Islet Cell Tumors of the Pancreas: Pathologic–Imaging Correlation Among Size, Necrosis and Cysts, Calcification, Malignant Behavior, and Functional Status

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OBJECTIVE. The purpose of our study was to correlate the imaging and pathologic features of islet cell tumors with regard to tumor size, necrosis and cysts, calcification, malignant behavior, and functional status.

MATERIALS AND METHODS. We retrospectively reviewed the clinical, pathologic, and imaging features of all 133 cases of pathologically proved islet cell tumors of the pancreas seen at the Armed Forces Institute of Pathology. Clinical data, including the patients' symptoms and serologic characteristics, were used to distinguish hyperfunctioning tumors (those causing symptoms related to elevated serum polypeptide levels) from nonhyperfunctioning tumors; hyperfunctioning tumors were divided further into insulin-producing and non–insulin-producing types. All patients had at least one cross-sectional imaging study, including CT (n = 118), sonography (n = 42), or MR imaging (n = 22). Clinical, pathologic, and imaging features were evaluated and correlated with tumor size, necrosis and cysts, calcification, local invasion, vascular invasion, metastases, and functional status.

RESULTS. Islet cell tumors with areas of necrosis or cystic change found pathologically and on imaging studies (56/133) were larger (8.4 cm in mean transverse diameter) than homogeneous solid lesions (2.9 cm in mean transverse diameter) and were predominantly non–insulin producing (48/56) and nonhyperfunctioning (36/56). Of the 43 insulinomas, 35 were small (2.2 cm in mean transverse diameter), solid, and homogeneous. Larger size also was associated with calcification and malignant behavior, including local invasion, vascular invasion, and distant metastases.

CONCLUSION. Our findings show that cystic and necrotic islet cell tumors are usually non–insulin-producing and nonhyperfunctioning neoplasms and larger than the typically solid and small insulinomas. Calcification, local invasion, vascular invasion, and metastatic disease are more commonly seen with larger neoplasms.

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Islet cell tumors constitute a broad group of endocrine neoplasms. They are best divided on clinical grounds into those that are hyperfunctioning (the so-called functioning islet cell tumors) and those that are nonhyperfunctioning (the so-called nonfunctioning islet cell tumors). One would expect hyperfunctioning tumors to be manifested earlier and to be small in comparison with nonhyperfunctioning tumors, which one would expect to be manifested later by virtue of mass effect, local invasion, or metastases. Furthermore, one would expect larger tumors to have areas of necrosis or cystic degeneration. We studied the imaging and pathologic features of 133 cases and correlated the findings of size, necrosis and cysts, calcification, malignant behavior, and functional status of the islet cell tumors.

Materials and Methods

We retrospectively reviewed the clinical records, radiologic appearance, and pathologic findings of all 133 islet cell tumors studied by cross-sectional imaging at the Armed Forces Institute of Pathology between January 1980 and January 1994. These tumors occurred in 124 patients; multiple tumors were found in seven patients. All cases were pathologically proved by surgical resection or surgical inspection and by biopsy results. Results of immunohistochemical staining performed to determine specific hormone production within each tumor

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Clinical data regarding the patients' presenting signs and symptoms were recorded. Criteria used to diagnose functioning islet cell tumors were as follows: insulinoma—symptomatic hypoglycemia with inappropriately elevated plasma insulin levels; gastrinoma—symptoms and signs of peptic ulcer disease and elevated serum gastrin levels; glucagonoma—diabetes mellitus, dermatitis, and painful glossitis; somatostatinoma—elevated serum somatostatin levels, diabetes mellitus, gallbladder disease, and steatorrhea; vipoma—profuse secretory diarrhea and elevated vasoactive intestinal polypeptide levels; and adrenocorticotropin hormone (ACTH)-producing tumors—Cushing's syndrome. Tumors causing slightly elevated serum peptide levels or positive immunohistochemical staining results but not causing symptoms were classified as nonhyperfunctioning tumors. Tumors causing elevated pancreatic polypeptide levels also were classified as nonhyperfunctioning tumors. Three patients with type 1 multiple endocrine neoplasia syndrome had gastrinomas.

