

A Systematic Review of the Histopathology and Immunohistochemistry in Duodenal Gangliocytic Paragangliomas with Lymph Node Metastases to Identify Predictors of Malignancy

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ABSTRACT

Gangliocytic paragangliomas (GP) are rare tumors, most commonly located in the 2nd portion of the duodenum. Their origin is poorly understood and management is uncertain. Typically exhibiting benign behavior, they infrequently metastasize to lymph nodes (LN) and distant sites. Due to their triphasic cellular distribution, tissue diagnosis pre-operatively remains a challenge, as well as prediction of which tumors may metastasize or act more aggressively. A systematic literature search was performed, and data for epidemiology, clinical history, gross pathology, and histopathology of duodenal (DGPs) with LN metastases was collected. Histopathology and Immunohistochemistry (IHC) was described and compared to a review by Okubo et al in an effort to identify predictors of malignancy. It is difficult to obtain a tissue diagnosis and predict malignant behavior of DGPs. Increased tumor size, depth of invasion, angio-lymphatic invasion and IHC findings may warrant further investigation for LN metastases. The presence of LN metastases does not seem to influence the prognosis, but rather the treatment modality.

Keywords

Gangliocytic paragangliomas, Duodenum, Lymph node, Tumors.

Introduction

Gangliocytic paragangliomas (GPs) were first described by Dahl et al. in 1957 [1]. With only approximately 200 case reports in the medical literature, GPs are rare tumors, most commonly located in the 2nd portion of the duodenum [2]. They have a 5-7% rate of lymph node (LN) metastases. Although these tumors typically behave in a benign fashion, reports of lymph node metastases, rare distant metastasis and a single case of a reported mortality have suggested that it is a tumor of uncertain malignant potential [3].

The pathogenesis of these tumors is still uncertain with several hypotheses about their origin. These tumors have a triphasic cellular distribution, often containing a pre-dominant epithelioid component, as well as spindle and ganglion cells of varying proportions. Tissue diagnosis pre-operatively remains a challenge, as well as prediction of which tumors may metastasize or act more aggressively. The presence of LN metastases is consequential, as currently, the majority of these patients are treated with a pancreatoduodenectomy (PD), instead of local excision. Herein we review the literature, describing the histopathology and immunohistochemistry (IHC) of these tumors. Case reports with the presence of LN metastases will be compared to the case series

of Okubo et al., with the significance of angiolymphatic invasion, mitotic rate, nuclear pleomorphism, tumor size, depth of invasion and IHC described and examined as predictors of malignancy [4].

Methods

Literature Search Strategy and Selection

A systematic literary research was performed independently by 2 different investigators. The search terms included the following: “Gangliocytic,” “Paraganglioma,” “Lymph node,” “Paraganglioneuroma,” “Pheochromocytoma,” “Duodenum,” “Pancreatic,” “Ampulla of Vater,” “Duodenal Papilla,” “Sphincter,” “Oddi,” “Neoplasm,” “Cancer,” “Adeno/Carcinoma,” “Sarcoma,” “Tumor,” “Metastasis,” “Malignant,” combined with AND/OR. The references of all selected articles were reviewed. Duplicate studies were eliminated. Agreement between the two reviewers was measured with the Cohen’s kappa coefficient. All retrieved articles were selected if they met inclusion criteria.

Selection Criteria

Selected studies contained patients with duodenal GPs (DGPs), with LN metastases, confirmed by histopathology on the resected specimen. All abstracts/conference proceedings, case reports, reviews, and meta-analyses of all languages were included. No selection on age, sex or ethnicity was adopted.

Data Extraction

Study data included year of publication and patient characteristics, including age, sex, and symptoms. Diagnostic procedures, such as endoscopic biopsy with forceps and endoscopic ultrasound fine needle aspirate (FNA) were recorded. Gross and histopathological data was only included if clearly recorded. Gross pathology features, including tumor location, size, and descriptions were gathered. Histopathology description was recorded including location within the bowel wall, mucosal ulceration, mitotic rate, angiolymphatic invasion, tumor necrosis, nuclear pleomorphism, muscularis propria invasion, and pancreatic involvement in resected specimens. Submucosal location was determined through either imaging by endoscopic ultrasound (EUS) or histopathology in the resected specimen, and IHC results were also summarized. After research ethics board approval, authors of all case reports were contacted on 3 separate occasions and the most current disease specific time interval was included.

