APPENDICEAL NEUROENDOCRINE TUMOURS – RECENT INSIGHTS

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ABSTRACT

Background: According to the consensus and the recommendations of the European Neuroendocrine Tumor Society (ENETS), the frequency of appendicular neuroendocrine tumours is 0.15-0.6/100 000 a year. Their evolution is usually asymptomatic, and they are diagnosed accidentally during conventional or laparoscopic appendicectomy.

Purpose: The idea of the article is to summarise the knowledge about the neuroendocrine tumours of the appendix and to present the current trends in the treatment and follow-up of patients with that pathology.

Materials and Methods: Literature overview that includes studies about neuroendocrine neoplasms of the appendix(NEN) comprising the last consensus guideline of ENETS 2017 on the topic.

Conclusion: Despite the lack of any prospective studies concerning appendiceal neuroendocrine tumours, there are some new consensus guidelines, regarding new trends in the optimal management of appendiceal NEN.

KEYWORDS neuroendocrine neoplasms of the appendix, right-sided hemicolectomy, appendicectomy, review

BACKGROUND

In 1907, Oberndorfer first described a tumour localised in the small intestine, similar to adenocarcinoma, but at the same time showing signs of a benign tumour. He called him a „carcinoid", that is a carcinoma-like. Several years later, it was found that carcinoids are composed of enterochromaffin-like cells present in the submucosa and lamina propria, which produce more than 90% of the serotonin in the human body. Today, carcinoids are called gastroenteropancreatic neuroendocrine tumours. Their frequency has grown considerably, and nowadays it reaches an annual incidence rate of 2-5 / 100,000 [1]. According to other authors, the incidence of appendicular neuroendocrine neoplasms is 0.15-0.6 / 100,000 per year [2]. Neuroendocrine tumours (NETs) of the appendix represent 30 to 80% of all appendicular neoplasms [2].

The idea of the article is to summarise the knowledge about the neuroendocrine tumours of the appendix and to present the current trends in the treatment and follow-up of patients with that pathology.

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EPIDEMIOLOGY

Neuroendocrine appendiceal neoplasms(NEN) are the third most frequent group of gastroenteropancreatic neuroendocrine tumours (GEP-NETs). According to SEER database, however, they classified in fourth place after NETs of the small intestine, rectum, stomach and pancreas. About 50% of all appendix tumours are neuroendocrine tumours. Up to 2.3% of appendicectomy are due to the neuroendocrine tumours of the appendix. From 1998 to 2001, the neuroendocrine tumours of the appendix were the most common neoplasm of the appendix

(17.3% - 19.7%). In 2015 their frequency reached 22%. Their prognosis is determined by the histomorphology, the individual malignant potential, the stage, and the degree of differentiation of the tumour. In a series of studies, 5-year survival was 100% or close to 100% in tumours with high differentiation [3, 4]. In large cohort studies involving tumours of varying degrees of differentiation, the 5-year survival rate is between 70% and 85% [5]. For advanced stages with distant metastases, 5-year survival is low and ranges from 12% to 28% [5].

CLINICAL PRESENTATION

Most of the NETs of the appendix are found accidentally, usually after appendicectomy, and that's why there are no specific symptoms to detect them preoperatively. The primary symptom is the pain due to tumour localisation, in 70% of cases a tumour is located at the top of the appendix[6, 7]. The symptoms could be divided into three main groups: symptoms due to acute appendicitis; symptoms associated with a metastatic process due to the localisation of metastases and symptoms due to carcinoid syndrome.

Symptoms associated with acute appendicitis are the typical symptoms of an acute surgical abdomen: pain in the ileocecal region accompanied by nausea and vomiting. The carcinoid syndrome is due to metastatic disease, occurring very rarely in NETs of the appendix, more common in small intestinal carcinomas[8].

DIAGNOSTIC PROCEDURES

Histological verification is a principal diagnostic method because a large percentage are diagnosed after appendicectomy. Endoscopy is not enough informative method unless a tumour is locally advanced and infiltrate the cecum. Fibrocoloscopy is recommended because of the increased incidence of secondary neoplasm, regarding colorectal cancer [9].

Genetic profile

There is no precise information for the genetic mutations in neuroendocrine tumours of the appendix. However, it is known that GI NETs show predominantly genetic alterations concentrated on chromosome 18, and losses of the entire chromosome, as well as smaller deletions, have both been documented. The most frequently identified mutation in GI NETs is that of beta-catenin, with overexpression of cyclin D1 and c-Myc[10].

