Eur Arch Otorhinolaryngol (2016) 273:533–536
DOI 10.1007/s00405-014-3351-5

REVIEW ARTICLE

Paraneoplastic syndromes in patients with laryngeal neuroendocrine carcinomas: clinical manifestations and prognostic significance

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Received: 14 October 2014 / Accepted: 20 October 2014 / Published online: 29 October 2014

Abstract Paraneoplastic syndromes are associated with a variety of malignant neoplasms and are systemic and non-metastatic manifestations that develop in a minority of cancer patients. This review examines all published cases of paraneoplastic syndromes associated with neuroendocrine carcinomas of the larynx. There are a total of ten patients reported with paraneoplastic syndromes associated with laryngeal neuroendocrine carcinomas in the literature. Of these, nine died and the tenth is alive with liver metastases. There were five cases of small-cell neuroendocrine carcinoma, four cases of moderately differentiated neuroendocrine carcinoma, and one case of well-differentiated neuroendocrine carcinoma associated with paraneoplastic syndromes. As these syndromes have significant clinical relevance, physicians should be aware of the possible presence of paraneoplastic syndromes in the diagnostic process of patients with neuroendocrine carcinoma of the larynx.

Keywords Paraneoplastic syndromes · Neuroendocrine carcinomas · Prognosis · Larynx · Diagnosis

This article was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).

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Introduction

Paraneoplastic syndromes (PNS) are systemic or organ-related functional tumor-associated symptoms that occur distant to the tumor. These disorders arise from tumor secretion of hormones, peptides, or cytokines or from immune cross-reactivity between tumor and normal tissues. PNS are almost always associated with malignancies although some exceptions have been reported in patients with benign tumors [1, 2].

When a patient without a known cancer presents with a PNS, a diagnosis of cancer should be considered and investigated. PNS often cause considerable morbidity, but effective treatment can improve patient quality of life, enhance cancer therapy and prolong survival.

PNS are categorized into six types: dermatologic or cutaneous, endocrine, hematologic, neurologic, osteoarticular or rheumatologic and ocular. PNS can precede, follow or be concurrent with the diagnosis of a malignancy. The most common malignancies that give rise to PNS are lung cancer (especially small-cell carcinoma and squamous cell carcinoma), breast cancer, gynecologic cancers and hematologic malignancies.

Head and neck tumors have been less frequently associated with PNS [3–12]. However, the exact incidence of PNS in association with these tumors is not known. Squamous cell carcinoma is the most frequent malignant tumor of the head and neck associated with PNS. Bazex's syndrome, a dermatologic disorder characterized by psoriatic lesions on the extremities and head, is the most frequent PNS seen in patients with malignancies of the larynx and hypopharynx [5]. PNS have further been observed in association with medullary thyroid carcinoma (MTC) [13, 14]. About 1 in 3 patients with MTC experience pseudocarcinoid or carcinoid-like syndromes that may precede diagnosis of MTC for several years, are attributable to serotonin production and resolve after removal of the tumor [13]. Symptoms due to ectopic corticotrophin-releasing hormone or ectopic adrenocorticotropic hormone (ACTH) by MTC are also not rare, whereas ectopic production of parathyroid hormone-related peptide, insulin and glucagon has been reported occasionally [14].

The last important group of head and neck tumors associated with PNS are the morphologically heterogeneous group of neuroendocrine neoplasms [8, 12]. These tumors may be benign or malignant and they have the ability to synthesize and secrete biologically active substances characteristic of their cell of origin, giving rise to clinically distinct PNS. In the larynx they can be categorized into five types: well-differentiated neuroendocrine carcinoma (WDNC) or typical carcinoid, moderately differentiated neuroendocrine carcinoma (MDNC) or atypical carcinoid, small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), all epithelial lesions and paraganglioma, a neural lesion [15, 16].

The purpose of the present paper is to review the current knowledge on PNS associated with laryngeal neuroendocrine carcinomas.