One hundred eighteen patients had CT, 42 had sonography, and 22 had MR imaging. Imaging features were analyzed independently by two radiologists and were correlated with pathologic and surgical findings. These features included the size and location of the mass; the presence of cystic changes; findings of local invasion into surrounding organs or adenopathy; vascular invasion into the splenic vein, superior mesenteric vein, or splenic artery; and the presence of metastatic disease involving the liver or other distant organs. MR imaging and CT findings also were used to identify solid nonenhancing areas and solid homogeneously enhancing masses. CT alone was used to detect the presence of calcification. Any discrepancies were resolved by consensus. With regard to location, in two cases in which the lesions were extremely large and replaced the entire pancreas, the center was recorded as being within the body of the pancreas. Imaging studies were performed on a wide variety of equipment over many years, and protocols regarding imaging parameters, contrast injections, and other details were not standardized.

Correlation was made among the description and photographs of the gross specimen, the histopathologic findings, and the internal morphology on imaging studies. Tumors were classified as solid homogeneous masses when no necrosis or cystic change was seen pathologically and when a uniform solid tumor was identified by CT, sonography, or MR imaging. All the remaining tumors were classified as heterogeneous and as having areas of necrosis; some of these tumors were classified further as cystic. Tumors were classified as cystic when fluid-filled or empty cavities were seen pathologically and were correlated with areas of water density on CT scans, anechoic areas with acoustic enhancement on sonograms, or areas of water signal intensity on T1- and T2-weighted MR images. Correlation also was made between the imaging and pathologic findings for the clinically hyperfunctioning tumors (which were grouped as insulin producing and non–insulin producing) and the nonhyperfunctioning tumors.

Results

The sizes, imaging features, and distribution of the various hyperfunctioning and nonhyperfunctioning islet cell tumors are given in Table 1. Of the hyperfunctioning islet cell tumors, insulinomas were the most common and the smallest, with a mean diameter of 2.2 cm. Most insulinomas (35 of 43) were solid homogeneous masses (Fig. 1). All eight lesions that had

TABLE 1: Imaging Features of Hyperfunctioning and Nonhyperfunctioning Islet Cell Tumors

Tumor	No. of Patients	No. of Lesions	No. of Tumors with the Following Imaging Features[a]:							
			Size	SH	HE	C	CA	LI	VI	DM
Insulinoma	39	43	2	35	8	3	4	11	8	4
Gastrinoma	18	18	4	15	3	2	4	6	3	4
Glucagonoma	11	11	6	5	6	6	2	4	2	6
Stomatostatinoma	5	5	7	2	3	6	1	3	3	0
Vipoma	4	4	4	4	0	0	1	2	0	0
ACTH[b] producing	2	2	5	2	0	2	2	2	2	0
Non–insulin producing[c]	40	40	5	28	12	12	10	17	7	12
Nonfunctioning	45	50	8	14	36	27	15	24	13	11
Total	124	133	5	77	56	42	30	52	28	27

[a] Size = mean diameter in centimeters, SH = solid homogeneous appearance, HE = heterogeneous appearance, C = cystic appearance, CA = calcification, LI = local invasion, VI = vascular invasion, DM = distant metastases.
[b] ACTH = adrenocorticotropin hormone.
[c] Subtotal for functioning tumors, excluding insulinomas.

