An ACC tumor is most often a large, well-demarcated, soft, round to lobular mass. The sizes range from 2 to 30 cm with a mean of 10 cm[5,6,19]. Chiou et al.[7] reported that the average tumor size was 7.2 cm (a range of 3.3~18 years). They are almost always well circumscribed, and may be partially or completely encapsulated. The cut surface reveals a tan to reddish mass separated into large lobules by thin, fibrous strands. Necrotic foci are frequent[5,6,47].

Local invasive and metastasis

Holen et al.[11] found that hepatic and lymph node metastases occur early and vascular invasion is common , and Kitagami et al.[4] reported that the percentages of positive portal vein invasion, arterial invasion, and extrapancreatic nerve plexus invasion for ACC were lower than that for ductal adenocarcinoma, indicating that vascular invasion is not necessarily common in ACC. The incidence of metastasis to lymph nodes and distant organs for ACC is lower than that for ductal adenocarcinoma. Although invasion into the main pancreatic duct is reportedly lower for ACC than for ductal adenocarcinoma, which comes from the pancreatic ductal system[48,49], histologically confirmed invasion into the main pancreatic duct was seen in 29.2% of the registered ACC patients, suggesting that invasion into the main pancreatic duct is not rare in ACC[4]. Knowing the above biological features is important in evaluating the resectability.

FNA cytologic features

ACC is a rare neoplasm. Consequently its morphological patterns with FNA cytology have not been well defined. Unlike ductal adenocarcinomas, endocrine tumors, and solid pseudopapillary tumors of the pancreas with their characteristic FNA cytological features, ACCs pose a particular diagnostic challenge by sharing many cytomorphologic features with endocrine tumors of the pancreas. The typical cytological features of ACC described by some authors include isolated and loose clusters of uniform cells with smoothly contoured, eccentric nuclei and clumped chromatin containing one or two conspicuous nucleoli. The cells are small to moderate-sized and polygonal with a moderate amount of granular cytoplasm[50,51].

Light microscopic features

Khalili et al.[1] reported that pathologic review of a pure ACC yields two predominant cellular patterns of growth: the acinar pattern consisting of cells growing in well-formed acini, and the solid pattern characterized by sheets and cords of cells separated by a thin fibrovascular stroma. The light microscopic features were highly suggestive of acinar differentiation. These included a hypercellular low-power appearance with a relatively circumscribed periphery and minimal desmoplastic stroma within the tumors. The cellular population is monotonous and arranged in solid sheets, and nests punctuated by acinar and small glandular spaces. Occasional trabecular formations also may occur. The cells exhibit evidence of polarization, even in solid areas, with the nuclei in cells adjacent to the stroma having a basal location[6]. The cytoplasm is moderate to focally abundant, and shows eosinophilic granularity in the apical regions, reflecting aggregates of zymogen granules. The nuclei usually are only moderately atypical; the focal anaplasia is unusual. Prominent single nucleoli are a helpful diagnostic feature[6,11,29].

Immunohistochemical features

Documentation of enzyme production is necessary for ACC diagnosis. ACCs display an immunohistochemical staining pattern viz., strong positivity for trypsin, lipase, amylase, and chymotrypsin, and negativity or only focal positivity for chromogranin, and synaptophysin[6,11,19,52]. Klimstra et al.[18] reported that immunohistochemistry revealed positive cytoplasmic staining for trypsin, chymotrypsin, and lipase, with negative staining for CEA, B72.3, chromogranin, synaptophysin, and alpha-fetoprotein. Some reports[5,6,19,53] have indicated that immunohistochemical stains for trypsin and chymotrypsin are positive in less than 90% of ACCs, whereas stains for lipase identify only 50% to 65%. Interestingly, amylase is uncommonly detected[5,6]. Another helpful immunohistochemical marker of acinar differentiation is pancreatic stone protein[5]. All of the ACCs studied immunohistochemically stained positively for at least one of these markers, but few of them were reactive for all.