Review of the literature

PNS associated with laryngeal neuroendocrine carcinomas are rare, but can cause severe symptoms. In the larynx, 10 cases of PNS (9 endocrine and 1 neurologic) associated with neuroendocrine carcinoma have been reported [17–26]. These include five cases of carcinoid syndrome [20, 22, 24–26]; three cases of Schwartz–Bartter syndrome (syndrome of inappropriate secretion of antidiuretic hormone [SIADH]) [17, 21, 23]; one case of ectopic ACTH syndrome [19]; and one case of Eaton–Lambert myasthenic syndrome [18]. One of the patients with carcinoid syndrome had WDNC [22] and four had MDNC [20, 24–26]). Of note, elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) may be found in patients who do not have carcinoid syndrome. Other syndromes associated with SCNC were ACTH syndrome [19], SIADH [17, 21, 23] and Eaton–Lambert syndrome [18]. PNS have not been reported in LCNC or in paraganglioma of the larynx. Of 10 reported patients with laryngeal neuroendocrine carcinomas who developed PNS, nine died [17–21, 23–26] and the single survivor has liver metastases [22].

In 1979, Trotoux et al. [17] described a patient with SIADH who presented with headache, confusion and temporo-spatial disorientation, hyperreflexia, hyponatremia, hypochloremia, serum hypo-osmolarity, reduced hematocrit level, negative free-water clearance and high plasma levels of antidiuretic hormone. SCNC of the subglottis was established 3 months after initial presentation. In 1984, Medina et al. [18] reported a case of SCNC of the larynx associated with clinical and electromyographic evidence of myasthenic syndrome. In 1985, Bishop et al. [19] reported the first case of laryngeal SCNC associated with ectopic ACTH syndrome. In 1987, Baugh et al. [20] reported a case of MDNC of the supraglottis. Twenty-six months after therapy, the patient was admitted with abdominal cramps, distention, alternating diarrhea and constipation and a generalized warm feeling. Urinary vanillylmandelic acid (VMA) and 5-HIAA levels were normal. Multiple liver metastases and a retroperitoneal mass were found. The patient died 41 months after surgical treatment. In 1989, Takeuchi et al. [21] reported a case of SCNC of the larynx associated with SIADH and hyponatremia that persisted until the patient's death, despite the administration of salt. In the same year, a case of WDNC of the larynx was identified from the files of the Department

Table 1 PNS associated with laryngeal neuroendocrine carcinomas

Authors	Year	Syndrome	Type of tumor	Treatment	*Follow-up (months)*
Trotoux et al. [17]	1979	SIADH	SCNC	Radiotherapy	DOD 7.7
Medina et al. [18]	1984	Eaton–Lambert	SCNC	Chemotherapy	DOD 11
Bishop et al. [19]	1985	ACTH	SCNC	Radiotherapy	DOD NR
Baugh et al. [20]	1987	Carcinoid	MDNC	Surgery	DOD 41
Takeuchi et al. [21]	1989	SIADH	SCNC	Radiotherapy Surgery	DOD 15
Wenig and Gnepp [22]	1989	Carcinoid	WDNC	Surgery chemotherapy	AWD 42[§]
Myers and Kessimian [23]	1995	SIADH	SCNC	Chemotherapy	DOD NR
Overholt et al. [24]	1995	Carcinoid	MDNC	Surgery chemotherapy	DOD 26
Kumai et al. [25]	1996	Carcinoid*	MDNC	Surgery	DOD 9
Yamanaka et al. [26]	1997	Carcinoid	MDNC	–	DOD rcc

SIADH syndrome of inappropriate secretion of antidiuretic hormone, *SCNC* small-cell neuroendocrine carcinoma, *DOD* dead of disease, *ACTH* adrenocorticotropic hormone, *MDNC* moderately differentiated neuroendocrine carcinoma, *NR* not reported, *rcc* rapid clinical course, *WDNC* well-differentiated neuroendocrine carcinoma, *AWD* alive with disease

