Review paper

Skin manifestations of neuroendocrine neoplasms: review of the literature

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Abstract

Neuroendocrine neoplasms (NENs) are a heterogeneous group of rare tumours derived from peptidergic neurons and specialized neuroendocrine cells capable of secreting various peptides or amines. These cells may be present in endocrine tissue or diffused in the tissues of the digestive or respiratory system. The article reviews the characteristic features of NENs, with particular emphasis on skin manifestations, such as necrolytic migratory erythema (NME), tongue inflammation, angular cheilitis, venous thrombosis and alopecia in glucagonoma; "flushing", "lion face", pellagra skin symptoms, "scleroderma-like features without Raynaud's phenomenon" in carcinoid tumours. The paper also presents the clinical picture of the neuroendocrine tumour of the skin – Merkel cell carcinoma. The aim of this study was to draw attention to the need for precise and comprehensive diagnosis of the patients, with particular emphasis on skin lesions as a revelator of neuroendocrine tumours. This management allows for the early implementation of appropriate treatment.

Key words: neuroendocrine neoplasms, NET, carcinoid tumour, skin manifestations, glucagonoma, dermatology.

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of rare tumours derived from peptidergic neurons and specialized neuroendocrine cells capable of secreting various peptides or amines [1]. A characteristic feature is the expression of neuroendocrine markers in the cells of these tumours, including an increased amount of somatostatin receptor protein (SSTR) [2]. These cells may be present in endocrine tissue (e.g. pituitary, parathyroid, adrenal), in glandular tissue (e.g. thyroid, pancreas) or diffused in the tissues of the digestive or respiratory system [3].

Among the neuroendocrine neoplasms, we distinguish tumours with different degrees of histological malignancy ("G" grading), ranging from highly differentiated NENs (from G1 to G3) to low differentiated neuroendocrine cancers (NECs) with a high degree of malignancy [4].

Depending on the degree of differentiation and histological maturity, determined by the percentage of cells with Ki-67 antigen and/or mitotic index, there are (according to WHO 2017) [5]:

1) Well-differentiated neuroendocrine tumours:
   a) NET G1 – neuroendocrine tumours G1 (Ki-67 < 3% or <2 mitoses per 10 fields of vision under high magnification),
   b) NET G2 – neuroendocrine tumours G2 (Ki-67 3–20% or 2–20 mitoses per 10 HPF),
   c) NET G3 – neuroendocrine tumours G3 (Ki-67 > 20% (usually ≤ 55%) or > 20 mitoses/10 HPF);
2) Low-differentiated neuroendocrine tumours – neuroendocrine cancers (NEC; Ki-67 > 20% (usually > 55%) or > 20 mitoses per 10 HPF):
   a) small cell carcinomas;
   b) large cell carcinomas.

Both hormonally active and inactive NENs can be well-differentiated. Low-differentiated NENs lose their secretory function (their immunohistochemical markers are non-specific – chromogranin A (CgA), in an insulin

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tumour – CgB (not routinely determined), synaptophysin or neuron-specific enolase) [4, 5].

Gastrointestinal NEN (GEP-NEN) are mostly malignant tumours. The clinical picture of an active tumour is usually dominated by symptoms caused by excessive hormone secretion, while the size of the tumour is small, which makes it difficult to locate. The neuroendocrine characteristics of clinically inactive tumours can be often demonstrated only by immunohistochemical examination [4].

Rare occurring mixed neoplasms – MiNENs (mixed neuroendocrine non-neuroendocrine neoplasms) – are most often located in the pancreas, containing components derived from the exocrine part of the pancreas and from neuroendocrine cells; treatment is the same as other pancreatic cancers [6].

Neuroendocrine tumours (NETs) can also be located within the respiratory system. There are 4 histological variants of pulmonary neuroendocrine tumours:
1) typical carcinoma;
2) atypical carcinoma;
3) large-cell neuroendocrine carcinoma; and
4) small cell lung cancer [7].

NEC represents about 0.5% of all cancers. In the last three decades, the incidence of these cancers has increased. The crude incidence is about 0.2/100,000. The risk of the disease increases with age and reaches a peak between 50 and 70 years of age. Based on available data, the incidence was estimated at 35/100,000/year. Unfortunately, most NENs are diagnosed at advanced stages of development, which makes effective treatment difficult. In patients from Western countries primary tumours are mainly located in the small intestine, rectum and pancreas [8–10].

