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Ocular Manifestations in Neuroendocrine Tumors: A Review Article

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ABSTRACT

Introduction: Neuroendocrine tumors (NETs) are a diverse group of tumors that arise from neuroendocrine cells and can synthesize and secrete neuropeptides or hormones. Although NETs usually originate from the gastrointestinal tract or bronchopulmonary tree, they can affect various organs, including the eye. The majority of ocular association with neuroendocrine tumors results from metastasis that affects the orbit, however, primary ocular tumors have been reported.

Purpose of the study: The article reviews the presentation of ocular manifestations in neuroendocrine tumors including pheochromocytoma, ocular paraganglioma, gastrointestinal and bronchial NETs, Merkel cell carcinoma and neuroendocrine metastasis.

Materials and methods: In order to summarize the current knowledge on the topic, a literature review of English language papers with a focus on the most current literature was performed. The review was conducted with the PubMed database with 43 works used, accessed before September 2024.

Conclusions: Instances of neuroendocrine tumors leading to ocular manifestations have become increasingly prevalent. These nonspecific symptoms can make it challenging to

diagnose ocular NETs. Ocular manifestations are not typically the primary symptom, but patients with tumors located in the eye may experience symptoms such as eye pain, blepharitis or exophthalmos. Ocular motility and vision may also be affected. It is crucial to study the association between those symptoms and NETs, in order to develop a more comprehensive understanding of the matter.
Keywords: neuroendocrine tumor; ocular; carcinoid; Merkel cell; pheochromocytoma; paraganglioma

INTRODUCTION

Neuroendocrine tumors are a diverse group of malignancies characterized by complex histology and terminologies. The term "neuroendocrine" results from cells that exhibit both "neuro" and "endocrine" features and are widely distributed throughout the body. The neurological property is based on the presence of dense-core granules (DCG4) that are similar to those found in serotonergic neurons, responsible for the storage of monoamines. However, unlike neurons, NE cells do not contain synapses. The endocrine property refers to the production and release of these monoamines [1]. In light of our research, we conducted a comprehensive review of scientific literature focused on neuroendocrine tumors in relation to the eye and eyelid. Our study aims to provide understanding of the pathophysiology and clinical presentation of these tumors, along with the current diagnostic and therapeutic approaches available for their management.

STATE OF KNOWLEDGE

Pheochromocytomas/paragangliomas

Pheochromocytomas/paragangliomas (PPGL) are a type of rare neuroendocrine tumors that develop from neural crest cells [2]. These neoplasms can produce and secrete various substances including catecholamines, vasoactive intestinal peptide (VIP), parathormone (PTH), calcitonin gene-related peptides (CGRPs), opioids, corticotropin-releasing hormone (CRH), adrenocorticotropin+ (ACTH), histamine, chromogranin and interleukin-6. PPGLs can be misdiagnosed as they trigger symptoms similar to panic syndrome, anxiety or hypoglycemia, due to the release of catecholamines by the tumor, which stimulates adrenergic receptors [3].

PPGLs are typically found in the adrenal glands. Only 10-15% occur extra-adrenally and are called paragangliomas (PGLs). PGLs can appear in the abdomen and testicles [3], however, there have also been reports of head and neck presentation [2]. Orbital localization is rarely observed, but when it is, it often originates from ciliary nerve ganglion or sustentacular cells [4]. It is usually located in the intraconical space and can affect the optic nerve. If the local invasion is present, it most commonly involves the extraocular muscles. PGL of the orbit affects both genders equally [5], predominantly adults, with an average age of 30-40 years at presentation [4].

Patients with primary orbital paraganglioma are frequently wrongly diagnosed with idiopathic orbital inflammatory pseudotumor. The presentation usually begins with exophthalmia and blepharitis. As the disease progresses, individuals may experience difficulty in ocular motility, diplopia, strabismus and decreased vision [4]. Eye pain can occur, but it is not frequent [5]. If the paraganglioma is located in the sellar or suprasellar region, symptoms of pressure on the optic chiasm may appear [6]. In the eye examination, conjunctival and scleral congestion can be observed, and in the posterior pole of the eye - choroidal wrinkling and papilledema [4].

Most paragangliomas are benign and progress slowly - the onset of proptosis can vary from 2 months to 17 years. However, there have also been described cases of fast-growing orbital paragangliomas that have recurred after excision [4]. Usually, orbital paragangliomas have an excellent prognosis and their mortality rate is approximately 7,1% [5].