[§] Wenig's personal communication 1997

* Soga's personal communication 2005

of Otolaryngic Pathology, Armed Forces Institute of Pathology, Washington, DC [22 and personal communication, 1997]. Based on the diagnosis of a malignant tumor, a total laryngectomy was performed. The patient remained disease-free for 3 years; then he noted a lump in his neck which proved to be a metastasis from the laryngeal primary. A left-sided radical neck dissection was performed, revealing multiple lymph node metastases. Six months later, the patient presented to his physician complaining of fever, malaise and right-sided upper quadrant abdominal pain. A computed tomography scan of the abdomen revealed multiple liver nodules; biopsy showed that the nodules were morphologically identical to the laryngeal neoplasm. The patient developed carcinoid syndrome following the liver metastases. Urine analysis revealed 5-HIAA level increased to 195 mg/24 h (1–5 mg/24 h, normal level), which decreased after therapy with streptozotocin and 5-fluorouracil. The patient much improved after treatment and was alive with disease at last follow-up. In 1995, Myers and Kessimian [23] described a case of SCNC of the larynx associated with SIADH. Diagnosis of the syndrome was confirmed by the finding of serum hyponatremia and hypo-osmolarity, urine hypo-osmolarity and an increased urinary sodium concentration. In the same year, Overholt et al. [24] reported a case of MDNC of the larynx. The patient presented with sore throat, flushing, diarrhea and hypertension, consistent with a carcinoid syndrome. The patient underwent supraglottic laryngectomy and modified radical neck dissection; and remained well for 1 year. However, he developed recurrent local disease with evidence of metastases to small intestine, mesentery and skin. An attempt to control the disease with chemotherapy was unsuccessful and the patient died after 26 months. In 1996, Kumai et al. [25] reported a case of MDNC involving the surface of the epiglottis with cervical metastases. The patient suffered carcinoid syndrome (Soga's personal communication, 2005). He died with multiple metastases (lung, heart, aorta, pancreas, gallbladder, skin) 9 months after surgical treatment. In 1997, Yamanaka et al. [26] reported another case of laryngeal MDNC with carcinoid syndrome and a rapid clinical course. All cases of laryngeal neuroendocrine carcinomas associated with PNS are summarized in the Table 1 [17–26].

Dermatologic or cutaneous, hematologic, osteoarticular or rheumatologic and ocular PNS have not been reported in association with neuroendocrine neoplasms of the larynx.

Conclusion

PNS can follow the clinical course of the tumor and thus be useful for monitoring its evolution [6]. The diagnosis involves a multidisciplinary approach, and detailed endocrinologic, neurologic, radiologic and histologic investigations are required. Correct diagnosis is essential as the treatment of choice will be different for each disorder, particularly in the case of malignant tumors. It is therefore important to develop appropriate means to correctly identify and localize primary and/or metastatic tumors. Early diagnosis and treatment of PNS may have an effect on clinical outcome, ranging from earlier primary tumor diagnosis and intervention to adequate delivery of tumor-directed therapy and improved quality of life.

PNS can sometimes arise in patients without any oncologic history. The recognition of PNS when there is no

history of a specific tumor requires a thorough search for a primary neoplasm. PNS in neuroendocrine carcinomas of the larynx are rare but can cause severe symptoms and nearly always have a poor prognosis.

It is questionable whether patients with newly discovered neuroendocrine carcinoma of the larynx should be screened based on these ten published cases of the literature. According to a recent meta-analysis, there are 436 reported cases of neuroendocrine carcinoma of the larynx [27]; however, this study misses most of the cases presented in the present series. Regarding the 10 cases reviewed here, the incidence of paraneoplastic syndromes in patients with neuroendocrine carcinoma of the larynx is 2.3 %. However, it is difficult to estimate the real incidence as there are surely clinical cases which have not been published. The present review should draw the attention of all clinicians dealing with head and neck cancer to the fact that patients with neuroendocrine carcinoma of the larynx may present with paraneoplastic symptoms. According to the known literature, patients with SCNC and MDNC are more likely having paraneoplastic syndromes, while patients with WDNC are less likely. There are no known cases of LCNC of the larynx known with paraneoplastic syndrome.

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