Different types of neuroendocrine tumours cause different symptoms, depending on the location of the tumour and whether NET is active or inactive. Active NETs are defined on the basis of the presence of clinical symptoms resulting from excessive hormone secretion by the tumour. Inactive NETs do not secrete hormones. They may produce symptoms caused by tumour growth [11].

The common feature is the secretion of hormones or bioactive substances, which cause both extensive multisystem effects and often various skin symptoms [10].

Typical symptoms of NET include redness and warmth sensation of the face and/or neck (without sweating), diarrhoea, dyspnoea, tachycardia, heart palpitations, elevated blood pressure, fatigue, weakness, abdominal pain, muscle cramps, flatulence, unexplained weight gain or loss, wheezing, coughing, swelling of feet and ankles, elevated blood glucose levels (frequent urination, increased thirst, increased hunger), decreased blood glucose levels (tremors, dizziness, sweating, fainting), and skin lesions [4, 12, 13].

This article reviews the main dermatological manifestations of NENs.

The aim of this study was to draw attention to the need for precise and comprehensive diagnosis of the patient, with particular emphasis on skin lesions as a revelator of NENs.

Skin manifestations of neuroendocrine tumours

Glucagonoma

Glucagonomas are rare tumours, derived from α cells of the pancreas. These neoplasms exhibit typical features of islet cell tumours; they are usually 2 to 25 cm in size and are most often located in the tail of the pancreas. According to the World Health Organization (WHO) classification of gastrointestinal tumours, glucagonoma is a type of active pancreatic neuroendocrine neoplasm (pNEN) [14]. Despite its mild histological appearance, most tumours are malignant, prone to metastases, which already occur at the time of cancer diagnosis.

Glucagonoma syndrome is an extremely rare disease with an estimated prevalence of 1/20 000 000/year. The peak incidence is in the fifth decade of life. Rarely, glucagonoma may be associated with multiple endocrine neoplasia (MEN) type 1 [15–17].

Glucagonoma is a neuroendocrine tumour of the pancreas (pNET), it secrets glucagon and causes symptoms called glucagonoma syndrome [18]. The clinical syndrome that is classically associated with glucagonoma includes necrolytic migratory erythema (NME), abdominal pain, diarrhoea, constipation, weight loss, diabetes, anaemia, lip inflammation, venous thrombosis and neuropsychiatric symptoms. NME and weight loss occur in approximately 65% to 70% of patients at the time of diagnosis [18]. Diabetes mellitus affects 75% to 95% of patients with glucagonoma. Hyperglycaemia is usually mild and easily controlled by diet and oral hypoglycaemic agents and is not associated with diabetic ketoacidosis because β cell function is preserved [19].

Surgical excision is currently the only fully effective method of glucagonoma treatment. An infusion of somatostatin analogues (SSA) and/or amino acid solution may cause rapid resolution of symptoms [20]. Transdermal chemotherapy, radiotherapy and radioligand therapy with peptide receptors can also be useful [18, 21].

Skin changes in the course of the glucagonoma

NME initially manifests itself by the occurrence of erythematous papules or plaques covering the face, perineum and limbs. Skin lesions usually occur in the periorificial, flexial and acral regions; they resemble changes associated with zinc deficiency [22, 23]. In the next 7 to 14 days the lesions increase with the next subsidence and leaving brown, hardened areas in the central part. On the periphery there are blisters (with tendency to epidermis exfoliation) and erosions covered with crusts. The affected areas are often itchy and painful [19, 21–23].

Disorders in the structure of the epidermis causing the skin changes observed in NME are probably the result of several interdependent factors including hypoaminoacidemia, zinc and essential fatty acid (EFA) deficiency and induction of inflammatory mediators in the epidermis [24]. Histology of NME revealing parakeratosis, the loss of the granular layer, necrosis, and separation of the upper epidermis with vacuolization of the keratinocytes, dyskeratotic keratinocytes, and neutrophils in the upper epidermis [25].