Laboratory Tests

Chromogranin A (CgA) can be used as a tumour marker, both in the appendiceal NET and in the small intestinal neuroendocrine neoplasms (NEN). European neuroendocrine tumour society (ENETS) recommends its investigation for follow-up in patients with metastatic disease. There is a correlation between the tumour size and the serum CgA level. In tumours over 2 cm, serum CgA is considered to be elevated whereas in tumours less than 2 cm may remain within the reference range. In patients with carcinoid syndrome, it is advisable to measure urinary 5-HIAA [11].

According to WHO, the classification of the neuroendocrine tumours of the appendix, they are divided into G1 and G2 neuroendocrine tumours of the appendix and G3 neuroendocrine carcinoma. The tables below show the WHO 2010 classification of the neuroendocrine neoplasms (NEN) and the TNM classification according to ENETS:

The American College of Pathologists in 2017 conducted a study to investigate the specimen from patients with neuroendocrine appendiceal tumors cancer [12]. The goal of such a protocol was to optimize and standardize the outcome with a view to accurately staging the disease. Below we apply a sample of the protocol:

Procedure:

- _ Appendicectomy
- _ Right hemicolectomy
- _ Other (specify):

Tumor Site (Note A):

- _Proximal half of appendix
- _Distal half of appendix
- _Diffusely involving appendix
- _Appendix, not otherwise specified
- _Other (specify):_____

Tumor Size (Note B):

- Greatest dimension (centimeters): ___ cm
- + Additional dimensions (centimeters): ___ x ___ cm ___
- Cannot be determined (explain): _____

Histologic Type and Grade (Notes C and D)

- __G1: Well-differentiated neuroendocrine tumor
- __G2: Well-differentiated neuroendocrine tumor
- __G3: Well-differentiated neuroendocrine tumor
- __Other (specify):_____
- __GX: Well-differentiated neuroendocrine tumor, grade cannot be assessed
- __Not applicable

Mitotic Rate (Note D)

- __<2 mitoses/2 mm2
- __2 to 20 mitoses/2 mm2 + Specify mitoses per 2 mm2:__
- __>20 mitoses per 2 mm2 + Specify mitoses per mm2:__
- __Cannot be determined (explain):__
- __Not applicable

Ki-67 Labeling Index (Note D)

- <3%
- 3% to 20%
- + Specify Ki-67 percentage: %
- >20%
- Cannot be determined (explain):
- Not applicable

Tumor Extension

- No evidence of primary tumor
- Tumor invades the lamina propria
- Tumor invades the submucosa
- Tumor invades the muscularis propria
- Tumor invades the subserosa/mesoappendix without involvement of visceral peritoneum
- Tumor perforates the visceral peritoneum (serosa)
- Tumor directly invades other adjacent organs or structures (specify):

- Cannot be assessed

Margins (Note E) Note: All margins are uninvolved by tumor + Distance of tumor from closest margin (millimeters or centimeters): mm or cm + Specify closest margin: Proximal Margin Cannot be assessed Uninvolved by tumor Involved by tumor

Radial or Mesenteric Margin Cannot be assessed Uninvolved by a tumour Involved by a tumour

Other Margin(s) (required only if applicable) Specify margin(s): Cannot be assessed Uninvolved by tumor Involved by tumor For right hemicolectomy specimens only Proximal Margin Cannot be assessed Uninvolved by tumor Involved by tumor

Distal Margin Cannot be assessed Uninvolved by a tumour Involved by a tumour Radial and Mesenteric Margin Cannot be assessed Uninvolved by a tumour Involved by tumour

Other Margin(s) (required only if applicable) Specify margin(s): Cannot be assessed Uninvolved by tumor Involved by tumor Lymphovascular Invasion Not identified Present Cannot be determined + Perineural Invasion + Not identified + Present + Cannot be determined Regional Lymph Nodes No lymph nodes submitted or found

Number of Lymph Nodes Involved: Number cannot be determined (explain):

Number of Lymph Nodes Examined: Number cannot be determined (explain):

TNM Descriptors (required only if applicable) m (multiple primary tumors) r (recurrent) y (posttreatment)