Electron microscopic features

Electron microscopy may be diagnostic, revealing exocrine secretory features, abundant endoplasmic reticulum, and numerous zymogen granules[6,11,19]. Electron microscopic analysis disclosed an epithelial tumor composed of small glands. There also was a well-developed rough endoplasmic reticulum[18]. In keeping with their exocrine secretory nature, the tumor cells exhibit abundant parallel arrays of rough endoplasmic reticulum and plentiful mitochondria. Klimstra et al.[6] demonstrated that homogeneous electron-dense zymogen granules ranging from 250 to 1000 nm are found in the apical cytoplasm. Another finding repeatedly encountered in pancreatic neoplasms with acinar differentiation is irregular fibrillary granules[6,54-56]. These elongated, irregularly shaped granules measure to 3500 nm in largest dimension and contain fibrillary internal structures. The exact nature of these structures is not clear, although they resemble the earliest zymogen granules encountered in the developing fetal pancreas[57]. Toyota et al.[58] indicated that finger-print-like zymogen granules detected by electron microscopy could be an important factor in the genesis of ACC.

Diagnosis and staging

Special attention should be paid to the patients presenting with abdominal pain, nausea, and weight loss, as these symptoms may indicate ACC. Furthermore, an imaging examination should be conducted. Various techniques for diagnosis of ACC need to be continually evaluated. Misdiagnosis, caused by vague early ACC symptoms, can critically delay a diagnosis. It has been reported that the median time interval between onset of clinical symptoms and the pathologic diagnosis was 8 months (a range of 1~36 months)[20]. Differential diagnosis from endocrine tumors, solid pseudopapillary tumors, pancreatoblastoma, and ductal adenocarcinoma is difficult[59-61]. Usually, a correct diagnosis is not made preoperatively, but is made from postoperative or postmortem pathological findings[2,6,62,63]. Only patients showing some clinical symptoms that are peculiar to ACC have been diagnosed correctly[36]. TNM staging of ACC plays an important role in treatment. One of the main goals in staging ACC is to determine tumor resectability as efficiently as possible. The largest study to date used tumor staging including T, N, and M categories which was based on the JPS staging system[4].

Treatment

Multidisciplinary therapy centering on the role of surgery will need to be established[4]. Surgical resection is the most common treatment for a resectable pancreatic ACC[4,6,11]. Kitagami et al.[4] reported that in 115 patients with ACC, the tumors were resectable in 76.5% of the patients, and the 5-year survival rate after resection was favorable at 43.9%. The 5-year survival rate for unresected cases was 0, with a mean survial time (MST) of 3 months. A significant difference was identified between resected and unresected cases ($P < 0.0001$). Holen et al.[11] reported that in 39 patients with ACC, approximately half the patients had metastatic disease at the time of presentation. Patients who were amenable to surgery had a 36 months median survival as opposed to 14 months in patients who did not receive surgery.

No established chemotherapeutic regimens have been reported for adjuvant therapy after the curative resection or for recurrence[11]. Kitagami et al.[4] proposed that if ACC is unresectable or recurrent, chemotherapy is likely to prove useful. Chen et al.[64] reported on the effectiveness of concurrent chemoradiation therapy for a patient with AFP-producing ACC, and Kobayashi et al.[65] indicated that intraperitoneal chemotherapy of CDDP after en-bloc resection was effective for intraperitoneal recurrence of ACC. Ukei et al.[66] and Hashimoto et al.[67] reported the effectiveness of intraarterial chemotherapy using 5-fluorouracil (5FU), cisplatin (CDDP), and mitomycin C (MMC) for cases of pancreatic ACC with liver metastases, respectively; and the patients survived for a long time. However, the optimal strategies of cases with synchronous or recurrent liver metastases remain unknown because of a paucity of available information.
Case reports have demonstrated some success with concurrent chemotherapy and radiotherapy which will likely be further elucidated as more data are obtained[11, 68].

Prognosis

Although not widely accepted, the patient's age, sex, size of the tumor, stage of the disease, surgery, and levels of serum lipase were found to correlate with sur-

vival[4,6,11].

Because of recent advances in diagnostic imaging and surgical techniques, resection has been actively performed, and long-term survival has been reported[11,65,69,70]. Kitagami et al.[4] showed in their study that the 5-year survival rate of 87 resected patients was 43.9%, with a MST of 41 months. These figures are more favorable when compared with resected DCC patients that had a 5-year survival rate of 12.2% and MST of 8.7 months[71]. But the 5-year survival rate for unresected cases was 0%, with a MST of 3 months.