The most commonly used imaging technique in diagnosing orbital PGLs is computed tomography (CT), which reveals a clearly defined, homogenous and hyperdense mass [5]. In magnetic resonance imaging **(**MRI), the appearance of "salt and pepper" is characteristic of paragangliomas, although not specific [7]. For confirmation electron microscopy is being used. The neoplasms are reported to have positive reactions with chromogranin, synaptophysin, neuron-specific enolase and S100 [5].

The most common method of management involves surgery, followed by adjuvant radiation therapy if necessary [5]. There have also been reports of the regression of the tumor after the biopsy alone [8].

The manifestation of primary adrenal neoplasm metastasizing to the eye differs from primary orbital paragangliomas. Pheochromocytoma usually presents with symptoms such as hypertension, headache, palpation and ephidrosis. It is not uncommon for the patient to present papilledema or visual blurring, although ocular symptoms rarely are the initial manifestation [9]. However, patients with metastatic pheochromocytoma to the orbit may initially present with painful eye movements, ocular pain and proptosis, without typical pheochromocytoma symptoms. Pheochromocytoma commonly metastasizes to the bone, intra-abdominal organs, lungs and pleura [10]. While ocular localization is rare, there have been reports of intraorbital metastasis [11].

NETs of the gastrointestinal system

Neuroendocrine tumors (NETs) are commonly found in the gastrointestinal system and it is the most frequent origin of metastases. When these tumors spread to the orbit, they typically locate in the extraocular muscles. This occurrence is considered rare; however, there has been a rise in reported cases [12]. Metastasis is frequently detected incidentally during a positron emission tomography–computed tomography scan (PET-CT) conducted as part of the primary tumor diagnosis [13].

Although systemic symptoms tend to manifest faster than ocular manifestations, ophthalmological symptoms can be the primary presentation of metastatic NETs. The most common manifestations are diplopia, proptosis or decreased vision [13], and less frequently, unilateral orbital pain, erythema and chemosis. The nerves can be affected by nerve palsy, which can present with a pupil non-reactive to light and no accommodation in the affected eye [12]. The presentation is usually unilateral [13].

The orbital fat, uvea, eyelid and apex can also be affected [14], but the rectus muscle is most commonly involved [13]. It can present as muscle enlargement and difficulty of movement [12]. The management of a muscle mass typically requires surgery, tumor debulking and adjuvant chemotherapy or radiotherapy depending on the case. Systemic treatment may involve the use of somatostatin analogs or everolimus [13]. After treatment, ophthalmological symptoms should subside, although complications may include residual disease and visual impairment [12].

Carcinoid syndrome is a frequently occurring condition in patients who have an underlying neuroendocrine tumor. It can present in various ways, both in mild symptoms or severe manifestations. The presentation depends on the hormonal effects of serotonin secreted by the tumor [15]. It can affect the digestive tract by mesenteric fibrosis, causing malabsorption and difficult-to-control diarrhea. That can lead to the necessity of bowel resection, resulting in vitamin deficiencies [16]. There has been reported inadequate absorption after resection of malignant ileal carcinoid, which led to vitamin A deficiency. Prolonged insufficiency of vitamin A can result in depleted functional rhodopsin, loss of visual sensitivity and eventual loss of photoreceptor outer segments. The patient may experience nonspecific night blindness, which can pose a challenge in diagnosis [17]. Patients have also presented with a deficiency of vitamin B12, which can cause gradual central vision loss and central scotoma [16].

According to reports, delayed optical presentations may appear long after initial neuroendocrine tumor diagnosis and resection. The study conducted by Mustak et al. proved that the average time from diagnosis of primary neuroendocrine neoplasm to orbital or ocular disease is 4,4 years [14].

Neuroendocrine midgut tumors can also cause optic manifestations due to a paraneoplastic process. There has been reported a presentation with an isolated sarcoid-like lesion in the choroidea, located in the macular region. The first symptoms that were observed were bilateral decreased vision and photophobia. Cases like this can pose a diagnostic challenge as it is difficult to distinguish between tumor spread and paraneoplastic reaction [18].