Statistical Analyses

Percentages, means, standard deviations and chi square tests of patient and tumor characteristics were reported. These were compared to those cases of DGPs from Okubo et al. [4]. Disease specific survival outcomes were reported in months, using both clinical symptoms and diagnostic imaging, as methods of surveillance.

Results

Selection

After removing duplicates, 1,276 titles and abstracts were reviewed and 34 articles were selected as potentially eligible for the study, with 29 reports meeting inclusion criteria on further review. Two

additional articles were identified after reviewing references. An additional case report, by Schick et al., was added to the data [5]. Agreement between the two investigators, who performed the literature search measured by Cohen’s Kappa Coefficient was 0.944, and disagreements were resolved with discussion involving both investigators. A total of 33 patients with DGPs with LN metastases were identified (Figure 1).

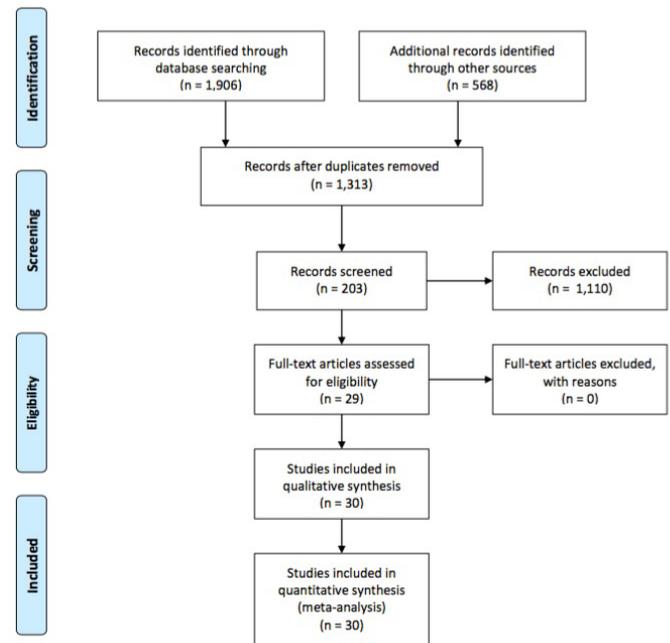


Figure 1. Prisma diagram of systematic review process.

Epidemiology and Gross Pathological Features

The mean age of patients was 48 years, with a range of 16 to 74 years in the 33 patients identified. Male to female ratio was 1:1 (Table 1).

Primary tumor location was the second portion of the duodenum in 28/32 cases (88%), with 21 of reported DGPs described as a sub/peri/ampullary mass. Other tumor locations included the third portion of duodenum, and two cases involving the head of the pancreas [5,6]. On gross appearance 19/23 (83%) had mucosal ulceration and 19/20 (95%) had a polypoid or exophytic appearance. Mean tumor size (maximum diameter) was 3.1 cm (standard deviation SD 1.6 cm), ranging from 1.0 to 9.0 cm (Table 1).

Serum and Urine Tumor Markers

Hormone levels and serum/urine tumor markers were reported in 6 cases. These values were relatively unremarkable, with one case of elevated somatostatin, which normalized post-operatively [7]. One case of elevated pancreatic polypeptide (PP) post-operatively was thought to be indicative of tumor recurrence [8] (Table 2).

Endoscopy, Endoscopic Ultrasound (EUS) and Diagnostic Biopsies

Of 9 reported esophagogastroduodenoscopy (EGD) biopsies, 1 suggested paraganglioma (11%) [8]. The method of biopsy was likely with biopsy forceps, but not recorded. However, EGD was a sensitive diagnostic tool, as in all 23 patients, it successfully

identified a polypoid duodenal mass. Endoscopic Ultrasound (EUS) was reported in 11 cases and identified the primary tumor in 11/11 cases (100%), detecting enlarged LNs in 7/11 cases (64%). Of 9 FNA biopsies reported by EUS, GP was correctly diagnosed in 1 case (11%), suspicious/indeterminate in 7 cases (78%), and misdiagnosed as adenocarcinoma in 1 case (11%) (Table 3).