In addition, patients with glucagonoma may develop tongue inflammation (red, shiny/smooth tongue), angular cheilitis, venous thrombosis and alopecia. Additionally, like other ulcerative dermatoses, NME may be complicated by secondary skin infections, most commonly caused by Candida and Staphylococcus aureus [26, 27].

Carcinoid tumours

Carcinoid tumours are rare, slow-growing tumours derived from the middle part of the gastrointestinal tract. The incidence rate is estimated at 5.25/100,000 [8, 28]. According to the new classification, carcinoid refers only to tumours that secrete serotonin. Histopathologically, these are highly differentiated serotonin-producing neuroendocrine tumours. Depending on the location of the tumour and the presence of metastases, in addition to serotonin, carcinoid tumours may also secrete histamine, corticotropin, dopamine, substance P, neurotensin, prostaglandins, kallikrein, bradykinin and tachykinin. Most of the tumours are located in the gastrointestinal tract, the main bronchi and the lungs. They constitute about 50% of gastro-entero-pancreatic neuroendocrine tutors (GEP-NETs) [4, 29, 30]. Single cases of primary skin carcinoma outbreaks and metastases of carcinoid tumour to skin were also described. The primary outbreaks were in the form of single, hard, non-inflammatory, domed nodules, and metastatic lesions in the form of pink, fast growing or subcutaneous nodules [28, 30–33].

About 10% of patients with carcinoid tumour develop a syndrome of symptoms called carcinoid syndrome. It is usually caused by the spread of neuroendocrine neoplasm. The symptoms mainly concern the gastrointestinal tract, respiratory system, cardiovascular system and skin. The criteria for diagnosing carcinoid syndrome include:

1) presence of metastases of neuroendocrine neoplasm to the liver or a primary tumour in the lungs,
2) peripheral vasomotor symptoms (a flushing few-minute redness of the face and neck) with tachycardia, dizziness, sometimes with swelling and excessive sweating, gradually leading to permanent telangiectasias,
3) gastrointestinal symptoms – watery diarrhoea (occurs in 30–80% of patients) with concomitant colic-like pain,
4) bronchospasm (rarely observed).

Other symptoms include a blood pressure drop, headaches, heart palpitations, weakness, weight loss and arthritis. In the course of the carcinoid syndrome, serotonin-induced fibrosis of the right endocardium may occur, and some patients develop tricuspid valve and pulmonary trunk defects [4, 29, 34].

Skin symptoms of the carcinoid syndrome include a characteristic "flushing" – sudden paroxysmal redness of the skin of the face, neck and anterior surface of the chest. As a result of repeated, prolonged relapses, the skin lesions become fixed, and a bluish erythema with telangiectasias develops. The aggravating factors include alcohol, stress and some foods. If the primary tumour is located in the stomach, where ECL cells primarily produce histamine, the face becomes blue in the course of the flushing and sometimes the skin overgrowth getting the characteristics of a "lion face" [4, 30, 35].

Patients may also develop pellagra skin symptoms caused by a deficiency of tryptophan, which consumption for serotonin synthesis is high – erythema, xerosis, scaling, hyperkeratosis and pigmentation. Cases of "scleroderma-like features without Raynaud's phenomenon" were also described. Some patients have dry skin and itching [4, 30, 35].

Neuroendocrine tumours of skin – Merkel cell carcinoma

Merkel cell carcinoma (MCC), otherwise known as neuroendocrine or trabecular carcinoma, is a rare skin neuroendocrine cancer, characterized by an aggressive course, prone to local recurrence and metastases to regional lymph nodes and distant organs. The aetiology is not fully understood, and the risk factors include UV exposure, immunosuppression and polyoma infection (Merkel-cell polyavirus, Merkel-cell polyomavirus – MCPyV). It is usually diagnosed in elderly people over 50 years of age (mean age about 75 years) [36, 37].

The most common locations where cancer from Merkel cells occurs include areas exposed to chronic UV exposure – mainly the head and neck, and less often, the limbs or trunk. It is usually a painless dome, purple-blue or cherry-red nodule with a cohesive consistency. Sometimes the skin lesions take on an erythematous and infiltrated form. Rare clinical manifestations include the "giant variant", mucosal form, ulcerative tumours and numerous nodular lesions. Merkel cell carcinoma is characterized by rapid growth [30, 36, 37].