Lung carcinoid tumors

Carcinoid tumors originate from neuroendocrine cells, primarily in the lungs. From the opthalmological point of view, they are important due to their potential to metastasize to the eye and orbit. The current state of knowledge indicates that tumors originating from the lungs have a predilection for the uveal tract, particularly the choroid. It also tends to involve the iris and ciliary body [19]. Most commonly, intraocular malignant tumor is metastatic. It often affects choroidea and at most times comes from the lung in males and breast in females [20]. It has been estimated that 2.2% of uveal tract metastases are attributed to carcinoid tumors. The bronchoalveolar is the most frequent origin of carcinoid tumors that metastasize to the uveal tract. Such metastases from mediastinal carcinoids are rare [19]. Uveal metastasis stands as the predominant intraocular malignancy observed in adults. Nevertheless, choroidal metastasis

originating from a carcinoid tumor is exceptionally uncommon, particularly within the pediatric population [21].

A primary ophthalmoscopic finding in ocular metastases is the presence of choroidal amelanotic masses, which may manifest in multiple locations and affect both eyes. Regular ocular screening is not typically performed to detect carcinoid metastasis to the eye [19], due to the fact that a typical carcinoid is a rare and low-grade lung neuroendocrine neoplasm. It should be, however, considered in any patient with a carcinoid tumor who presents with visual symptoms [20]. In asymptomatic patients with metastatic carcinoid whose visual acuity remains excellent, observation of the ocular lesions seems to be an acceptable management approach [22]. The presence of metastases in the choroid membrane significantly increases the probability of having multiple metastatic lesions in other organs [23].

Cancer-associated retinopathy (CAR) is a paraneoplastic neurological syndrome characterized by retinal degeneration [24]. CAR is linked with a range of malignancies, with small cell lung cancer (SCLC) among them. For around 40% of the tumors associated with CAR accounts lung cancer. The majority of patients with SCLC-associated CAR typically do not present evident vasculitis upon fundoscopy or fluorescein angiography (FA) [25]. Large-cell neuroendocrine carcinoma (LCNEC) is a rare, aggressive subtype of neuroendocrine tumors characterized by rapid growth. Pulmonary LCNECs comprise approximately 2-3% of all lung cancers. Most reports concentrate on ophthalmologic assessments, lacking thorough descriptions of tumor pathology. Its prevalence is gradually increasing. The most common manifestations of orbital metastatic NETs include a palpable mass and diplopia, while inflammatory symptoms and visual impairment are less frequent. Uveal metastatic NETs on the other hand, most commonly manifest with decreased vision. It is uncommon for NETs to present with ocular symptoms prior to symptoms from the primary site. According to the limited available literature, only 22–30% of patients present initially with ocular or orbital disease [26]. So far, only three cases of CAR-complicated LCNEC have been documented. Given the rarity of LCNEC, its clinical characteristics remain not specified. Accurate diagnosis demands meticulous pathological analysis. Furthermore, there are limited case reports of CAR-complicated lung adenocarcinoma [24]. No single clinical sign or radiological feature definitively diagnoses metastatic NETs [26]. Retinopathy might serve as an early indicator preceding systemic symptoms by months [25].

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare, but highly aggressive form of skin cancer with a significant potential for metastasis. The metastatic form of Merkel cell carcinoma (mMCC) is characterized by a poor prognosis, with reported 5-year overall survival (OS) rates lower than 18% [27]. In 22% of cases, metastasis affects nearby lymph nodes, while 38% of cases are associated with distant lymph nodes [28]. Non-enveloped, double-stranded DNA virus - MCPyV, belonging to the polyomavirus family, is present in most MCCs. Infection with MCPyV is common and typically asymptomatic, except when clonal integration of viral DNA into the host genome takes place [29]. The incidence of this disease increased 3.5 times in the United States between 2012-2016 compared to 1987-1991 [30].

Due to frequent exposure to sunlight, eyelids account for 5-10% of all Merkel cell carcinomas [31]. While other parts of the eye are rarely affected, there have been reports of involvement of the conjunctiva and lacrimal gland [32,33], and metastases to the iris and orbit [34,35].

This malignancy predominantly affects patients in their sixth decade of life or older and has a poor prognosis, characterized by a mortality rate of approximately 40% [36].

The lesions, typically appearing as purple, painless lumps, are commonly observed on the upper eyelid's edge and can often be misdiagnosed as skin cysts, hemangiomas or chalazions. The presence of symptoms such as eyelash loss, ulceration, telangiectasia and regional spread manifestations such as enlarged cervical and submandibular lymph nodes, swelling of the parotid glands and proptosis should be interpreted as an indication of cancer [37].