Histopathology

All tumors had a triphasic cellular distribution containing epithelioid cells, spindle cells, and ganglion cells of varying amounts. Epithelioid cells were predominant in the majority of tumors [9]. In 20 cases, there were comments on mitotic rate or proliferative index (Ki-67/MIB-1), with 19 (95%) showing minimal to no mitotic/proliferative activity. In the remaining case, the mitotic activity was not quantified, but the reports stated that the epithelioid cells were sometimes mitotic. In 10 cases,

the presence or absence of primary tumor necrosis was reported, which was present in 1 case (10%) [6]. Angiolymphatic invasion was reported in 7/9 (78%) cases by both hematoxylin and eosin (HE) stain, and D240 IHC. Nuclear pleomorphism of epithelioid cells was present in 5/10 (50%) of reported cases. In all 27 cases where it was described, the primary tumor involved the submucosal portion of the duodenal wall, with an infiltrative margin involving the mucosa and/or muscularis propria in 25/27 cases (93%); the pancreatic head was involved in 6/29 cases (21%) [10-15]. There were no reports of encapsulated tumors, and psammoma bodies were rarely described in 1 case [14] (Table 4).

Immunohistochemistry

Immunohistochemistry (IHC) findings were documented in 29 cases and are recorded in table 5. The results were compared to Okubo et al., which contain IHC findings from 173 DGPs [4] (Table 5).

Year	Author (first, et al.)	Age, Sex	Presenting complaint	Tumor location	Mucosal ulceration	Polypliod /exophytic	Size (cm)
1981	Dookhan [15]	41, M	Abdominal discomfort; Partial gastric outlet obstruction	D2	1	1	2.5
1985	Buchler [24]	50, M	UGI bleed	D2, Peri-ampullary	0	1	3
1987	Korbi [10]	73, F	Abdominal discomfort, Fever, UGI bleed; Melena	D2	1	1	9
1989	Burke [25]	NR	NR	NR	NR	NR	NR
1989	Burke [25]	45, M	NR	Duodenum	NR	NR	NR
1989	Inai [17]	17, M	UGI bleed	D2, Ampulla	1	1	2
1992	Hashimoto [26]	47, M	Incidental finding	D2, Ampulla	1	1	6.5
1993	Takabayashi [27]	63, F	Epigastralgia; Biliary/Pancreatic ductal dilatation	D3	1	1	3.2
1996	Tomic [7]	74, F	Steatorrhea, N/V, Abdominal discomfort	Head of pancreas	NR	NR	4
1997	Sundararajan [19]	67, F	NR	D2, Ampulla	1	1	5
2003	Henry [6]	50, M	Obstructive jaundice	Head of pancreas	NR	NR	3
2004	Bucher [11]	31, F	Anemia; Subclinical jaundice	D2, Peri-ampullary	NR	NR	3
2005	Wong [8]	49, F	Melena, RUQ discomfort	D2, Ampulla	1	1	1.4
2007	Witkiewicz [28]	38, F	RUQ discomfort	D2, Peri-ampullary	0	1	1.5
2009	Mann [29]	17, F	Duodenal obstruction, N/V, Abdominal discomfort	Junction D2-D3	1	NR	3
2010	Saito [37]	28, M	UGI bleed	D2, Ampulla	1	1	1.7
2010	Uchida [30]	67, F	Anemia	D2	1	1	4.2
2010	Okubo [4]	61, M	Epigastralgia; UGI bleed	D2, Ampulla	1	1	3
2011	Fiscaletti [31]	61, M	RUQ discomfort, Weight loss	D2	NR	1	1.2
2011	Rowell [14]	52, F	Incidental Liver Metastasis on Imaging	D2, Peri-ampullary	0	1	1
2011	Ogata [2]	16, M	Anemia; UGI bleed; Dyspnea; Fever	D2, Ampulla	1	1	3.5
2012	Barret [12]	51, F	Anemia, UGI bleed	D2, Ampulla	1	1	2.5
2013	Dustin [22]	56, F	Epigastralgia, Weight loss	D2, Peri-ampullary	0	NR	1.8
2013	Amin [9]	57, M	N/V, Abdominal discomfort	D2, Ampulla	NR	NR	3
2013	Park [16]	54, F	UGI bleed	D2	NR	NR	2
2014	Li [3]	47, M	Epigastralgia	D2, Peri-ampullary	1	NR	3
2014	Shi [13]	47, M	LLQ discomfort; Weight loss	D2, Ampulla	1	1	4
2015	Choi [32]	41, M	UGI bleed	D2, Periampullary	1	NR	2.5
2015	Wang [33]	49, M	Epigastralgia	D2	1	NR	4
2015	Dowden [34]	59, F	Abdominal discomfort, Weight loss	D2, Ampulla	NR	NR	2.8
2015	Sun [35]	40, F	Abdominal discomfort	D2, Ampulla	NR	1	2
2016	Hu [36]	65, M	UGI bleed	D2, Peri-ampullary	1	1	3
2016	Schick [5]	35, F	Abdominal discomfort; Dyspepsia	D2, Ampulla	1	0	3.2

