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REVIEW

Neuroendocrine tumors and smoking

Tanja Miličević[1], **Maja Radman**[2]

1 Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital Center Split, University of Split Medical School, Spinčićeva 1, 21000, Split, Croatia

Corresponding author:
Tanja Miličević, Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital Center Split, University of Split Medical School, Spinčićeva 1, 21000, Split, Croatia;
E-mail: tanja.milicevic2@gmail.com

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Abstract

Neuroendocrine cells are dispersed around the body and can be found within the gastrointestinal system, lungs, larynx, thymus, thyroid, adrenal, gonads, skin and other tissues. These cells form the so-called ''diffuse neuroendocrine system'' and tumors arising from them are defined as neuroendocrine tumors (NETs). The traditional classification of NETs based on their embryonic origin includes foregut tumors (lung, thymus, stomach, pancreas and duodenum), midgut tumors (beyond the ligament of Treitz of the duodenum to the proximal transverse colon) and hindgut tumors (distal colon and rectum). NETs at each site are biologically and clinically distinct from their counterparts at other sites. Symptoms in patients with early disease are often insidious in onset, leading to a delay in diagnosis. The majority of these tumors are thus diagnosed at a stage at which the only curative treatment, radical surgical intervention, is no longer an option. Due to the increasing incidence and mortality, many studies have been conducted in order to identify risk factors for the development of NETs. Still, little is known especially when it comes to preventable risk factors such as smoking. This review will focus on smoking and its contribution to the development of different subtypes of NETs.

Key words: neuroendocrine tumors, carcinoid tumor, smoking, risk factors, carcinogenesis

1. Introduction

NETs are poorly understood and hence are an often under diagnosed group of neoplasms. Although slow-growing when compared with carcinomas, they can behave aggressively. In 2004, they comprised 1.25% of all neoplasms, and the incidence is increasing at a rate of 3–10% per year depending on the subtype [1,2]. The increase in incidence is in a great part due to the introduction of more sensitive diagnostic techniques as well as an overall increased awareness among physicians [3]. Recently, the World Health Organization (WHO) introduced a tumor-based classification, which distinguishes tumor by size, localization, proliferative rate, differentiation and hormone production, and consequently has far greater clinical applicability. In general, NETs are divided into well-differentiated and poorly differentiated categories. Well-differentiated NETs are also referred to as carcinoid tumors and include low- and intermediate grade groups. Poorly differentiated NETs are considered high grade by definition and include small cell and large cell neuroendocrine carcinoma [4]. NETs may present a considerable diagnostic and therapeutic challenge, as their clinical presentation is nonspecific and usually late, when metastases are already evident. Moreover, 15–25% of NETs exhibit a synchronous or metachronous association with other tumors, and tend to be multicentric (2% overall, 33% in the small bowel) [5,6].

NETs have been increasingly described in recent years, but the contribution of various risk factors to the development of NETs remains unclear. This is probably due to the general rarity of these types of tumors and the lack of relevant studies that are manly limited to case reports or small series [1]. The majority of studies have examined the influence of constitutive risk factors such as family history and genetics. Little is known about the influence of preventable environmental risk factors, such as smoking, on this type of malignancy.

2. Gastrointestinal NETs

Approximately 60% of all NETs originate in the gastrointestinal tract. The most frequently affected sites are the small intestine (29%), rectum (14%), stomach (5%) and appendix (5%) [7]. Although the small intestine has long been recognized as the most common primary site, the widespread use of colonoscopy for colorectal cancer screening has led to a rise in the incidence of rectal NETs [8]. Taghavi et al. compared the frequency of rectal and small intestinal NETs between 1992 and 2008 and demonstrated that small intestinal NETs were more frequent in the years before 2000, whereas rectal NETs were more common after 2000 [9]. Gastrointestinal NETs are more frequent among African Americans when compared with Caucasians and characteristically present at early ages [2]. Men appear to be more frequently affected with small intestinal NETs when compared to women (0.8 vs 0.57/100,000) while appendiceal and cecal subtypes occur equally between both sexes [4].

Because NETs usually cause no or only vague symptoms, diagnosis is generally delayed. As a result, the actual age of disease onset is usually lower than that reported by studies. Patients who are less than 60 years have a twofold higher risk of NET development than those who are over 60 [10]. Patients in the appendiceal subgroup are generally younger at the time of diagnosis, but the true age is likely even lower because most small tumors found incidentally at appendectomy are considered benign and not reported to the Surveillance, Epidemiology and End Results (SEER) program [4]. Most of these tumors are slow growing, but they have the potential to be aggressive, metastasize, and to be resistant to therapy [8]. Local-regional NETs often present with nonspecific abdominal symptoms such as cramping, bloating, and episodic diarrhea and patients are often mislabeled as having irritable bowel disease. Severe symptoms occur secondary to acute obstruction from the primary tumor or mesenteric fibrosis or ischemia secondary to mesenteric vascular involvement. Flushing and diarrhea, part of the classic carcinoid syndrome, is more likely to be present in advanced disease [4].

