ELSEVIER

Auris Nasus Larynx 36 (2009) 513–520

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

www.elsevier.com/locate/anl

Paraneoplastic syndromes in patients with nasopharyngeal cancer

C. Toro [a], A. Rinaldo [b], C.E. Silver [c], M. Politi [a], A. Ferlito [b,*]

[a] *Department of Surgical Sciences, Maxillofacial Surgery Clinic, University of Udine, Udine, Italy*
[b] *Department of Surgical Sciences, ENT Clinic, University of Udine, Udine, Italy*
[c] *Departments of Surgery and Otolaryngology-Head and Neck Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA*

Received 22 August 2008; accepted 14 October 2008
Available online 27 December 2008

Abstract

Paraneoplastic syndromes (PNS) represent the clinical manifestation of the remote and indirect effects produced by tumor metabolites or other products. Paraneoplastic effects are not directly mediated by tumor invasion of normal tissue, or by the disruption of normal function of the involved organ, or by distant metastases. More than 260 cases of nasopharyngeal carcinoma (NPC) associated with PNS have been reported in the literature. These syndromes can be divided into six main groups: cutaneous or dermatologic, endocrine, hematologic, osteoarticular or rheumatologic, neurologic, and ocular. The most common dermatologic manifestation is dermatomyositis, while the syndrome of inappropriate secretion of antidiuretic hormone and occasionally Cushing's syndrome due to ectopic ACTH production are the endocrinologic manifestations. Tumor fever and leukemoid reaction, osteoarticular or rheumatic syndromes, including clubbing of the fingers and toes, sensory neuropathy and demyelinating motor polyneuropathy, and rarely optic neuritis represent the most prominent examples of the other groups of syndromes.

PNS may occur before the NPC is manifest, or while it is in an occult stage, and thus the possibility of NPC should be considered in patients with these various disorders. While some PNS will respond to direct treatment, most often the PNS subsides in parallel to response of the NPC, and thus may be useful for monitoring tumor response or recurrence.

Keywords: Nasopharyngeal carcinoma; Paraneoplastic syndromes; Early detection; Pathogenesis; Treatment; Hormones

Contents

1. Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is relatively uncommon in Western countries, but is 10–50 times more common

* Corresponding author at: Department of Surgical Sciences, ENT Clinic, University of Udine, P.le S. Maria della Misericordia, 33100 Udine, Italy.
E-mail address: a.ferlito@uniud.it (A. Ferlito).

0385-8146/$ – see front matter
doi:10.1016/j.anl.2008.10.006

in the Far East, and is endemic in the Southern parts of China with the yearly incidence rate varying between 15 per 100,000 and 50 per 100,000 [1]. In Hong Kong, NPC is the third most common malignancy in male and the fifth in female patients with an incidence of 27.5 and 11.2 per 100,000, respectively [2]. The particularly high frequency of malignancies of the nasopharynx in the Far East is not well understood, although metaplasia and eventual carcinoma in situ is associated with chronic sinusitis, which is extremely common in southeast Asian countries [3].

A spectrum of risk factors has been described including environmental carcinogenesis from inhaled or chewed tobacco, racial factors, hereditary trends, and infection with the Epstein–Barr virus (EBV). Undifferentiated carcinoma is the only EBV related NPC. The undifferentiated NPC was initially designated lymphoepitelioma by Schminke [4] and Regaud and Reverchon [5] because of the mixture of lymphoid and epithelial cells seen in the primary tumor. It has subsequently been established that only the epidemoid cells are neoplastic, as evidenced by the absence of lymphoid tissue in metastatic lesions. Thus, undifferentiated NPC is an epidermoid-lineage cancer, and because of various unique features constitutes a clinical entity different from other head and neck squamous cell carcinomas.

The typical presenting symptoms of NPC are usually cervical lymphadenopathy, epistaxis, audiologic or neurologic symptoms, and nasorespiratory symptoms. A small percentage of patients present with the clinical manifestation of the indirect and remote effects produced by the tumor.

2. Paraneoplastic syndromes

Paraneoplastic syndromes (PNS) represent the clinical manifestation of the remote and indirect effects produced by tumor metabolites or other products. Paraneoplastic effects are not directly mediated by the invasion of normal tissue, or by the disruption of normal function of the involved organ, or by distant metastases [6].

PNS occur in 1–7.4% of all cancer patients [7]. Different terms such as paraneoplastic effects, remote effects, paraneoplastic events, non-metastatic syndromes, paraneoplastic manifestations, paraneoplastic phenomena, and paraneoplastic disturbances have all been employed as synonyms to the term ‘‘paraneoplastic syndrome.’’[8].

The mechanism of most PNS is not well known. Only few cases clearly demonstrate an etiologic or a pathogenetic factor. PNS can precede, follow or be concurrent to the diagnosis of a malignancy. Physicians who deal with cancer-associated syndromes should be able to differentiate the PNS from the benign disorders that mimic them.

PNS associated with NPC can be divided into six main groups: cutaneous or dermatologic, endocrine, hematologic, osteoarticular or rheumatologic, neurologic, and ocular. The exact incidence of PNS associated with NPC is not known, because numerous ‘‘false-PNS’’ have been reported in which symptoms are directly related to the invasion of normal tissue by the tumor or by distant metastases [9]. Moreover, sometimes the same cases have been reported in different journals (for example: Botsios et al. [10] and Botsios et al. [11].

We have reviewed the literature in order to underline the various PNS related to NPC and their relevance to the diagnosis.

3. Paraneoplastic cutaneous or dermatologic syndromes

First described in 1916 by Stertz [12], the association of connective tissue diseases, particularly dermatomyositis (DM) and scleroderma, with a variety of malignancies has been reported frequently in recent decades. DM seems to have a robust association with malignancy, with studies showing a frequency of cancer of 15–34% in some medical centers. In the upper aerodigestive tract, this phenomenon is seen most commonly with NPC [13]. DM is a severe systemic disorder characterized by typical cutaneous lesions and an inflammatory myopathy. The five main diagnostic findings of DM include: (1) systemic proximal muscle weakness, with or without dysphagia or respiratory muscle involvement; (2) abnormal muscle biopsy findings; (3) elevated skeletal muscle-derived enzymes; (4) abnormal electromyographic findings; and (5) a typical skin eruption (Gottron papules) overlying the knuckles, elbows, and knee joints. Special skin features include a characteristic heliotropic rash on exposed surfaces, periungual telangiectasia, and poikiloderma.

The first cases of NPC associated with a dermatologic syndrome were reported in 1969 [14]. Since that time, more than 100 such cases have been reported. NPC has long been reported as the predominant type of cancer associated with DM in several Asian countries, including Hong Kong, Singapore, and Southern-China [15]. Although in the Orient NPC is more frequently found in the general population and in patients with DM, the proportion of individuals with both NPC and DM is approximately 3–4 times greater than in the general population [16]. Ang et al. [17] reported 28 cases with DM from the National Skin Centre of Singapore; malignancies were detected in 12 patients, half of which were NPC. They concluded that screening for malignancies, especially NPC, is recommended for all DM patients. In Hong Kong, 10 of 1154 patients with NPC developed DM [18]. Leow and Goh [19] reported 38 cases of DM in patients affected by cancer, 5 of which were NPC. A photodistributed urticarial vasculitis with DM was described as the presentation of a NPC [20]. The autoimmune basis of DM was confirmed by the presence of a lymphoplasmic cellular infiltrate of the muscular interstices.

This clinical entity has mainly been described in patients from southern Chinese groups, and there are fewer reported