Some series have estimated ACCs to be equally as aggressive as pancreatic ductal adenocarcinomas of the pancreas[72,73], and some have estimated ACCs to be more indolent, similar to the neuroendocrine pancreatic tumors[74]. Klimstra et al.[6] reported a 1-year survival of 57%, 3-year survival of 26%, and 5-year survival of 5.9% compared to 11.9% 1-year survival and 2%~4% 5-year survival for ductal adenocarcinoma patients[75]. Thus, short-term survival is better for ACC, but long-term survival is poor for both tumors[11]. Among 39 patients with ACC, the median survival was 19 months. This median survival falls between that of ductal adenocarcinoma (6 months) and endocrine neoplasms of the pancreas (40~60 months).

Conclusion

ACC will remain a challenging problem to us. Improvements in early detection, screening, and staging of patients will be expected to facilitate progress in the management of patients with this disease. Multidisciplinary therapy centering on the role of surgery will need to be established. Most promising is the potential of basing treatment on our rapidly evolving understanding of the molecular biology of ACC.

References

1 Khalili M, Wax BN, Reed WP, et al. Radiology-pathology conference. Acinar cell carcinoma of the pancreas. Clin Imaging 2006; 30: 343-346.
2 Chen JD, Wu MS, Tien YW, et al. Acinar cell carcinoma with hypervascularity. J Gastroenterol Hepatol 2001; 16: 107-111.
3 Kuerer H, Shim H, Pertsemlidis D, et al. Functioning pancreatic acinar cell carcinoma: immunohistochemical and ultrastructural analyses. Am J Clin Oncol 1997; 20: 101-107.
4 Kitagami H, Kondo S, Hirano S, et al. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from Pancreatic Cancer Registry of Japan Pancreas Society. Pancreas 2007; 35: 42-46.
5 Hoorens A, Lemoine NR, McLellan E, et al. Pancreatic acinar cell carcinoma. An analysis of cell lineage markers, p53 expression, and Ki-ras mutation. Am J Pathol 1993; 143: 685.
6 Klimstra DS, Heffess CS, Oertel JE, et al. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol 1992; 16: 815-837.
7 Chiou YY, Chiang JH, Hwang JI, et al. Acinar cell carcinoma of the pancreas: clinical and computed tomography manifestations. J Comput Assist Tomogr 2004; 28: 180-186.
8 Shi HY, Wei LX, Li XH, et al. Pancreatic acinar cell carcinoma: a clinicopathological analysis of 14 cases. J Clin Exp Pathol 2005; 20: 419-421 (Chinese).
9 Abraham SC, Wu TT, Hruban RH, et al. Genetic and immunohistochemical analysis of pancreatic acinar cell carcinoma: frequent allelic loss on chromosome 11p and alterations in the APC/ß-catenin pathway. Am J Pathol 2002; 160: 953.
10 Jones PG, Campbell PE, eds. Tumors of Infancy and Childhood. London: Blackwell Scientific Publications. 1976; pp662.
11 Holen KD, Klimstra DS, Hummer A, et al. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. J Clin Oncol 2002; 20: 4673 - 4678.
12 Rigaud G, Moore PS, Zamboni G, et al. Allelotype of pancreatic acinar cell carcinoma. Int J Cancer 2000; 88: 772-777.
13 Moore PS, Orlandini S, Zamboni G, et al. Pancreatic tumours: molecular pathways implicated in ductal cancer are involved in ampullary but not in exocrine nonductal or endocrine tumorigenesis. Br J Cancer 2001; 84: 253-262.
14 Quaife CJ, Pinkert CA, Ornitz DM, et al. Pancreatic neoplasia induced by ras expression in acinar cells of transgenic mice. Cell 1987; 48: 1023-1034.
15 Konish Y, Denda A, Inui S, et al. Production of pancreatic acinar cell carcinoma by combined administration of 4-hydroxyaminoquinoline 1-oxide and azaserine in partial pancreatectomized rats. Cancer Lett 1978; 4: 229-234
16 Longnecker DS. Lesions induced in rodent pancreas by azaserine and other pancreatic carcinogens. Environ Health Perspect 1984; 56: 245-251.
17 Schaeffer BK, Terhune PG, Longnecker DS. Pancreatic carcinomas of acinar and mixed acinar/ductal phenotypes in Ela-1-myc transgenic mice do not contain c-K-ras mutations. Am J Pathol 1994; 145: 696.
18 Klimstra DS, Adsay NV. Acinar Cell Carcinoma of the Pancreas: A Case Associated With the Lipase Hypersecretion Syndrome. Lippincott Williams & Wilkins, Inc. 2001; pp 121-126.
19 Morohoshi T, Kanda M, Horie A, et al. Immunocytochemical markers of uncommon pancreatic tumors. Acinar cell carcinoma, pancreatoblastoma, and solid cystic (papillary-cystic) tumor. Cancer 1987; 59: 739-747.
20 Tatli S, Mortele KJ, Levy AD, et al. CT and MRI features of pure acinar cell carcinoma of the pancreas in adults. Am J Roentgenol 2005; 184: 511-519.
21 Itoh T, Kishi K, Tojo M, et al. Acinar cell carcinoma of the pancreas with elevated serum alpha-fetoprotein levels: a case report and a review of 28 cases reported in Japan. Gastroenterol Jpn 1992; 27: 785-791.
22 Mizuta Y, Isomoto H, Futuki Y, et al. Acinar cell carcinoma of the pancreas associated with hypoglycemia: involvement of "big" insulin-like growth factor-II. J Gastroenterol 1998; 33: 761-765.
23 Illyés G, Luczay A, Benyó G, et al. Cushing's syndrome in a child with pancreatic acinar cell carcinoma. Endocrine Pathology 2007; 18: 95-102.
24 Huerta S, Arteaga J, Li Z, et al. Acinar cell carcinoma of the pancreas in a morbidly obese patient. Pancreas 2002; 25: 414-415.
25 Sun Y, Wasserman PG. Acinar cell carcinoma arising in the stomach: a case report with literature review. Hum Pathol 2004; 35: 263-265.