Table 1: Patient Demographics and Characteristics of Duodenal Gangliocytic Paragangliomas.

Author	Pre-operative	Post-operative
Buchler [11]	NR	Serotonin (-), 5HIAA (-), Gastrin (-)
Ogata [2]	Serum markers WNL	NR
Tomic [7]	Somatostatin (+++) Calcitonin, VIP, PP, Gastrin, Serotonin level WNL	Somatostatin normalized
Uchida [30]	Dopamine, A/NoA, Urine catecholamines, CEA, Ca19-9 WNL	NR
Amin [9]	Somatostatin and CG WNL; PP NR	PP (+++); Gastrin, Insulin, Glucagon, VIP, 5-HIAA, Catecholamine, CG WNL;
Saito [37]	Glucagon, Gastrin, Urinary 5 - HIAA, A/NoA; Met/NoMet; VMA WNL	NR

Table 2: Recorded Serum and Urine Tumor Markers of Duodenal Gangliocytic Paragangliomas.

NR = Not recorded; WNL = Within Normal Limits; VIP = Vasoactive Intestinal Peptide; PP = Pancreatic Polypeptide; A/NoA = Adrenaline/Noadrenaline; CG = Chromogranin A; 5-HIAA = 5 Hydroxyindoleacetic acid; CEA = Carcinoembryonic antigen; Met/NoMet = Metanephrine/Nometanephrine; VMA = Vanillylmandelic acid; (+++) = strongly positive; (-) = negative.

Endoscopic biopsy	Endoscopic U/S biopsy
1/9 correct dx	1/9 correct dx; 1/9 incorrect dx; 2/9 suspicious but not dx; 5/9 inconclusive.

Table 3: Biopsy Diagnostic Results of Duodenal Gangliocytic Paragangliomas. dx = diagnosis; U/S = Ultrasound.