Histological examination, particularly immunohistochemical analysis of tumor tissue samples, is the primary method of diagnosing Merkel cell carcinoma [38].

The treatment of Merkel cell carcinoma usually involves surgical removal of the tumor through wide local excision, coupled with radiotherapy. Surgical excision with a margin of 1-2 cm is generally the primary mode of treatment for local cases. However, it can be difficult to perform this procedure in the case of eyelid tumors due to their cosmetic significance and role in protecting the eye. Therefore, a margin of 5 mm may be appropriate, as long as there is histologic evidence of negative margins. Chemotherapy, which was previously used to treat MCC, has been replaced by a combination of chemotherapy and immunotherapy [39]. While

chemotherapy may initially improve the patient's condition, its effects tend to fade quickly and do not lead to increased overall survival rates. As a result, immunotherapy has become the preferred first-line systemic treatment for advanced MCC [40].

Metastasis

Imaging modalities are used to identify and localize lesions, yet they often fail to provide insights into tumor composition. On CT scan, orbital metastatic NETs typically present as contrast-enhancing soft tissue masses, exhibiting similar density to the surrounding extraocular muscles on magnetic resonance imaging. The management of metastatic orbital or ocular NETs depends on the histological diagnosis and both patient's systemic and affected eye condition. Given the rarity of the disease, there is currently no universally accepted treatment guideline. However, existing literature suggests that for orbital NETs, small lesions may be managed with local excision alone, while larger orbital metastases may require excision coupled with palliative radiotherapy. Systemic chemotherapy may also be considered as an adjunctive treatment. In cases of intraocular NETs, systemic chemotherapy is often administered as first-line therapy, with additional radiotherapy if necessary. If ocular or orbital metastases fail to respond to other treatments, exenteration or enucleation may ultimately be necessary [26]. Alongside systemic chemotherapy and surgical interventions, 177Lu-DOTATATE peptide radionuclide receptor therapy has emerged as a potential treatment option for patients experiencing symptomatic metastases originating from orbital involvement [41].

Orbital metastases originating from neuroendocrine tumors are exceedingly uncommon, with fewer than 40 reported cases to date. Initial presentation with ocular symptoms is even rarer [41]. Intraocular metastasis often accompanies systemic metastasis. It usually spreads by hematogenous transport, with the choroid serving as a route due to its rich vascularization. Reported cases of metastatic orbital tumors include breast cancer (53%), prostate cancer (12%), lung cancer (8%), melanoma (6%) and kidney cancer (5%) [42]. The metastases typically appear as heterogeneous, well-circumscribed and contrast-enhancing lesions on neuroimaging. The appearance of new ocular symptoms in addition to a history of neuroendocrine tumors and these characteristic radiological findings should raise a high clinical suspicion of metastatic disease. In cases of atypical radiological findings biopsy may be necessary to rule out alternative causes of orbital lesions [43].

Orbital metastases originating from breast cancer typically present unilaterally, manifesting approximately 4.5 to 6.5 years after the primary lesion's treatment. Despite ductal carcinoma being the most frequent histologic type of breast cancer, orbital metastases predominantly arise from lobular carcinoma, accounting for the majority of cases of metastases. Orbital metastasis from ductal carcinoma of the breast has been documented, but it remains rare, with infrequent case reports [42]. Differently from other primary malignancies leading to orbital metastases, patients with neuroendocrine tumors involving the orbit demonstrate an excellent prognosis, as their 10-year survival rate oscillates around 40% [41].

CONCLUSIONS

This review paper provides a comprehensive analysis of the existing literature regarding ocular symptoms in endocrine tumors, including pheochromocytomas/paragangliomas, NETs of the gastrointestinal system, carcinoid tumors, Merkel cell carcinoma and metastases. This article encompasses various aspects of neuroendocrine tumors, including mainly ocular clinical symptoms and their pathomechanism, along with diagnosis and treatment. Given the lack of literature on these conditions, obtaining a comprehensive understanding of these diseases can be challenging. Ocular symptoms associated with neuroendocrine tumors are often nonspecific, which may lead to misdiagnosis of them as other ocular conditions. The prognosis of these symptoms is greatly dependent on the type of neuroendocrine tumor involved, its degree of advancement, malignancy and available treatment options.

Therefore, it is crucial that the scientific community continues to diligently observe this topic and conduct further research to develop a more comprehensive understanding of the matter.

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