26 Mizuno Y, Sumi Y, Nachi S, et al. Acinar cell carcinoma arising from an ectopic pancreas. Surg Today 2007; 37: 704-707.
27 Ishizaki A, Koito K, Namieno T, et al. Acinar cell carcinoma of the pancreas: a rare case of an alpha-fetoprotein-producing cystic tumor. Eur J Radiol 1995; 21: 58-60.
28 Matsuyama T, Ogata S, Sugiura Y, et al. Acinar cell carcinoma of the pancreas eroding the pylorus and duodenal bulb. J Hepatobiliary Pancreat Surg 2004; 11: 276-279.
29 Webb JN. Acinar cell neoplasms of the exocrine pancreas. J Clin Pathol 1977; 30: 103-112.
30 Eriguchi N, Aoyagi S, Hara M, et al. Large acinar cell carcinoma of the pancreas in a patient with elevated serum AFP level. J Hepatobiliary Pancreat Surg 2000; 7: 222-225.
31 Cingolani N, Shaco-Levy R, Farruggio A, et al. Alpha-fetoprotein production by pancreatic tumors exhibiting acinar cell differentiation:study of five cases,one arising in a mediastinal teratoma. Hum Pathol 2000; 31: 938-944.
32 Itoh T, Kishi K, Tojo M, et al. Acinar cell carcinoma of the pancreas with elevated serum alpha-fetoprotein levels: a case report and a review of 28 cases reported in Japan. Gastroenterol Jpn 1992; 27: 785-791.
33 Shimizu E, Kikuyama M, Murohisa G, et al. J Jpn Soc Gastroenterol. 1996; 93:55Y60. (Japanese).
34 Radin DR, Colletti PM, Forrester DM, et al. Pancreatic acinar cell carcinoma with subcutaneous and intraosseous fat necrosis. Radiology 1986; 158: 67.
35 Mustert BR, Stafford-Johnson DB, Francis IR. Appearance of acinar cell carcinoma of the pancreas on dual-phase CT Am. J Roentgenol 1998; 171: 1709.
36 Sahani D, Prasad RS, Maher M, et al. Functioning acinar cell pancreatic carcinoma: diagnosis on mangafodipir trisodium (Mn-DPDP)-enhanced MRI. J Comput Assist Tomogr 2002; 26: 126-128.
37 Van Hoe L, Gryspeerdt S, Marchal G, et al. Helical CT for the preoperative localization of islet cell tumors of the pancreas: value of arterial and parenchymal phase images. AJR 1995; 165: 1437-1439.
38 Stafford Johnson DB, Francis IR, Eckhauser FE, et al. Dual-phase helical CT of nonfunction islet cell tumors. J Comput Assist Tomogr 1998; 22: 59.
39 Mergo PJ, Helmberger TK, Buetow PC, et al. Pancreatic neoplasms: MR imaging and pathologic correlation. RadioGraphics 1997; 17: 281-301.
40 Lim JH, Chung KB, Cho OK, et al. Acinar cell carcinoma of the pancreas. Ultrasonography and computed tomography findings. Clin Imaging 1990; 14: 301-304.
41 Buetow PC, Parrino TV, Buck JL, et al. Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cyst, calcification, imaging, malignant behavior, and functional status. AJR 1995; 165: 1175-1179.
42 Chung EM, Travis MD, Conran RM. Pancreatic tumors in children: radiologic-pathologic correlation. RadioGraphics 2006; 26: 1211-1238
43 Solcia E, Capella C, Kloppel G. Tumors of the exocrine pancreas. In: Rosai J, Sorbin L, eds. Atlas of Tumor Pathology, 3rd series, fasc. 20 Washington, DC: Armed Forces Institute of Pathology 1997; 31-144.
44 Longnecker DS, Shinozuka H, Dekker A. Focal acinar cell dysplasia in human pancreas. Cancer 2006; 45: 534-540.
45 Cubilla AL, Fitzgerald PJ. Morphological patterns of primary nonendocrine human pancreas carcinoma. Cancer Res 1975; 35: 2234-2248.