Author (first, et al.)	Tumor location	Mitotic rate	Angio-lymphatic invasion	Tumor Necrosis	Epithelioid pleomorphism	Submucosal location	Muscularis propria Invasion	Mucosal ulceration	Pancreatic involvement
Dookhan [15]	D2	NR	NR	NR	NR	1	1	1	0
Buchler [24]	Periampullary	0	NR	0	0	1	1	0	0
Korbi [10]	D2	1	NR	NR	1	1	0	1	0
Burke [25]	NR	NR	NR	NR	NR	NR	NR	NR	0
Burke [25]	Duodenum	NR	NR	NR	NR	NR	NR	NR	NR
Inai [17]	Ampulla	NR	1	NR	0	1	1	1	1
Hashimoto [26]	Ampulla	0	1	NR	1	1	0	1	0
Takabayashi [27]	D3, ampulla	NR	NR	NR	NR	1	1	1	0
Tomic [7]	Pancreas	0	NR	NR	NR	NR	NR	NR	NR
Sundararajan [19]	Ampulla	0	NR	0	0	1	1	1	0
Henry [6]	Pancreas	NR	NR	NR	NR	0	0	NR	1
Bucher [11]	Periampullary	NR	NR	NR	NR	0	0	NR	1
Wong [8]	Ampulla	NR	NR	NR	NR	1	1	1	0
Witkiewicz [28]	Periampullary	2/10 hpf	NR	0	1	1	1	0	0
Mann [29]	D2-D3	NR	1	NR	NR	1	1	1	0
Saito [37]	Ampulla	MIB-1 2.2%	1	NR	NR	1	0	1	0
Uchida [30]	D2	NR	NR	NR	NR	1	0	1	0
Okubo [4]	Ampulla	0	1	0	0	1	1	1	0
Fiscaletti [31]	D2	2/10 hpf	NR	NR	NR	NR	NR	NR	NR
Rowse [14]	Periampullary	Ki-67 < 1%	NR	NR	NR	1	0	0	0
Ogata [2]	Ampulla	0	1	NR	NR	1	0	1	0
Barret [12]	Ampulla	0	NR	0	NR	1	1	1	0
Dustin [22]	D2	0	NR	0	1	1	1	0	0
Amin [9]	Ampulla	Ki-67 < 1%	NR	0	0	NR	NR	NR	NR
Park [16]	D2	NR	NR	NR	NR	1	0	NR	0
Li [3]	Periampullary	0	NR	0	1	1	1	1	1
Shi [13]	Ampulla	Ki-67 < 1%	NR	NR	NR	1	1	1	1
Choi [32]	Periampullary	< 1/50 hpf	NR	NR	NR	1	1	1	0
Wang [33]	D2	0	NR	0	NR	1	1	1	0
Dowden [34]	Ampulla	0/10 hpf	0	NR	NR	1	1	NR	0
Sun [35]	Ampulla	NR	0	NR	NR	1	1	0	0
Hu [36]	D2	NR	NR	NR	NR	1	0	1	0
Schick [5]	Ampulla	Ki-67 < 1 %	1	1	NR	1	1	1	1

Table 4: Histopathology. NR = Not reported; D2 = 2nd portion of duodenum; D3 = 3rd portion of the duodenum; hpf = high power field; 1 = present; 0 = absent.

Immunohistochemistry	Hartford et al. (2018) Epithelioid cells	Okubo et al. (2011) Epithelioid cells	Hartford et al. (2018) Spindle-shaped cells	Okubo et al. (2011) Spindle-shaped cells	Hartford et al. (2018) Ganglion-like cells	Okubo et al. (2011) Ganglion-like cells
NSE	90.9% (10/11)	93.9% (77/82)	45.5% (5/11)	84.0% (63/75)	45.5% (5/11)	84.0% (63/75)
Chromogranin A	90.9% (20/22)	67.4% (60/89)	4.7% (1/21)	7.2% (6/83)	0.0% (0/21)	15.4% (12/78)
Synaptophysin	95.2% (20/21)	90.0% (36/40)	30.0% (6/20)	64.7% (22/34)	85.7% (18/21)	94.3% (33/35)
S-100	4.2% (1/24)	3.8% (4/104)	96.0% (24/25)	94.2% (98/104)	8.3% (2/24)	9.3% (9/97)
Cytokeratins	84.6% (11/13)	48.3% (28/58)	0.0% (0/12)	4.0% (2/50)	0.0% (0/12)	3.9% (2/51)
Somatostatin	81.8% (9/11)	81.8% (63/77)	0.0% (0/11)	8.7% (6/69)	54.5% (6/11)	44.1% (30/68)
Pancreatic polypeptide	71.4% (5/7)	89.7% (70/78)	0.0% (0/7)	0.0% (0/72)	57.1% (4/7)	22.2% (16/72)
Serotonin	20.0% (1/5)	22.0% (13/59)	0.0% (0/5)	0.0% (0/55)	20.0% (1/5)	16.7% (9/54)
Insulin	16.7% (1/6) very weak	2.2% (1/46)	0.0% (0/6)	0.0% (0/41)	0.0% (0/6)	0.0% (0/42)
Glucagon	0.0% (0/6)	6.4% (3/47)	0.0% (0/6)	0.0% (0/44)	0.0% (0/6)	2.4% (1/42)
Gastrin	0.0% (0/3)	5.9% (4/68)	0.0% (0/3)	0.0% (0/64)	0.0% (0/3)	0.0% (0/63)
VIP	40.0% (2/5)	12.1% (4/33)	40.0% (2/5)	12.9% (4/31)	20.0% (1/5)	9.7% (3/31)

Table 5: Immunohistochemistry (IHC): Comparison of Hartford et al. cases with lymph node metastasis to Okubo et al. review.