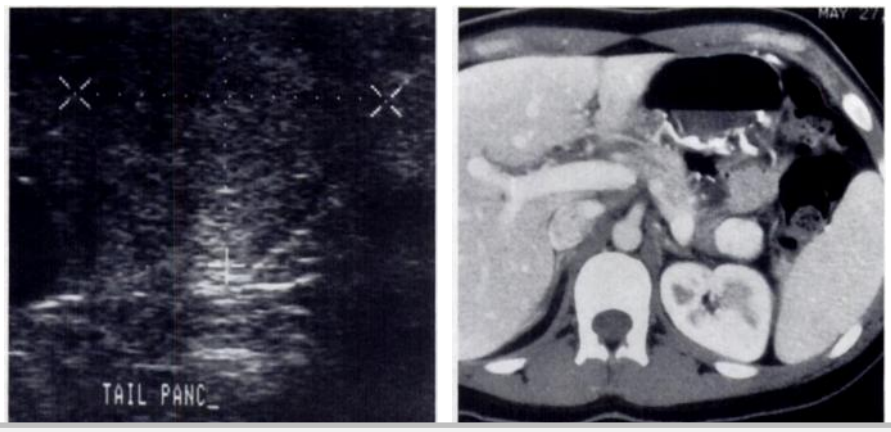
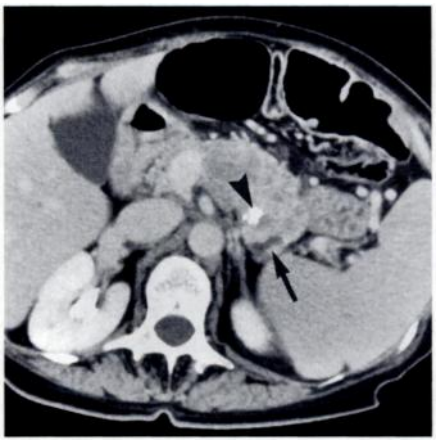


Fig. 1.—22-year-old woman who had insulinoma and whose symptoms included confusion, agitation, blurred vision, and hypoglycemia. Insulinomas are usually small solid lesions, as in this case.
***A*, Intraoperative sonogram shows solid isoechoic mass within tail of pancreas (TAIL PANC); mass measured approximately 2 cm in diameter.**
***B*, Contrast-enhanced CT scan shows homogeneously enhancing solid mass within tail of**

cystic components seen on gross examination and on imaging studies were larger than the mean. Calcification, local invasion, vascular invasion, and distant metastases were less common than with nonhyperfunctioning tumors.

The 18 gastrinomas were larger than the insulinomas (mean diameter, 4.2 cm). The majority of these lesions (15 of 18) also were solid homogeneous masses. The three lesions that had cystic characteristics measured 1, 6, and 3 cm. Vipomas were similar in size to gastrinomas (4.1 cm) and were all solid homogeneous masses. The other hyperfunctioning islet cell tumors, including glucagonomas, somatostatinomas, and ACTH-producing tumors, were larger (Figs. 2 and 3).

The nonhyperfunctioning islet cell tumors had a mean diameter of 7.7 cm. Thirty-six of these tumors had heterogeneous areas, and over half (n = 27) had cystic degeneration (Fig. 4). Only 14 of the 50 nonhyperfunctioning tumors were



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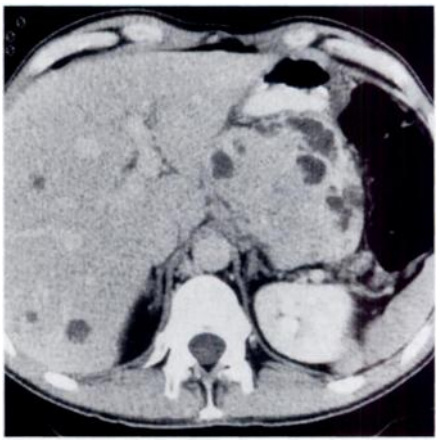

