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Review Article

Pancreatic Ganglioneuroma: A Literature Review and Clinical Case

Stepanova YuA[1]*, Gurmikov BN[2], Gruzdev IS[3], Kalinin DV[4], Zhavoronkova OI[5], Shevchenko TV[6] and Ruzavin VS[6]

[1]Doctor of Medical Science, Professor, Leading Researcher, Ultrasound Diagnostics Department, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

[2]Doctor of Medical Science, Surgeon, Oncologist, Head of the Oncological Diseases Department of Surgical Methods for Treating, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

[3]Candidate of Medical Sciences, Research Associate at Roentgenology and Magnetic Resonance Department, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

[4]Candidate of Medical Sciences, Head of Pathological Anatomy Department, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

[5]Candidate of Medical Sciences, Senior Researcher, Ultrasound Diagnostics Department, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

[6]Candidate of Medical Sciences, Surgeon, Oncological Diseases Department of Surgical Methods for Treating, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

***Corresponding Author:** Stepanova YuA, Doctor of Medical Science, Professor, Leading Researcher, Ultrasound Diagnostics Department, A.V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia.

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Abstract

Pancreatic ganglioneuroma is an extremely rare pathology in routine medical practice without specifically formulated modern protocols and guidelines for diagnosis and treatment. Accurate diagnosis of pancreatic ganglioneuroma using instrumental methods at the preoperative stage is extremely difficult. Surgery resection with negative margins is the main treatment option and in most cases the only way to make a correct diagnosis.

We present our own clinical case of successful treatment of a 19-year-old woman with pancreatic head ganglioneuroma. A detailed path of diagnostic search, choice of surgical tactics, and the results of histological and immunohistochemical studies are presented.

Conclusion: In case of accidental detection of a pancreatic lesion that does not have distinctive radiology signs, ganglioneuroma should be considered in differential diagnostics even in older people, and biopsy is also justified.

Keywords: Pancreatic Ganglioneuroma, Diagnostics, Radiology Characteristics, Surgery Treatment, Morphology, Immunohistochemistry

Introduction

Ganglioneuroma (ganglioma, ganglion neuroma, gangliocytoma) is a benign tumor formed from elements of the sympathetic nerve nodes (ganglion). The mechanisms of ganglioneuroma development are not fully understood. Researchers suggest that certain disorders in the development of the sympathetic nervous system structures are involved in the development of the disease and are inclined to believe that the genetic factor plays a significant role in this issue [1]. Ganglioneuroma can have a variety of localizations. Most often, it is associated with various parts of the spine, can be located in the brain, less often - in the adrenal glands, gastrointestinal tract, skin, bladder wall [2-4]. Ganglioneuromas are more common in older children and young people, almost all cases are registered in people under 60 years old, more than 60% of cases occur in people under 20 years old [5,6]. They have both benign and malignant growth patterns, especially in children. They are capable of recurrence and metastasis [7].

Pancreatic localization of ganglioneuroma is extremely rare. M. Mazzola., *et al*. report that less than 10 similar cases have been published in the literature [3], although in fact they analyze only 5 cases and one of their own. The authors analyze various parameters of ganglioneuromas in the clinical cases they have identified. In other publications, in terms of statistics, all refer to this work in one form or another.

We analyzed publications in the Pubmed, SCOPUS, Uptodate.com, and eLIBRARY.RU databases and have identified 10 publications for the queries “pancreatic ganglioneuroma” and “ganglioneuroma of the pancreas” to date [3,6,8-15]. In one case, a ganglioneuroma of the posterior mediastinum was simultaneously identified [14], in two cases these were isolated cases within the framework of studies of ganglioneuromas of different localizations [6,12]. We also identified a clinical case of ganglioneuromatosis with simultaneous damage to the small intestine and pancreas of a child [16]. This indicates the possibility of multiple lesions.

In two cases, the literature presents cases of composite (or compound) pancreatic ganglioneuroma. F. Inzani., *et al*. reported a paraganglioma with a ganglioneuroma component [17]. S. Majumder., *et al*. described the case of a 34-year-old patient with neurofibromatosis type 1, who was also diagnosed with a paraganglioma with features of ganglioneuroma [18].

The extremely low incidence of ganglioneuromas determines significant scientific interest and the need to accumulate clinical experience on this type of tumor. We present our own experience in diagnosing and surgery a patient with the pancreatic head ganglioneuromas.