As for NETs in general, very little is known about the influence of smoking on gastrointestinal NETs. Epidemiological studies have reported diverse results. Some small studies found that smokers had an approximately twofold increased risk of developing gastrointestinal NETs [11,12]. The large case-control study by Rinzivillo et al. confirmed that smoking (OR: 1.47; 95% CI: 1.07-2.03, p = 0.01) and in particular heavy smoking (OR: 1.94; 95% CI: 1.29-3.84, p= 0.0008) are associated with an increased risk for NETs of the small intestine [13]. On the contrary, the NANETS Consensus Guidelines reported an insignificant correlation between smoking and gastrointestinal NETs [4].

3. Pancreatic NETs

Pancreatic neuroendocrine tumors (PNETs) are relatively uncommon, accounting for 10% of all pancreatic malignancies and 4–7% of all gastrointestinal NETs [14,15]. Analysis of the SEER data shows that the annual incidence in Western societies is 0.3 per 100,000 people with a slight, but persistent annual increase [2]. Most PNETs are sporadic, although they can be associated with inherited syndromes such as multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau disease. With an exception of genetic abnormalities in inherited syndromes, it is not known whether PNETs share the same risk factors as pancreatic adenocarcinomas such as smoking, family history of pancreatic cancer, or personal history of diabetes [15].

Given that the incidence of PNETs may be increasing, further investigation is needed in order to clarify risk factors for PNET development. The systematic review and meta-analysis by Haugvik et al. analyzed 4 studied populations and showed that any history of smoking was not a significant risk factor for sporadic PNET (OR: 1.21, 95% CI: 0.92–1.58; p = 0.18) while a heavy smoking history was a borderline significant risk factor (OR: 1.37, 95% CI: 0.99–1.91; p = 0.06) [14].

4. Bronchopulmonary NETs

Bronchopulmonary neuroendocrine tumors (BP-NETs) constitute approximately 20% of all lung cancers [1]. The WHO classification recognizes 4 types of lung neuroendocrine tumors: low-grade typical carcinoid tumor (TC), intermediate-grade atypical carcinoid tumor (AC) and 2 high-grade malignancies: large-cell neuroendocrine carcinoma (LCNEC), and small-cell lung carcinoma (SCLC) [16]. The most common lung NET is SCLC (20%), followed by LCNEC (3%), TC (2%), and AC (0.2%) [17]. Although BP-NETs are frequently discussed together; carcinoids are very different from high-grade SCLC and LCNEC [18]. Although BP-NETs share similar morphological and immunohistochemical features, low-grade tumors present with different biological characteristics when compared with more malignant groups [1]. The treatment approach to each of the BP-NETs is distinctly different, which emphasizes the importance of accurate pathologic diagnosis. Solitary carcinoid tumors are primarily a surgical disease. On the other hand, metastatic carcinoids are generally insensitive to chemotherapy or radiation therapy, and little can be offered to these patients [17]. Both SCLC and LCNEC progress aggressively and have a poor prognosis. SCLC is generally considered a nonsurgical disease, but is highly sensitive to initial chemo-radiation therapy. However, long-term survival is rare and most patients eventually die of recurrent disease. As there have only been a small number of patients with LCNEC recorded in literature, there is no consensus about the clinical management of this subtype of BP-NET [1,17,19].

The etiology of LCNEC and SCLC is strongly related to tobacco usage, whereas a correlation with bronchopulmonary carcinoids and tobacco smoking is uncertain [2,19,20,21]. Approximately 20-40% of patients with both typical and atypical carcinoid tumors are non-smokers, while virtually all patients with SCLC are cigarette smokers [22]. Moreover, the association between SCLC and smoking is so strong that this diagnosis in a nonsmoker is considered exceptional and should be carefully reviewed [17].

5. Adrenal NETs

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare subtypes of NETs arising from the chromaffin cells of the adrenal glands or extra-adrenal ganglia along the sympathetic and parasympathetic chains [23]. They affect approximately 1 in 2500-6500 individuals but the true incidence may be even higher due to delayed diagnosis until after death that is estimated to account for 0.05% more cases [24,25]. PHEOs comprise 80-85% of adrenal NETs, but these tumors account for only 5-7% of all adrenal incidentalomas [23]. The mean age at diagnosis is approximately 43 years and 10-20% of PHEO/PGLs are diagnosed in children, mainly associated with underlying genetic syndromes [26]. Adrenal NETs are capable of producing, storing, synthesizing and metabolizing catecholamines and consequently present with cardiovascular, gastrointestinal, nervous system and metabolic effects.

