INTRAOPERATIVE ULTRASONOGRAPHIC EVALUATION OF INSULINOMAS: AN UPDATE*

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INTRODUCTION

The pancreas is a solid organ and should be easily demonstrated by ultrasonography(1). However, because of its retroperitoneal localization with anteposition of hollow viscera, the gas present in the viscera may complicate its study by means of ultrasonography(2).

During abdominal surgeries, the bowel loops can be manually moved apart, and the transducer can be placed directly on the pancreas surface, resulting in an increment of the image quality(2).

In this article, the authors review the role of the intraoperative ultrasonography (IOUS) in the evaluation of pancreatic insulinomas, comparing its applicability with that of other methods like ultrasound (US) and computed tomography (CT), as well as establishing a correlation with surgical staging data.

DISCUSSION

Hormone-secreting pancreatic tumors with clinical repercussions are rarely seen. The occurrence of these tumors is estimated in about four to five cases per million inhabitants(3). However, they awake a great clinical interest because of the different syndromes they may produce as a result of their excessive hormone production(3).

The treatment of these lesions has caught both clinicians and surgeons’ attention, and, currently, the most appropriate approach is the multidisciplinary one, involving endocrinologists, gastroenterologists, surgeons and oncologists(3). Usually the therapy is aimed at controlling the increased hormone secretion, and the tumor resection afterwards. In case of metastasis, chemotherapy represents an alternative at-tending endocrinologists, gastroenterologists, surgeons and oncologists(3).

In the literature, one may find that endocrine cells of the digestive system are derived from neural crest cells and present common features in relation to biochemical and ultrastructural aspects related to the synthesis of amines and peptides(3,4). These cells are considered as pertaining to the APUD (amine precursor uptake and decarboxilation) concept(3).

It should be reported that there are experimental evidences discussing the origin of the gastroenteropancreatic APUD cells in the neural crest(5). Notwithstanding, in spite of this controversy, the application of the APUD system concept explains the diversity of syndromes associated with endocrine pancreatic tumors(3).

The term APUD originates from the three initial letters of the words in English designating three important characteristics of these cells: 1) high amines concentration; 2) amine precursor uptake capacity; 3) presence of an amino acid decarboxylase(3). They are widely distributed in different locations of the organism such as the central nervous system, thyroid (parafollicular cells), pancreas, bowel, supra-renal medulla and urogenital tract(6).

Tumors originating from APUD cells may be called “apudomas”. Endocrine pancreatic tumors contain APUD system cells and, therefore, may be considered as apudomas(3).

At least five types of pancreatic islet cells are found in the normal pancreas. Each type produces a different peptide or...
amine. Beta cells produce insulin, alpha cells produce glucagon; gamma cells, somatostatine; F cells, pancreatic polypeptide; and enterochromafin cells produce serotomine.

Insulinaomas are the most frequent neuroendocrine pancreatic tumors and usually are of benign nature. Gastrinoma is the second more frequent neuroendocrine pancreatic tumor, and 60% of them, or more, may be of malignant nature.

Hormone secreting tumors, like insulinaomas, gastrinomas and glucagonomas, may produce identifiable clinical syndromes as a consequence of the excessive hormones production. The presence of these symptoms determines an earlier presentation than the usual presentation of other pancreatic neoplasms. So, usually, these tumors are small, frequently measuring less than 1.5 cm.

On the other hand, somatostatinomas and neuroendocrine tumors producing pancreatic polypeptide define the presentation of no or few symptoms, although, at the moment of diagnosis, they may present large dimensions.

The insulinaomas were the first pancreatic neuroendocrine tumors to be identified, as reported by Whipple & Frantz. The most important finding in cases of insulinaomas is the prevalence of high levels of autonomous insulin secretion in the presence of concurrent hypoglycemia. This behavior leads to a diagnosis based on the finding of high fasting (72 hours) levels of plasmatic insulin. Consequently, they cause hypoglycemia and symptoms characteristic of the hypoglycemic syndrome. A wide variety of symptoms may occur, including tremor, flutter, irritability, weakness, hunger, sweating, tachycardia and, occasionally, nausea and emesis. Additionally, behavioral and consciousness disturbances may occur. More severe cases may progress to unconsciousness and coma as a result of hypoglycemia. As a result of these behavioral disturbances, about 20% of patients are initially misdiagnosed with psychiatric or neurological disorders.

Insulinaomas may occur at any age range, but the greatest majority occurs between 30 and 60 years of age. Similarly, Machado et al. report a casuistic with 54.2% of patients in this age range, with 94.8% with less than 60 years.

As regards sex, insulinaomas would have a slight incidence in females. Other authors, like Norton et al., have observed an even higher (about 83%) incidence in females.

Most of insulinaomas are benign and small, and in 80%-90% of cases are solitary lesions. Comi et al. also report that insulinaomas usually are intrapancreatic (about 100%) and small (less than 2 cm). Others report benign insulinaomas with less than 1.5 cm in 70% of cases. Approximately 10% of insulinaomas are malignant and present with metastasis at the moment of diagnosis.