46 Morohoshi T, Held G, Kloppel G. Exocrine pancreatic tumours and their histological classification. A study based on 167 autopsy and 97 surgical cases. Histopathology 1983; 7: 645-661.
47 Solcia E, Capella C, Kloppel G. Tumors of the Pancreas. In: Rosai J, Sorbin L, eds. Atlas of Tumor Pathology, 3rd series, fasc. 20 Washington, DC: Armed Forces Institute of Pathology 1997; 103-114.
48 Fabre A, Sauvanet A, Flejou JF, et al. Intraductal acinar cell carcinoma of the pancreas. Virchows Arch 2001; 438: 312-315.
49 Hashimoto M, Matsuda M, Watanabe G, et al. Acinar cell carcinoma of the pancreas with intraductal growth: report of case. Pancreas 2003; 26: 306-312.
50 Stelow EB, Bardales RH, Shami VM, et al. Cytogy of pancreatic acinar cell carcinoma. Diagn Cytopathol 2006; 34: 367-372.
51 Labate AM, Klimstra D, Zakowski MF. Comparative cytologic features of pancreatic acinar cell carcinoma and islet cell tumor. Diagn Cytopathol 1997; 16: 112-116.
52 Ishihara A, Sanda T, Takanari H, et al. Elastase-1-secreting acinar cell carcinoma of the pancreas. A cytologic,electron microscopic and histochemical study. Acta Cytol 1989; 33: 157-163.
53 Klimstra DS, Wenig BM, Adair CF, et al. Pancreatoblastoma. A clinicopathologic study and review of the literature. Am J Surg Pathol 1995; 19: 1371-1389.
54 Chong JM, Fukayama M, Shiozawa Y. Fibrillary inclusions in neoplastic and fetal acinar cells of the pancreas. Virchows Arch 1996; 428: 261-266.
55 Hassan MO, Gogate PA. Malignant mixed exocrine-endocrine tumor of the pancreas with unusual intracytoplasmic inclusions. Ultrastruct Pathol 1993; 17: 483-493.
56 Tucker JA, Shelburne JD, Benning TL, et al. Filamentous inclusions in acinar cell carcinoma of the pancreas. Ultrastruct Pathol 1994; 18: 279-286.
57 Lebenthal E, Lev R, Lee PC. Prenatal and postnatal development of the human exocrine pancreas. In: Go VLW, Brooks FP, DiMagno EP, Gardner JD, et al, eds. The Exocrine Pancreas. Biology, Pathobiology, and diseases. New York: Raven 1986; 33-43.
58 Toyota N, Takada T, Ammori BJ, et al. Acinar cell carcinoma of the pancreas showing fingerprint-like zymogen granules by electron microscopy: immunohistochemicalstudy. J Hepatobiliary Pancreat Surg 2000; 7: 102-106.
59 Stephens DH. CT of pancreatic neoplasms. Part II: the unusual tumors. Curr Probl Diagn Radiol 1997; 26: 81-106.
60 Cantisani V, Mortele KJ, Levy A, et al. MR imaging features of solid pseudopapillary tumor of the pancreas in adult and pediatric patients. AJR 2003; 181: 395-401.
61 Skacel M, Ormsby HA, Petras RE, et al. Immunohistochemistry in the differential diagnosis of acinar and endocrine pancreatic neoplasms. Appl Immunohistochem Mol Morpho 2000; 8: 203-209.
62 Muramatsu T, Kijima H, Tsuchida T, et al. Acinar-islet cell tumor of the pancreas: report of a malignant pancreatic composite tumor. J Clin Gastroenterol 2000; 31: 175-178.
63 Tobita K, Kijima H, Chino O, et al. Pancreatic acinar cell carcinoma with endocrine differentiation: immunohistochemical and ultrastructural analyses. Anticancer Res 2001; 21: 2131-2134.
64 Chen CP, Chao Y, Li CP, et al. Concurrent chemoradiation is effective in the treatment of alpha-fetoprotein-producing acinar cell carcinoma of the pancreas: report of a case Pancreas 2001; 22: 326-329.
65 Kobayashi S, Ishikawa O, Ohigashi H, et al. Acinar cell carcinoma of the pancreas successfully treated by en