NOTE: The numbers 1-31 are used in Table 4 and correspond to the descending order of authors in Tables 1 & 4.

Weak positive and partially positive findings are not included in this table.

Compared to Okubo et al. [5]

NSE = Neuron Specific Enolase; VIP = Vasoactive Intestinal Peptide.

Surgical Management and Outcomes

Pancreatoduodenectomy (PD) was the definitive surgery in 27/31 cases. Local excision had a high rate re-operation 4/7 (57%). Distant metastases were present in 6 cases, including liver, mesentery, pelvis, retroperitoneum, and bone. Reported clinical follow up showed quite good disease specific survival. Local recurrence was reported in 1 case, with another case likely, but not definitively identified [15]. The recorded mean and median times post-operatively with no evidence of disease was 34 and 24 months respectively. There were 3 mortalities (9%) recorded; one from post-operative complications, one from metastatic disease, and one of unknown cause at 156 months [2,6,10].

Discussion

We examined the gross pathology, histopathology, and IHC characteristics of 33 cases of DGP with LN metastases, exploring significant factors associated with LN or distant metastases. These rare triphasic neoplasms are most commonly located in the 2nd portion of the duodenum, but have also been described in the jejunum, appendix, esophagus, spinal cord and lung.

Serum and Urine Tumor Markers

Of the tumor markers reported, only somatostatin was confirmed to be elevated pre-operatively and drop post-operatively in one case [7]. More information is needed to determine the significance of this, as well as of PP. While there are few reports of functioning tumors, this contributes to the possibility of misdiagnosis of these tumors as neuroendocrine tumors (NETs) and conversely duodenal NETs having GP, but reported otherwise.

Diagnostic Biopsies

Although EGD is sensitive in detecting a polyploid/ulcerated lesion in the duodenum, it is not specific in diagnosing DGPs, and the submucosal location of these tumors results in a high proportion of false negative biopsies by forceps. FNAs by EUS may be more specific, but are often indeterminate for a diagnosis

of GP. This likely reflects the relative difficulty for pathologists to diagnose a rare tumor with a triphasic cellular distribution with limited sampling of a submucosal lesion. A core tissue sample may be more useful but is difficult to obtain given the location of the tumor.

Histopathology and Immunohistochemistry

On histopathology, epithelioid, spindle, and ganglion cells were present in all primary tumors. All three cellular components were also identified within the LN metastases. The epithelioid cell component predominated in the primary tumor, as well as in metastases. The presence of only epithelioid cells in some LN metastases may represent the dominance of that component or under sampling.

GPs with LN metastases do not appear to show increased mitotic rate or necrosis compared with those without LN metastases. Nuclear pleomorphism does not seem to correlate with LN metastases. Angiolymphatic invasion was identified in 7/9 reported cases (78%), and further investigations including D240 IHC would be helpful to further define the role of angiolymphatic invasion as a predictor of LN metastases.

The muscularis propria was involved in 18/28 (64%) with 7/27 cases (26%) reported to have extension into the subserosa or adjacent connective tissues. This is not significantly different from the 108 cases of GP where depth of tumor invasion was described in Okubo et al. [4] ($P = .50$). In their study, 62/108 cases (57%) had invasion of the muscularis propria, while extension into connective tissue beyond the muscularis propria was seen in 4/108 cases (4%), and 12 of these 108 cases had lymph node metastasis. We support their evidence that increased tumor size, extension beyond the submucosal layer and depth of invasion are significant risk factors for LN spread (Table 4).