Clinical case of a woman I., 19 years old

- **Complaints:** Nagging pain in the epigastric region, weight loss of 4 kg in 3 months.
- **Anamnesis:** During treatment for community-acquired pneumonia five months ago, the patient noted nagging pain in the epigastric region. At her place of residence, MSCT was performed, where a neoplasm of the pancreatic head was detected. She contacted A.V. Vishnevsky National Medical Research Center of Surgery for consultation and determination of further treatment tactics.
- **Examination data upon admission:** General condition is satisfactory. Consciousness is clear, the patient is sociable, adequate, oriented in place, time and his own person. The skin is moderately pale, clean. Vesicular breathing in the lungs, no wheezing. Respiratory rate is 16 per minute. Heart sounds are muffled, rhythmic. HR is 76 beats per minute. BP = 120/70 mm Hg. The tongue is moist, clean. The abdomen is not distended, soft on palpation, painless in all areas. There are no peritoneal symptoms. The kidneys are not palpable, their projection is moderately painful on the right. The stool is regular, formed, of normal color. Urination is spontaneous, painless. At the time of treatment, the BMI was 22.15 kg/m^2.
- An examination was carried out.
- **Ultrasound:** In the projection of pancreatic head and body along its posterior surface a solid lesion up to 70.0 mm in the largest dimension is determined (Figure 1a). The lateral surface of the lesion contacting the porta hepatis and touching the gallbladder, the medial surface extending along the inferior vena cava. The lesion has reduced, fairly uniform echogenicity in B-mode. One vascular locus in the central part and several along the periphery are located in the lesion in Color Doppler Imaging (Figure 1b).

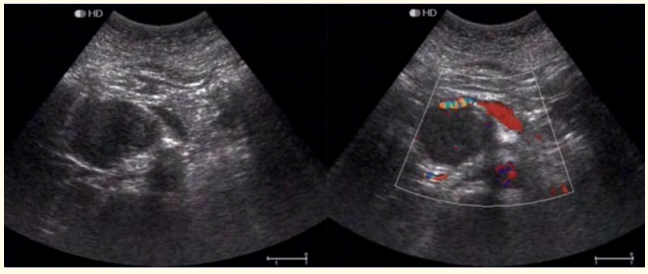

Figure 1: US-imaging of pancreatic head lesion: right - B-mode; left – Color Doppler Imaging.

Conclusion: Moderately vascularized pancreatic head tumor.

Consultation with MSCT performed at the place of residence

The lesion is visualized originating from the dorsal surface of pancreatic head, a solid structure, with a progradient gradual accumulation of contrast agent along the periphery to the delayed phase up to 60 HU (Figure 2), measuring 65×38×65 mm. Along the right contour, the lesion borders on the porta hepatis, gallbladder, descending part of the duodenum, compressing its lumen, without signs of invasion. The pancreaticoduodenal artery is traced fragmentarily, partially located in the structure of the tumor. The lesion displaces the portal vein anteriorly, the inferior vena cava posteriorly, without signs of invasion. There is contact of the lesion with the celiac trunk, common hepatic artery, right hepatic artery, superior mesenteric artery, without signs of invasion.

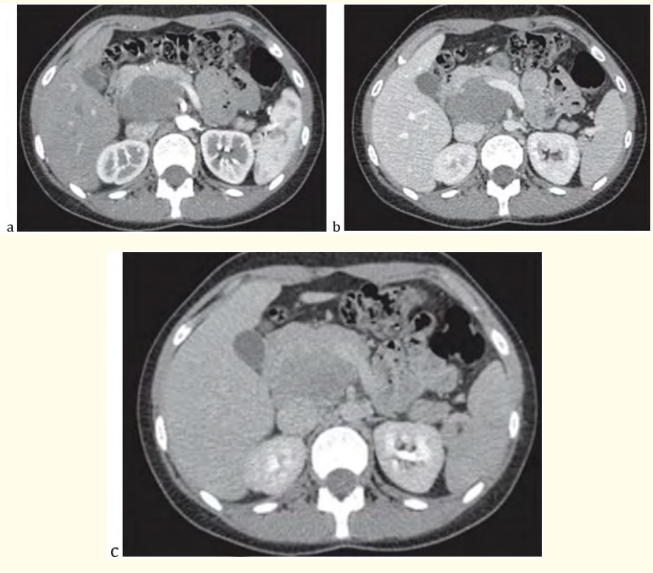

Figure 2: MSCT-images of the pancreatic head lesion: a - arterial phase; b - portal phase; c - delayed phase.