AEIOU acronym (asymptomatic, expanding rapidly, immune suppression, older than 50 years, and ultraviolet-exposed site) is used to describe the most common symptoms. In histopathological examination, the tumour is made up of blue cells with blurred boundaries (kurky cells), evenly distributed, or sometimes arranged in a trabecular system. The gold standard in the treatment is surgical removal of the lesion [30, 36, 37].

Neuroendocrine tumours treatment

Patients diagnosed with metastatic disease are usually not eligible for curative surgery since the disease has spread to other parts of the body.

Systemic treatment can be administered to individuals who are not candidates for surgery, which can help alleviate symptoms as well as slow the growth of tumours. Cancer treatment options based on evidence include Somatostatin analogues, mTOR inhibitors, TK inhibitors, peptide receptor radionuclide therapy (PRRT), chemotherapy, as well as cytoreductive techniques.

There is, nevertheless, a growing demand for new treatments.

Somatostatin

Somatostatin (SST) is a neuropeptide that is released by paracrine cells located throughout the gastrointestinal tract and the brain. It works by binding to five G-protein-coupled receptors (SST receptors 1–5, SSTR1–5) [38]. It suppresses the release of numerous hormones, works as an immunological regulator, and acts as a neurotransmitter [39]. It also has cytotoxic and cytostatic properties, and under some conditions, may trigger apoptosis [40].

SSAs are usually well tolerated and with limited side effects, the more frequent being pain in the injection site and gastrointestinal side effects (abdominal pain, diarrhoea, nausea) [39].

Although many patients treated with SSA have symptomatic improvement and tumour growth stabilization for varied periods, tumour regression is uncommon, and hence multimodal therapy techniques are required to further improve the clinical care of patients with advanced NETs [38, 39].

Interferon (IFN) α

In the 1980s, IFN-α was approved for the treatment of NETs [41]. It acts through a variety of methods on cell proliferation and differentiation [42].

IFN is reserved for patients who are resistant to, or are unable to tolerate, SSA and other systemic medications, in addition to SSA for improved symptom control, or as a bridge therapy before initiating other treatments [43].

Telotristat ethyl

Telotristat ethyl is a new oral inhibitor of tryptophan hydroxylase, which is required for serotonin production. Based on the results of the clinical trials [44, 45], the United States Food and Drug Administration (FDA) recently approved telotristat ethyl (Xermelo, Lexicon Pharmaceuticals, Inc.) as the first and only oral treatment, in combination with SSAs, for adult patients with carcinoid syndrome-related diarrhoea who are not adequately controlled with SSA therapy alone.

Targeted therapies – mammalian (mechanistic) Target of Rapamycin (mTOR) inhibitors

mTOR is a protein kinase that controls cell growth, proliferation, and survival [46]. Many cancer models, including NETs, have abnormal over-activation of mTOR, and inhibition of mTOR by rapamycin and its analogues, such as everolimus (Afinitor, Novartis Oncology), has been shown to arrest tumour cell proliferation and slow tumour growth [46, 47].

Everolimus was approved (by FDA) for the treatment of PNETs non-functional progressive intestinal and lung NETs. Importantly, the combination of everolimus and SSAs is thought to have a synergistic effect and should be used in patients with progressive NETs [48].

Sunitinib maleate (Sutent®, Pfizer, Inc.) is a tyrosine kinase inhibitor (TKI) with anti-tumoral and antiangiogenic properties against several solid tumours. Sunitinib has been shown to be effective in both preclinical and clinical studies for pNETs [49].

Vascular endothelial growth factor inhibitor

Bevacizumab is a vascular endothelial growth factor inhibitor (VEGF). In the treatment of GI-NETs, the combination of bevacizumab and capecitabine demonstrated clinical activity and a manageable safety profile that warrants validation in a randomised phase III trial [50].

Summary

In our article we wanted to draw attention to the characteristics of skin symptoms occurring among patients suffering from neuroendocrine tumours. Precise examination of the patients, with particular emphasis on dermatological examination, may significantly accelerate the diagnosis of neuroendocrine tumours, allowing for early implementation of appropriate treatment.

Conflict of interest

The authors declare no conflict of interest.

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