IHC was similar to those without LN metastases, which

is consistent with both Okubo et al. and Park et al. [4,16]. However, in comparing GPs without LN metastases to GPs with LN metastases: epithelioid cells more frequently had uptake of chromogranin A (20/22 (91%) vs 60/89 (67%), $P = .03$) and cytokeratin (11/13 (85%) vs 28/58 (48%), $P = .02$). In cases of GPs with LN metastases, spindle cells had less frequent uptake of neuron specific enolase (NSE) (5/11 (46%) vs 63/75 (84%), $P = .004$) and synaptophysin (6/20 (30%) vs 22/34 (65%), $P = .01$). Ganglion cells from GPs with LN metastases also had less frequent uptake of NSE (5/11 (46%) vs 63/75 (84%), $P = .004$). More study is needed to determine whether IHC is able to predict a more aggressive course of DGPs (Table 5).

Outcomes

In our review of the literature of patients with DGP, there were three mortalities. In one case, death was thought to be directly secondary to the tumor; in one case, death from cardiopulmonary failure occurred as a complication of a PD procedure; in another case, death of an unknown cause occurred after 13 years [2,6,10]. Although there appears to be relatively good 1 and 5-year disease specific survival rates, analysis is limited by lack of extended follow up data. Only two cases showed evidence of local recurrence and 5/33 cases showed evidence of distance metastasis. This continues to suggest that GP, even with evidence of local spread with LN metastases, typically behaves in a benign fashion.

Origin

Despite extensive IHC and ultrastructural studies, the histogenesis of GPs is still debatable, and authors have been unable to reconcile the combination of endocrine, ganglion and spindle cells observed in a single tumor [3]. The tumor components are of different embryologic origins, the first being of endodermal origin and the others originating from neural crest tissue. All components normally occur in the duodenum, and given the relatively benign nature, some contend that it is a hamartoma [12]. Others postulate it is a hyperplastic or neoplastic lesion from ectopic cells of the ventral primordium of the pancreas, possibly explaining its relatively consistent location in the second portion of the duodenum [2,15,16]. Also suggested is an ectodermal origin, originating from pluripotent stem cells of the crypts of Lieberkuhn or celiac ganglion [17-21]. GPs discovered distant to the duodenum and pancreas, such as lung, esophagus, appendix, and spinal cord, as well as the presence of rare metastatic lesions, argue against GPs being a true hamartoma [20].

Although regarded by some as a neuroendocrine tumor, which may rarely show hormone secreting function, neuroendocrine tumors lack ganglion and spindle cells [22]. While the epithelioid component is often immunopositive for PP, this is not specific to pancreatic neuroendocrine tumors [16].

Comments

Many articles did not include all data examined. Therefore, data was only included if recorded clearly leading to a small sample size in many data categories and led to many different proportion characteristics. As there is a tendency to only publish positive

results, published diagnostic modalities, as well as patient and tumor characteristics of DGP cases may be biased leading to a type I error. For this reason, sensitivity, specificity, and predictive values of tests were not calculated. As the majority of GPs are treated with local excision, this does not allow examination of the nodes, the number of cases with LN metastases may be underestimated. With such a rare diagnosis, the only articles obtained were case reports, abstracts, and reviews. As such, all studies met criteria for level 4 evidence, and therefore all recommendations were grade C.

Conclusion

Pre-operative tissue diagnosis of DGP is difficult due to the rarity, triphasic cellular distribution, and submucosal location of the tumor.

It is difficult to predict malignant behavior of DGPs by histopathology or IHC;. There is low-grade evidence to warrant further investigation for LN involvement with increased tumor size, depth of invasion and presence of angiolymphatic invasion. More information is needed to determine if IHC may assist in identification of malignant DGPs. More evidence is needed to confirm the utility of serum hormone and tumor markers, such as somatostatin and PP, in the role of diagnosis and post-operative surveillance.

Despite LN and distant metastasis, disease specific survival has been shown to be relatively good in our review, the presence of LN metastases does not seem to influence the prognosis, but rather treatment modality. PD is likely the most effective method of ensuring complete tumor excision and removal of affected LNs. Pathologists and treating clinicians should continue to be aware of the rare potential for metastases, and a multidisciplinary approach should be utilized in the approach and treatment of this rare diagnosis.

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