Primary Tumor (pT) pTX: Primary tumour cannot be assessed pT0: No evidence of a primary tumour pT1: Tumor 2 cm or less in greatest dimension pT2: Tumor more than 2 cm but less than or equal to 4 cm pT3: Tumor more than 4 cm or with subserosal invasion or involvement of the mesoappendix pT4: Tumor perforates the peritoneum or directly invades other adjacent organs or structures (excluding direct mural extension to adjacent subserosa of adjacent bowel), e.g., abdominal wall and skeletal muscle Regional Lymph Nodes (pN) pNX: Regional lymph nodes cannot be assessed pN0: No regional lymph node metastasis pN1: Regional lymph node metastasis

Distant Metastasis (required only if confirmed pathologically in this case) pM1: Distant metastasis pM1a: Metastasis confined to liver pM1b: Metastasis in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone) pM1c: Both hepatic and extrahepatic metastases Specify site(s), if known: Additional Pathologic Findings (select all that apply) (Note G) + None identified + Tumor necrosis + Acute appendicitis + Other (specify): The protocol shows the factors that are attributable to the patient's prognosis which are the tumor size, localizations and the degree of invasion into the mesoapendix and vascular evasion. Tumors of less than 1 cm have the best prognosis. Tumors between 1 and 2 cm are prone to nodular metastases, especially in tumors over 1.5 cm. In tumors over 2 cm, the risk of metastases is up to 40%. Therefore, these patients require oncological right-sided hemicolectomy and then follow-up.

Most appendiceal NEN is located at the tip of the appendix (60-75%), less than 10% are found at the base of the appendix. There is no established correlation between tumour localisation and prognosis; it is assumed that metastases are more frequent in tumours located at the base of the appendix. The invasion of the mesoappendix above 3 mm is considered to have a worse prognosis for these patients.

Imaging methods:

There are no specific imaging studies available for appendiceal NEN. Those used in GEP-NET could be applicable. Computer tomography (CT-scan) and nuclear magnetic resonance (MRI) find their use in metastatic disease. Somatostatin receptor imaging (SPECT) and positron emission tomography (PET) are useful in cases where resection is not radical or when there is suspicion of metastases [13].

Genetic Study of VEGF in DPN

Several studies have discovered the role of VEGF gene variants in DPN. The polymorphism of VEGF gene in the position 7 C/T, 936 C/T, 1001 G/C, 1154 G/A, dan 2578 C/A location has been investigated in subjects with DPN [21,29,30]. In those variants, polymorphism of VEGF gene 7 C/T and 936 C/T were associated with DPN. According to Kim et al. (2009) and Zhang et al. (2014) [21,29], the polymorphism of VEGF gene 936 C/T (rs3025039) was also related with VEGF level. Zhang et al. (2014) [21] found that the polymorphism of VEGF gene 936 C/T '3UTR was associated with DPN. The CC genotype in that location associated with an increased risk for DPN. Moreover, VEGF serum in CC genotype was significantly higher compared to other genotypes.

Kim et al. (2009) [29] previously emphasized the role of VEGF 936 C/T gene polymorphism in the event of diabetic microvascular complications in Korea. This study was not able to find the relation of polymorphism gene in the diabetic neuropathy or nephropathy. Nevertheless, this study confirmed that the VEGF 936 C/T gene polymorphism was related to VEGF plasma. In this study T allele and TT genotype were associated with higher VEGF level compared to other allele and genotype. The basic mechanism of correlation between VEGF 936 C/T gene polymorphism was not known entirely. One possible explanation is that VEGF 936 C/T gene polymorphism probably interacts with other SNP form of VEGF gene that is not known yet and acts together in transcription. The mRNA analysis in VEGF 936 C/T gene mutation product showed no changes that can explain the increase and decrease of VEGF plasma. The polymorphism of VEGF gene 936 C/T probably caused the loss of the binding site to AP-4 factor, a transcription factor in a helix-loop-helix form that is important in VEGF expression [31].

Conclusion

The starting point of these several neuronal damage processes in DM was hyperglycemia as other microvascular complications. Hyperglycemia triggers some series of processes, specifically increase of sorbitol, PKC, DAG, and AGE, within which trigger the ROS and oxidative stress formation along with the increased proinflammatory cytokine expression. These processes also increased the production and expression of VEGF, resulting in angiogenesis, endotheliopathy, and increased vascular membrane permeability. The VEGF acts in DPN pathogenesis through this process. Nevertheless, VEGF also has a neuroprotective characteristic as it can trigger remyelination and neurogenesis.

Competing Interests

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Availability of data and materials

All data and materials supporting the conclusion of this article are included within the article.

Authors' contribution

PV designed the article. SI contributed to the patient clinical care and data collection. TB supervised the pathological investigation. SI, PV and TB wrote the manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable

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