It is estimated that almost 25% of all PHEOs are inherited and half of them are associated with mutations in 1 of 17 susceptibility genes [23,27]. There is a lack of studies clarifying the influence of environmental risk factors such as smoking on this type of tumor.

6. NETs of the other sites

6.1 Larynx

While bronchopulmonary NETs are quite common, those affecting the larynx account for only 0.6% of all NETs [3]. The histological classification and prognosis of lung and laryngeal NETs is similar. Out of the four subtypes, AC is considered the most frequent non-squamous carcinoma of the larynx, followed by small cell carcinoma [3,28]. The majority of these tumors arise from the supraglottis. They affect men, with an average age of onset of 61 years for AC (range 36–83 years) and 50–70 years for small cell cancer (range 23–91 years). Similar to lung NETs, a majority of patients have a history of tobacco abuse [3,29].

6.2 Thymus

Since its first description in 1972, the incidence of thymic NETs is increasing with an average prevalence of 0.3% of all NETs [3]. Until now, more than 300 cases have been described. Next to the sporadic cases, thymic carcinoids may occur in association with MEN1. Among 185 mediastinal masses and among 65 tumors arising from the thymus, neuroendocrine differentiation and association with MEN1 is found in a significant percentage of cases [30]. More than 90% of cases are men, particularly heavy smokers [3].

6.3 Genital tract

NETs can also originate from the genital tract and they are generally more frequent in women. The most common types are uterine small cell carcinoma (SCC) and ovarian carcinoids. In contrast to the relatively benign ovarian carcinoids, poorly differentiated ovarian neuroendocrine carcinomas include both SCC and large cell carcinoma (LCC). They have an aggressive presentation and a poor prognosis. SCC and LCC may also arise from the endometrium and cervix [3].

In men, the most common and probably underestimated site of NETs is the prostate. However, what must be emphasized is that true prostate NETs are very rare tumors, whereas most of the prostate tumors with neuroendocrine appearance are consistent with non-NET adenocarcinomas with positive immunostaining for neuroendocrine markers [31]. SCC has been sporadically described in the scrotum, penis and urethra [3]. There is no relevant data on preventable risk factors and their influence on carcinogenesis of this type of tumor.

6.4 Thyroid gland

Medullary thyroid cancer is a rare tumor that appears in two forms: as a part of the MEN II syndrome, or as a more common sporadic form. However, its etiology has not been clearly defined. In a case-control study by Kalezic et al., when multiple risk factors for the development of this malignancy were evaluated, cigarette smoking was found to be protective (OR: 0.46, 95%, CI: 0.20-0.90) [32].

6.5 Urinary bladder

Small cell carcinoma of the bladder (SCCUB) is rare and aggressive malignancy with an incidence between 0.5% and 1% of all bladder cancers [33]. Risk factors contributing to SCCUB development are not fully clarified because of its rarity. Bhatt et al. found a high incidence of active smoking (78%) in the group of patients suffering from urinary bladder NET [34].

6.6 Pituitary gland

Pituitary tumors account for approximately 10% of all intracranial masses and mainly present as adenomas that are hormone-secreting or non-functioning [35]. However, the etiology of these tumors remains unclear, with no firmly recognized environmental risk factors. The study by Shoemaker et al. found no increase in the incidence of this type of tumor among smokers, which was confirmed by the results of the Million Women Study (RR in current vs. never smokers: 0.91, 95% CI: 0.60–1.40, P=0.7) [35,36].

7. Conclusion

In last decade, both sensible and reliable diagnostic techniques as well as increased awareness among physicians has resulted in an increased incidence of NETs at different sites. However, there are few confident data resolving the influence of variable risk factors, especially preventable ones, on the development of this type of malignancy. Smoking has been clearly recognized as a major risk factor in patients suffering from bronchopulmonary NETs while its connection with other types of NETs (gastrointestinal and genitourinary tract, adrenal and pituitary gland) is uncertain. Moreover, for some types of NETs, e.g. medullary thyroid cancer, it appeared

to be protective. Further studies are required in order to validate these findings.

Author contributions

MR gave an idea for the article, participated in drafting the article and gave the final approval. TM reviewed the previously published literature, participated in drafting the article and gave the final approval.

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