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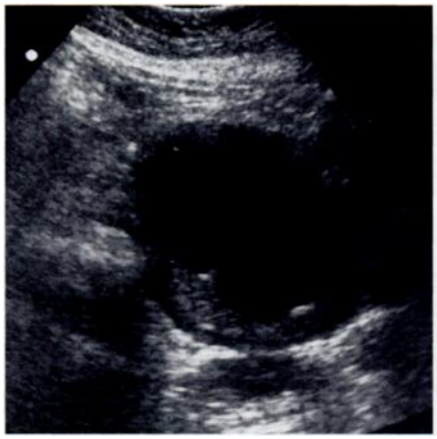
Fig. 2.—69-year-old woman who had glucagonoma and whose symptoms included rash and painful glossitis. Six-centimeter mass noted within tail of pancreas had crescentic area of cystic degeneration (*arrow*). Note central area of calcification (*arrowhead*). Note also evidence of vascular invasion into splenic vein, with multiple perisplenic varices. Metastasis was noted within liver (*not shown*). These findings were documented at attempted surgical resection. Calcification and vascular invasion are common findings with such non–insulin-producing tumors as well as with nonhyperfunctioning islet cell tumors.

Fig. 3.—42-year-old man who had necrotizing migratory erythema caused by glucagonoma. CT scan shows 10-cm heterogeneous mass with internal focus of cystic degeneration. Hypodense liver metastases also were noted. Cystic degeneration and metastatic disease are common findings with nonhyperfunctioning islet cell tumors as well.



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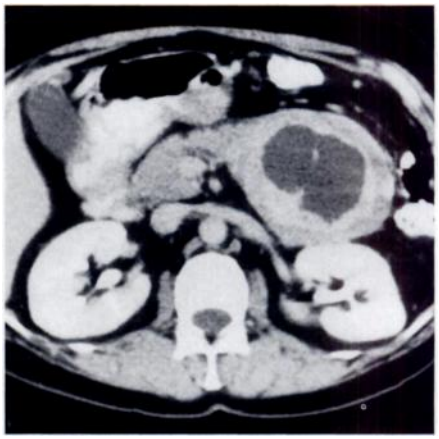

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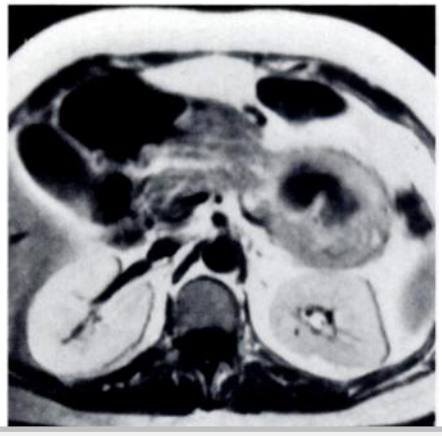


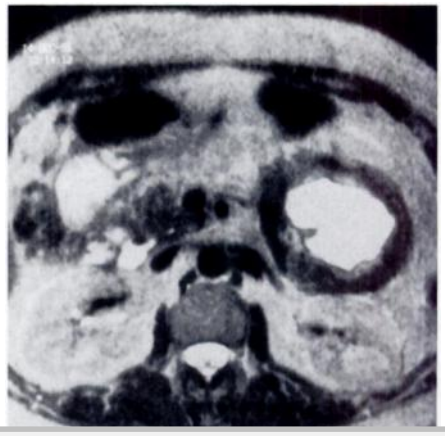
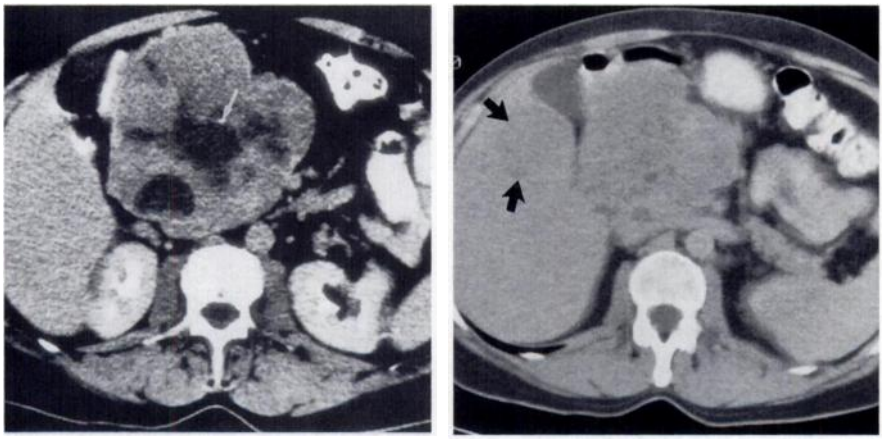