Conclusion: Solid tumor of pancreatic head, probably a solid pseudopapillary tumor.

Contrast-enhanced magnetic resonance imaging was performed to verify the diagnosis. The lesion is visualized, originating from the posterior surface of the pancreatic head, a solid structure (Figure 3a), gradually accumulating contrast agent towards the delayed phase more along the periphery, without signs of diffusion limitation (Figure 3 b-e).

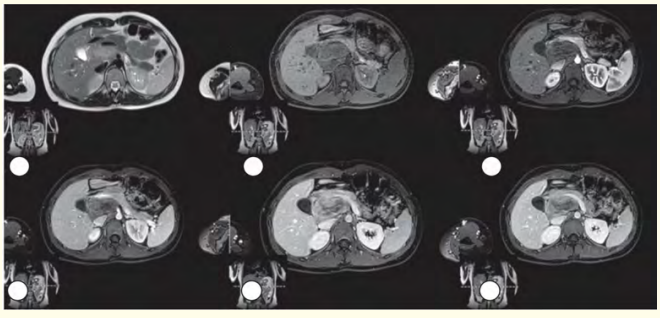

Figure 3: MRI-imaging of the pancreatic head lesion: a - T2 WI; b - eTHRIVE native; c-e - eTHRIVE with contrast enhancement sequentially.

Conclusion. Solid tumor of pancreatic head, probably a solid pseudopapillary tumor.

Laboratory diagnostics did not show any clinically significant deviations from reference values. The levels of tumor markers: CEA, AFP and CA19-9 were also within normal limits.

Based on the examination data, the patient was diagnosed with solid pseudopapillary tumor of the pancreas. Given the specific location of the neoplasm and its potentially malignant nature, a decision was made to perform pancreatoduodenal resection. As a result of which, during an urgent histological examination, no tumor elements were found at the resection margin of the pancreas.

Macroscopy

A massive lesion protruding into the parapancreatic tissue along the dorsal and medial surfaces, measuring 8×6×6 cm, was found in the pancreatic head (Figure 4a). A whitish-gray tumor with clear boundaries was found on the section in the area of the uncinate process of the head of the pancreas, spreading into the parapancreatic tissue along the dorsal and medial surfaces (Figure 4b). The tumor tissue is cord-like, with areas of myxoid changes.

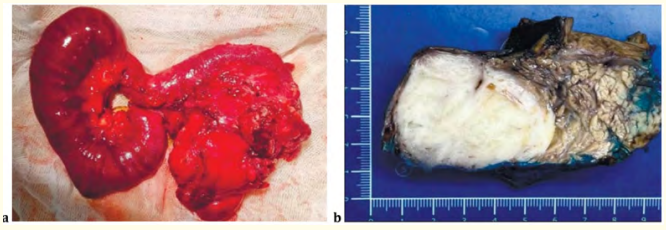

Figure 4: Macroscopy: a - removed pancreatoduodenal complex; b - ganglioneuroma of the pancreatic head on section, the tumor is of a stringy appearance, with a clear border, extending into the parapancreatic tissue along the dorsal (stained black) and medial (stained blue) surfaces.

Histology

A solid tumor of the pancreatic head consisting of multidirectional bundles of intertwined spindle-shaped and elongated cells with abundant light eosinophilic cytoplasm and ovoid normochromic nuclei with minimal signs of atypia (Figure 5A). Individual walled-up ganglion cells were found among the tumor bundles (Figure 5b). Foci of myxomatosis of the tumor stroma and focal lymphocytic infiltrates were noted. The number of mitoses was 0 per 50 RPC at 400 magnification. There were no foci of necrosis. The tumor extended to the head of the pancreas, the lymph node in the area of the uncinate process, and to the parapancreatic tissue along the dorsal and medial surfaces. The remaining lymph nodes of the parapancreatic tissue were not affected. The lymph nodes of the parapancreatic tissue and the regional removed lymph nodes were without tumor elements.

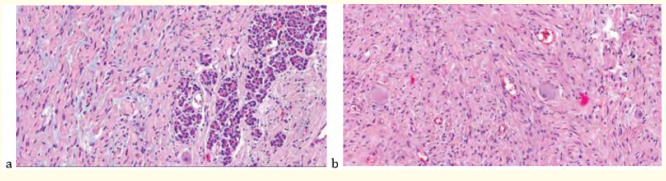

Figure 5: Microscopy of the tumor, hematoxylin and eosin, staining ×20: a - solid tumor of multidirectional bundles of intertwined spindle-shaped and elongated cells, stroma areas with myxoid changes, among the bundles - a walled ganglion cell; b - among the bundles are walled-up individual ganglion cells.