Multiple and benign lesions may occur in about 10% of cases, and are more frequent in patients with MEN type I syndrome (multiple endocrine neoplasia). Some authors, like Welbourn et al., report that the number of patients with MEN type I would correspond to 5% of all the patients with insulinaomas.

Benign insulinaomas have no predilection to a specific site within the pancreas, and have been usually identified with the same frequency in different portions of the pancreas: head (30%), body (35%) and tail (35%). The tumors may be on the surface of the gland or within the pancreatic parenchyma. The majority of lesions is covered by a layer of pancreatic parenchyma and is typically firmer than the normal pancreas.

As regards patients with MEN-1, DeMeure et al. report the significance of a careful evaluation of these patients, considering the higher possibility of malignancy (about 20%) when compared with non-MEN-1-related sporadic insulinaomas (malignancy in about 10% of cases). They have observed that in patients with MEN-1 insulinaomas were multiple in 76% of cases.

Machado et al. have described cases where multiple insulinaomas in patients with MEN-1 were localized in the pancreatic body and tail in 87%. In this study, the patients underwent left pancreatectomy (caudal body) associated with enucleation in cases of concurrent cephalic lesions. This surgical alternative had already been previously proposed with excellent results.

At US, insulinaomas, in 90% of cases are small, well-defined, round, homogeneous and hypoechoic lesions. In Figures 1, 2, 3 and 4. The pancreatic tail presents a special difficulty for insulinaomas localization. Calcifications, configured as areas of higher echogenicity may, occasionally, be identified.

Norton et al. and Lo et al. have observed that insulinaomas may be of difficult localization due their small dimensions, and their correct identification, both preoperatively and during the surgical procedure is of paramount importance for their therapeutical management.

Machado et al. have described the IOUS as an extremely useful method for insulinaomas management, routinely utilized by the authors for allowing an adequate localization of lesions, with a correct definition of the pancreatic anatomy and for avoiding extensive pancreatic resections, besides identifying small-sized lesions usually missed by preoperative examinations.

Machado et al. have also observed that, notwithstanding the progress of diagnostic methods during the latest years, the identification of insulinaomas remains a difficult clinical problem both for clinicians and surgeons.

According to Norton et al. the main advantages of the IOUS for the treatment of benign insulinaomas include: precise operative localization; enucleation of nonpalpable, nonvisible tumors; and avoidance of ductal and vascular injuries as well as injuries to other vital structures by precise localization of adjacent vital structures. These authors have observed that the IOUS is capable of accurately identifying insulinaomas in a higher number than those identified by palpation.

Norton et al. have described a benign insulinaoma presenting at IOUS as typically hypoechoic and well-defined lesions in relation to the adjacent pancreatic parenchyma. Notwithstanding, these authors have described a case of an insulinaoma appearing to have an echogenicity pattern similar to the surrounding pancreas, thus making it difficult to visualize. On the other hand, even this isoechogenic tumor presented a sonolucent peripheral rim that allowed it to be successfully visualized.
These authors have reaffirmed that the pancreas evaluation should be precisely performed, with perpendicular and oblique insonation of pancreatic regions in order to maximizing the US scanning results, identifying pancreatic insulinomas. This careful and systematic evaluation allows the visualization of lesions with high diagnostic difficulty, as it can be observed in this case of an isoechoic insulinoma reported by the authors (19).

Norton et al. (19) have also demonstrated that IOUS has affected the surgical procedure, facilitating the excision of occult insulinomas, and in about 41% of cases the IOUS has allowed enucleation of cephalic insulinomas which could not be removed except by means of higher morbidity methods like duodenopancreatectomy. In these 41% of cases reported by the authors, IOUS has defined the incision, determining the most direct and shorter route to the tumor, without traversing the pancreatic duct or other vascular structures. Also, according these authors, after the surgical incision, the shortest route was continually reconfirmed by IOUS up to the complete enucleation of the lesion.

Doherty et al. (27), in a study with 25 patients, have concluded that IOUS was particularly useful for identifying cephalic pancreatic tumors detected in all the cases, and for definition of the relationship between the tumor and the pancreatic duct in the 25 patients evaluated. Additionally, IOUS was utilized to guide the dissection during enucleation both in cases of palpable and nonpalpable lesions. Also, they have affirmed that the higher significance of the IOUS is not in the fact of identifying lesions, but rather in the utility of this information for the success of the surgical procedure. Grant et al. (10) have corroborated such IOUS relevance, demonstrating its influence on the surgical conduct in 62% of the patients with insulinoma, also for the finding of nonpalpable lesions in the head of the pancreas in four of 29 patients.

In any of the surgical alternatives available for approaching insulinomas, it is defined that IOUS is of paramount significance for the evaluation of the pancreatic parenchyma, since it may guide the characterization of the pancreatic ducts and vascular structures (28), resulting in reliable anatomical information for definition of the surgical strategy.