Fig. 4.—45-year-old man who had nonfunctional islet cell tumor and whose symptoms included 8-month history of vague abdominal pain. Large lesions such as this one are predisposed to cystic degeneration and aggressive behavior (splenic vein invasion was noted on this image as well as on other images [*not shown*]).

***A*, Sonogram shows well-circumscribed 10-cm mass with large anechoic central area and acoustic enhancement compatible with cystic degeneration.**

***B*, Contrast-enhanced CT scan shows central area of fluid attenuation similar to attenuation of gallbladder. Thick line of enhancing viable tumor was noted around periphery.**

***C* and *D*, Contrast-enhanced T1-weighted (6851/15 [TR/TE]) (*C*) and T2-weighted (6751/90) (*D*) axial MR images confirm central cystic degeneration. Decreased signal intensity on T1-weighted image and markedly increased signal intensity on T2-weighted image parallel signal intensity of CSF. Enhancing viable tumor was noted peripherally on contrast-enhanced T1-weighted image (*C*).**



A B

Fig. 5.—60-year-old man with nonhyperfunctioning islet cell tumor. Tumor shows cystic degeneration, calcification, and liver metastasis.

***A*, Lobulated 13-cm mass was noted within head of pancreas. Note central areas of cystic degeneration with attenuation similar to that of gallbladder. Small punctate area of calcification also was noted (*arrow*).**

***B*, Unenhanced CT scan shows large metastasis within right lobe of liver (*arrows*), typical feature of nonhyperfunctioning islet cell tumors.**

solid homogeneous masses. Local invasion, vascular invasion, calcification, and distant metastases were more common than with insulinomas (Fig. 5).

Twenty-seven of the 40 tumors with cystic components were nonhyperfunctioning islet cell tumors. Heterogeneous areas corresponding to necrosis or cystic degeneration were noted in 56 tumors with a mean diameter of 8.4 cm. The mean diameter of the cystic tumors was 7.9 cm. Thirty-six of the tumors with heterogeneous areas were nonhyperfunctioning islet cell tumors. Solid homogeneous masses were seen in 76 cases. Only 14 of these lesions were nonhyperfunctioning islet cell tumors. The mean diameter of the solid homogeneous tumors was 2.9 cm.

Using an analysis of variance and Duncan's multiple-range test, we found the difference in mean diameter between the two largest groups, insulinomas and nonhyperfunctioning tumors, to be statistically significant (p = .0001). Using a t test, we found a statistically significant correlation between the size of the tumors and whether they were cystic (p < .0005), solid homogeneous (p = .0001), or heterogeneous (p = .0001). Similarly, we found statistically significant differences in size between tumors that were cystic (mean diameter, 7.9 cm) or heterogeneous (mean diameter, 8.4 cm) and solid homogeneous tumors (mean diameter, 2.9 cm) (p = .0001 for both comparisons).

A statistically significant correlation between the size of the tumors and the presence of all the characteristics that we analyzed also was documented: calcification (mean diameter, 8.2 cm) (p < .00005), local invasion (mean diameter, 6.5 cm) (p = .00006), and vascular invasion (mean diameter, 7.2 cm) (p = .0019). The larger the tumor, the more likely it was to contain all of these features.

We also found statistically significant differences in the internal morphology of the tumors, depending on whether they were hyperfunctioning or nonhyperfunctioning. Heterogeneity was significantly correlated with nonhyperfunctioning tumors (p < .0005, χ^2 test).