Immunohistochemistry

Diffusely expressed nuclear-cytoplasmic expression of S100 (Figure 6a), diffusely expressed nuclear expression of SOX10 (Figure 6b), focal moderate nuclear expression of BCL2 (Figure 6c), cytoplasmic expression of Synaptophysin in ganglion cells (Figure 6d). Expression of CD117, CD34, Desmin, CD99, aSMA was not observed.

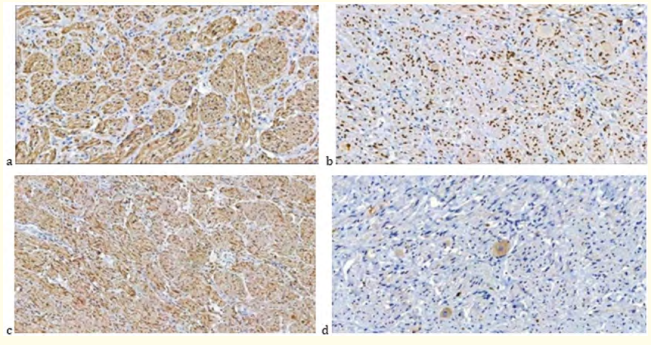

Figure 6: Immunohistochemistry of the tumor: a - diffuse pronounced nuclear-cytoplasmic expression of S100; b - diffuse pronounced nuclear expression of SOX10; c - focal moderate nuclear expression of BCL2; d - cytoplasmic expression in ganglion cells of Synaptophysin.

The morphological picture of the pancreatic tumor corresponded to ganglioneuroma, a benign neoplasm of the autonomic peripheral nerve. The patient's weight loss was most likely due to pneumonia.

The postoperative period was complicated by pancreatitis and suppuration of the postoperative wound. Despite the complications, repeated surgical interventions were avoided. The patient was discharged in satisfactory condition on the 27th day after the operation. At present, the patient is in satisfactory condition and is under the supervision of a surgeon.

Discussion

Ganglioneuromas are formations originating from both the central and peripheral nervous systems, being a tumor of mature cells of the nerve ganglia, arising against the background of a violation of the anlage of cells of the sympathetic nervous system, which are localized, as a rule, in the posterior mediastinum, the adrenal medulla, the retroperitoneal space, the pelvic cavity and often grow into the spinal canal with the formation of paravertebral and extramedullary components [19,20].

The extreme rarity of this pathology, as well as the absence of an obvious clinical picture with small sizes of lesions causes objective diagnostic difficulties, so that they are, as a rule, an accidental finding during examination, which requires an individual approach to each case in order to select an active surgical tactic or a dynamic observation option. Table 1 presents the cumulative data of patients with pancreatic ganglioneuroma, published to date, as well as our own clinical case.

№	Authors	Year	Number of cases	Gender	Age, years	Localization in the pancreas	Dimensions, mm
1	Bodner E., *et al*. [8]	1972	1	-	-	-	-
2	Christein J.D., *et al*. [9]	2002	1	F	28	isthmus and body	-
3	Domanski H.A. [6]	2005	1 of 3	-	-	-	-
4	Poves I., *et al*. [10]	2009	1	F	33	uncinate process	40
5	Ikoma N., *et al*. [11]	2016	1	F	4	head	25x25x33
6	Scandavini C., *et al*. [12]	2018	1 of 13	-	-	-	-
7	Mazzola M., *et al*. [3]	2019	1	M	30	tail	70
8	Shaheen A.A., *et al*. [13]	2021	1	F	86	body	13x8
9	Satoh T., *et al*. [14]	2021	1	M	15	head	15x9
10	Yildirim O., *et al*. [15]	2022	1	F	24	isthmus	35x25
11	Personal case	2025	1	F	19	head	70

Table 1: Pancreatic ganglioneuromas: clinical cases based on literature data.

It should be noted that at least 54.5% of patients were women. Patients were mostly over 20 years old. Large lesions were a minority (no more than 20%). The clinical picture was specific only for large lesions. Tumors were mainly localized in the proximal parts of the gland. The options for examining patients were different and, apparently, depended on the capabilities of a particular clinic.