bloc resection and intraperitoneal chemotherapy for peritoneal relapse: a case report of a 15-year survivor. Pancreas 2001; 23: 109-112.
66 Ukei T, Okagawa K, Uemura Y, et al. Effective intra-arterial chemotherapy for acinar cell carcinoma of the pancreas. Dig Surg 1999; 16: 76-79.
67 Hashimoto M, Miki K, Kokudo N, et al. A long-term survivor of metastatic acinar cell carcinoma. Pancreas 2007; 34: 271-272.
68 Lee JL, Kim TW, Chang HM, et al. Locally advanced acinar cell carcinoma of the pancreas successfully treated by capecitabine and concurrent radiotherapy: report of two cases. Pancreas 2003; 27: e18-22.
69 Kuopio T, Ekfors TO, Nikkanen V, et al. Acinar cell carcinoma of pancreas. Report of three cases. APMIS 1995; 103: 69-78.
70 Riechelmann RP, Hoff PM, Moron RA, et al. Acinar cell carcinoma of the pancreas. Int J Gastrointest Cancer 2003; 34: 67-72.
71 Matsuno S, Egawa S, Fukuyama S, et al. Pancreatic Cancer Registry in Japan: 20 years of experience. Pancreas 2004; 28: 219-230.
72 Kloppel G, Pancreatic non-endocrine tumors, In: Kloppel G, Heitg Fu, eds. Pancreatic Pathology. Edinbargh: Churchill Livingstone 1984; 17-113.
73 Zinner MJ, Shurbaji MS, Cameron JL. Solid and papillary epithelial neoplasms of the pancreas. Surgery 1990; 108: 475-480.
74 Hartman GG, Ni H, Pickleman J. Acinar cell carcinoma of the pancreas. Arch Pathol Lab Med 2001; 125: 1127-1128.
75 Ivy EJ, Sarr MG, Reiman HM. Nonendocrine cancer of the pancreas in patients under age forty years. Surgery 1990; 108: 481-487.