It is very important to highlight that the major breakthrough in the localization of occult insulinomas is the use of IOUS. Some authors have reported their concern related to the results of the blind resection, a method until recently utilized. According to Norton et al. (19), in cases where insulinomas could not be identified, blind (distal, subtotal or even total) pancreatectomy would be performed with high morbidity, possibly resulting in pancreatitis, pancreatic fistulas, pancreatic abscesses and even progress to exocrine pancreatic failure and diabetes mellitus. On the other hand, Kaplan et al. (29) have also observed that blind distal pancreatic resections (caudal bodies) would have a 33% chance of not removing the insulinoma because some occult insulinomas will be in the pancreatic head. Norton et al. (19), reported a casuistic with 45% of cephalic insulinomas which would have not been successfully removed by blind distal pancreatectomy.
All of these difficulties were resolved with the utilization of IOUS to identify occult insulinomas, probably in association with a careful palpation of the pancreas.

Demeure et al.\textsuperscript{(33)} reported the possibility of demonstrating malignant and ectopic extrapancreatic insulinomas. Extrapancreatic insulinomas would occur in less than 1\% cases.

Brazilian and foreign authors concern in searching for a more accurate method for identifying pancreatic insulinomas is a result of the poor diagnostic capacity of preoperative examinations (US and CT) when compared with IOUS\textsuperscript{(10,16,27–30–34)} Many series report varied frequencies of preoperative US detection rates for insulinomas of 0\%\textsuperscript{(32)}, 26\%\textsuperscript{(27)}, 28.1\%\textsuperscript{(16)}, 29.5\%\textsuperscript{(33)}, 59\%\textsuperscript{(18)} and 62\%\textsuperscript{(31)}. Preoperative CT detection rates also vary, with some authors identifying low rates like those reported by Doherty et al.\textsuperscript{(27)}, of 17\%. Machado et al.\textsuperscript{(16)} have reported rates of about 25\% and Grant et al.\textsuperscript{(18)}, of 36\%. However, other studies report higher values, like those of Stark et al.\textsuperscript{(30)}, ranging between 50\% and 60\%.

As regards palpation, Kuzin et al.\textsuperscript{(33)} have reported a 90\% detection rate with this procedure. The precise localization of insulinomas by inspection/palpation depends on the surgeon experience. Doherty et al.\textsuperscript{(27)} have identified 64\% of insulinomas by means of palpation. Machado et al.\textsuperscript{(16)} have reported the detection of 98.2\% of cases by means of inspection/palpation, a result similar to those of other authors\textsuperscript{(35–37)}.

The literature review demonstrates that smaller the lesions to be evaluated, the greater will be the limitations of preoperative examinations. For insulinomas <1.00 cm, authors\textsuperscript{(33)} have demonstrated IOUS detection rate of about 10\%, and 20\% for preoperative CT. Kuzin et al.\textsuperscript{(33)}, considering only <1.00 cm insulinomas, have reported a 82\% detection rate with palpation.

In a recent study, Machado et al.\textsuperscript{(16)}, showed that IOUS, in association with palpation, allows a precise localization of in 100\% of cases, as previously reported in the literature by authors like Van Heerden et al.\textsuperscript{(38)} and Kisker et al.\textsuperscript{(37)}.

The clinicians and surgeons' confidence in the IOUS capacity of identifying pancreatic insulinomas has been publicized in several recent publications\textsuperscript{(16,34)}.

As a matter of fact, Machado et al.\textsuperscript{(16)} have affirmed that patients with a confirmed diagnosis for hyperinsulinism could be evaluated exclusively with conventional abdominal US associated with inspection/palpation during the surgery for insulinomas resection in association with IOUS, virtually succeeding in all the cases. Later complications, like diabetes, could be avoided by preserving a larger amount of pancreatic tissue.

Zeiger et al.\textsuperscript{(39)} have confirmed that IOUS is an unique and safe method for assisting in the localization of insulinomas and is supplementary and additional to the other diagnostic methods. As a result of the practice, the IOUS may reduce the use of other imaging methods, influence the decision making and the surgical conduct, allowing a complete resection of the primary pancreatic lesion and even the resection of possible associated metastases.

It is important to mention that some of our studies have been developed with the first publications in 1997, evidencing the applicability of the videolaparoscopic intraoperative ultrasound or conventional (non-videolaparoscopic) IOUS (with an open abdominal cavity – laparotomy) in the hepatobiliary/pancreatic surgical procedures\textsuperscript{(40–49)}.

CONCLUSIONS

The authors conclude that IOUS presents higher accuracy for identification of insulinomas when compared with other methods of preoperative staging, proving to be of high value during surgeries, effectively supplementing the surgical staging (palpation) itself.

REFERENCES

Intraoperative ultrasonographic evaluation of insulinomas