The clinical symptoms of ganglioneuromas depend on the localization of the neoplasm, as well as its size and relationship to adjacent organs. Ganglioneuromas are characterized by slow growth with minimal clinical symptoms. That is why in most cases tumors of this type reach impressive sizes. This tumor can be detected by palpation or appear when adjacent structures are compressed if they reach large sizes. Most often, they are an accidental finding during a routine medical examination [21].

Since ganglioneuromas are often asymptomatic and have non-specific imaging characteristics, they can cause diagnostic difficulties. Based on the analysis of clinical cases presented in Table 1, in the part where publications provided data on radiology, as well as literature data, we present below the main signs of ganglioneuromas according to radiology.

Pancreatic ganglioneuromas during look like homogeneous solid masses of reduced echogenicity with clear smooth contours at ultrasound. However, these signs are non-specific [3]. N.N. Varlamova and E.N. Zinovieva described in their clinical case the lesion measuring 33×33×35 mm with clear smooth contours, a homogeneous structure, in which blood flow was not detected during Color and Power Doppler Imaging [22]. However, in our clinical case, vascular loci represented by arteries and veins were located in the lesion, which is most likely due to the large size of the lesion.

As a rule, on MSCT, ganglioneuroma is a homogeneous, ovoid-shaped lesion with clear contours. However, it is not always possible to determine whether the neoplasm belongs to the nervous system, even with modern imaging techniques. Nevertheless, MSCT provides precise characterological details of the tumor and allows assessing the relationship with vascular structures. On contrast MSCT, the lesion is usually not enhanced. Delayed heterogeneous

contrast may be observed. On MRI, the lesion usually appears as a hypointense mass on T1 WI and heterogeneously hyperintense on T2 WI. Gradual enhancement is observed in dynamic studies. In contrast, higher density on non-enhanced MSCT and lower hyperintensity on T2 WI are observed in ganglioneuroblastoma and neuroblastoma, which allows them to be differentiated. Discrete and point calcifications can also be observed in ganglioneuroma. On the other hand, amorphous and coarse calcifications are more often observed in ganglioneuroblastoma and neuroblastoma [2,23,24].

Ganglioneurinomas do not absorb fluorodeoxyglucose (FDG), which makes PET of no diagnostic value [2]. PET-CT has never been used in pancreatic ganglioneuroma, and in general, it is used very rarely. Z. Wu., *et al*. reported that the tumor did not absorb FDG [2]. This case indicates that the degree of FDG uptake may be associated with the aggressive behavior of the tumor.

Differential diagnosis includes a large number of benign and malignant neoplasms, including neurofibroma, schwannoma, neuroblastoma, ganglioneuroblastoma, pheochromocytoma, etc. [25].

It should be noted that accurate diagnosis of pancreatic ganglioneuroma using instrumental methods at the preoperative stage is extremely difficult. This has not occurred in any of the documented clinical cases. First of all, this is due to the extreme rarity of this type of neoplasms in this localization.

Accurate diagnosis of ganglioneuroma requires analysis of tissue samples using excisional biopsy, core needle biopsy or fine needle aspiration [6]. Of the neuroblastic tumors, ganglioneuromas are the most differentiated and have the best prognosis [26]. Ganglioneuroma consists of spindle-shaped and ganglion cells. The absence of immature neuroblasts, nuclear polymorphism, necrosis and inflammation allows differentiating ganglioneuroma from malignant ganglioneuroblastoma and neuroblastoma. In immunohistochemical studies, positivity for S-100 protein, neurofilament and synaptophysin indicates a neurogenic origin of the tumor [9].

Despite the fact that ganglioneuroma is benign in nature, complete surgical removal of this lesion is the method of choice, although it is a technically complex intervention, given the anatomical origin and location [3,27]. This is especially important when there is an increased risk of compression of adjacent organs and vascular structures. Currently, the laparoscopic approach is actively used [28]. Even if tumor excision is problematic, incomplete resection is sufficient, since the probability of progression is low for tumors <2 cm. Tumors <2 cm may progress after incomplete resection [29]. A comprehensive review of the literature did not reveal cases of minimally invasive therapy for ganglioneuromas, such as radiofrequency ablation or cryodestruction. However, this may be due to the rarity of this tumor.

Conclusion

Pancreatic ganglioneuroma is an extremely rare pathology in routine physician practice without specifically formulated modern protocols and guidelines for diagnosis and treatment. In cases of incidentally discovered pancreatic masses that do not have distinctive radiographic features, ganglioneuroma should be considered in differential diagnosis even in older people, and biopsy is also justified. Surgical resection with negative margins is the main treatment option and in most cases the only way to make a correct diagnosis.

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