Liver metastases were least common with insulinomas. Liver metastases were seen with both ACTH-producing tumors, with six of 10 glucagonomas (Fig. 3), and with 11 of 50 nonhyperfunctioning islet cell tumors (Fig. 5).

Discussion

All islet cell tumors are capable of producing polypeptides. Although individual tumors may elaborate more than one hormone to various degrees in different parts of the tumor, the vast majority of patients have symptoms related to the overproduction of a single hormone or have no hormone-related symptoms at all [1–5]. However, because of this variability, islet cell tumors can be divided, on clinical grounds, into hyperfunctioning and nonhyperfunctioning tumors. Hyperfunctioning tumors may be subdivided into insulin-producing and non–insulin-producing types.

Our data demonstrate that size, function, consistency, and malignant behavior are integrally related. The most common hyperfunctioning islet cell tumors, the insulinomas, were typically small homogeneous masses measuring about 2 cm in diameter. Cystic changes and necrosis were uncommon features. On the other hand, nonhyperfunctioning islet cell tumors were typically larger, heterogeneous tumors with a propensity for cystic degeneration and central areas of necrosis; these tumors measured almost 8 cm in diameter. These differences were statistically significant, although there was some overlap. The other hyperfunctioning islet cell tumors, including gastrinomas, glucagonomas, somatostatinomas, vipomas, and ACTH-producing tumors, were, as a group, larger than the insulinomas and shared a number of the characteristics noted for nonhyperfunctioning islet cell tumors.

In our study, larger tumors, regardless of their hyperfunctioning or nonhyperfunctioning status, were more likely to be associated with cystic and necrotic areas, calcification, local invasion, vascular invasion, and liver or distant metastases. Other associations, in fewer patients, have been found between nonhyperfunctioning tumors and the presence of calcification [6, 7], increased size and necrosis [8], and metastases [9]. Seven of 10 islet cell tumors with calcification were shown to have malignant characteristics [10]. Venous invasion was shown in 10 of 76 patients with islet cell tumors; seven of these 10 patients had hepatic metastases [11]. However, not all of these findings have been specifically addressed in a large series and correlated with the size, consistency, and functional status of the

tumor, as we have done in this study. Larger surgical and pathologic series have not addressed these associations directly [6, 7, 12, 13].

Direct correlation between the size of the tumor and cystic or necrotic areas has not yet been formally addressed, probably because the research done so far has included predominantly surgical series in which the external appearance was emphasized [12]. Cross-sectional imaging allows assessment of the internal structure as well. Before this study, cystic changes within islet cell tumors were viewed as rare, with only 20 cases previously being reported [14]—partly because the surgical community is not familiar with these tumors [15] and partly because the tissue examined by pathologists and prepared for slides is, appropriately, from the solid portion of the tumor. Also, these earlier reports concerned tumors that were predominantly cystic, not partially cystic.

The cases considered in this study were collected from a large referral population. Thus, our findings are unavoidably biased in that regard. However, the proportion of hyperfunctioning islet cell tumors in our series parallels that noted in larger epidemiologic studies [5, 16, 17], supporting the veracity of the sampling even if it was not from a single patient population. An additional deficiency is that the imaging studies and protocols were acquired without the benefit of standardized equipment. However, our analysis of the gross specimens and surgical reports helped ensure that the radiologic interpretation of these cases was correct.

In summary, we have demonstrated an association among size, consistency, behavior, and function of islet cell tumors. Smaller tumors tend to be homogeneous masses without local invasion or distant metastases and typically are insulinomas. Larger tumors more commonly demonstrate cystic changes, necrosis, calcification, local invasion, vascular invasion, and distant metastases and are nonhyperfunctioning lesions or are associated with a less clinically evident functional syndrome than that seen with insulinomas. Knowledge of these features is important to radiologists in identifying and characterizing masses within the pancreas.

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