REVIEW ARTICLE

Paraneoplastic syndromes in patients with primary head and neck cancer

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Abstract Paraneoplastic syndromes represent the clinical manifestations of the indirect and remote effects produced by tumor metabolites or other products. The clinical spectrum of the various paraneoplastic syndromes related to primary malignancies of the head and neck region is presented. A review of the literature on paraneoplastic syndromes in patients with primary head and neck cancer was carried out. Paraneoplastic syndromes related to primary malignancies of the head and neck region can be categorized as: endocrine, cutaneous or dermatologic, hematologic, neurologic, osteoarticular or rheumatologic, ocular syndromes. Sometimes, paraneoplastic syndromes can be more serious than the consequences of the primary tumor itself and can precede, follow or be concurrent to the diagnosis of a malignancy; moreover, they can dominate the clinical picture and thus lead to errors with respect to the origin and type of the primary tumor. Physicians who deal with cancer-associated syndromes should be able to differentiate the paraneoplastic syndromes from the benign disorders that mimic them. Patients with a suspected paraneoplastic disorder should undergo a complete panel of laboratory studies, in addition to imaging studies and endoscopy. Identification of paraneoplastic syndromes allow the clinician to make an early diagnosis and to provide adequate treatment of tumors, with a favorable oncologic outcome and improved life expectancy for the patient. These syndromes can follow the clinical course of the tumor and thus be useful for monitoring its evolution.

Keywords Paraneoplastic syndromes · Head and neck cancer · Pathogenesis · Treatment · Hormones

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Introduction

Paraneoplastic syndromes represent the clinical manifestations of the indirect and remote effects produced by tumor metabolites or other products. It is not mediated directly by the invasion of normal tissue, or by the disruption of normal function of the involved organ, or by metastases. Specifically, many forms of primary and metastatic malignancies in the head and neck area may occasionally cause a variety of metabolic and other disturbances that are important causes of symptoms [1, 2]. These symptoms may be endocrine, cutaneous or dermatologic, hematologic, neurologic, osteoarticular or rheumatologic, ocular in nature. Small cell carcinoma and squamous cell carcinoma of the lung may metastasize to the head and neck area and may produce a variety of paraneoplastic syndromes [3]. Exceptionally, an association of different paraneoplastic syndromes (Bazex's syndrome and triple palm) has been reported in a patient

with a squamous cell carcinoma of the lung with a cervical mass [4].

Different terms such as paraneoplastic effects, paraneoplastic events, paraneoplastic manifestations, non-metastatic syndromes, paraneoplastic phenomena, paraneoplastic disturbances, and remote effects have all been employed at one time or another as an alternative to paraneoplastic syndromes [2].

Paraneoplastic syndromes occur in 1–7.4% of all cancer patients [5, 6]. In the literature, paraneoplastic syndromes rarely affect patients with head and neck cancer; however, they may be the first or most prominent manifestation. As patients of all ages may be affected by cancers, any age may be affected by their related paraneoplastic syndromes. Race and sex predilection have not been reported, and the real incidence of deaths and complications related to paraneoplastic syndromes is also unknown.

Squamous cell carcinoma is the most common histopathology of the primary malignancy of the head and neck associated with paraneoplastic syndromes. Also other histological types such as neuroendocrine neoplasms (carcinoid tumor, atypical carcinoid tumor, small cell neuroendocrine carcinoma, paraganglioma), undifferentiated carcinoma, adenocarcinoma, adenoid cystic carcinoma, esthesioneuroblastoma, melanoma, lymphoma, and sarcomas [2–13] have been reported in association with paraneoplastic syndromes. Thymoma, papillary, medullary, primary squamous cell carcinoma of the thyroid gland and parathyroid cancer can also be associated with paraneoplastic phenomena [3, 14, 15].

The literature has been reviewed in order to analyze the various paraneoplastic syndromes related to primary malignancies of the head and neck region (see Table 1).

Etiology and pathophysiology of paraneoplastic syndromes

The exact nature of the paraneoplastic phenomena associated with underlying cancers is not fully understood. Only few cases clearly demonstrate an etiologic or a pathogenetic factor. However, it was suggested that neoplastic cells synthesize many organic materials that may have pharmacological or hormonal effect. If the concentration of these physiologically active compounds is large enough, distinctive clinical paraneoplastic syndromes will occur [3].

Another associated pathogenetic theory suggested that several cancers also produce fetal proteins that are physiologically expressed in embryonic cells during

Table 1 Paraneoplastic syndromes occurring in patients with head and neck cancer

Endocrine syndromes
Syndrome of inappropriate antidiuretic hormone production
Cushing syndrome
Hypercalcemia
Carcinoid syndrome
Ileus
Ectopic production of beta-HCG
Cutaneous or dermatologic syndromes
Acanthosis nigricans
Dermatomyositis
Bazex's syndrome
Sweet's syndrome
Acral ischemia and digital necrosis
Pruritus
Pemphigus
Tylosis
Yellow nail syndrome
Necrolytic migratory erythema
Bowen's disease
Hematologic syndromes
Trousseau's syndrome
Neutrophilic leukemoid reactions
Neurologic syndromes
Cerebellar degeneration or cerebellar cortex degeneration
Ataxia
Eaton–Lambert myasthenic syndrome
Encephalomyelitis
Osteoarticular or rheumatologic syndromes
Polyarthritis or polymyalgia rheumatica
Hypertrophic osteoarthropathy
Pseudo-Still disease
Osteomalacia
Ocular syndromes
Retinopathy
Optic neuritis or optic neuropathy

fetal life but not expressed by normal adult cells. These substances may help laboratories detect malignancies and usually are used as tumor markers [e.g., carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), cancer antigens (CA 19.9)] [1].

In addition, cancer-fighting antibodies or white blood cells (T cells) may mistakenly react with normal tissues; this cross-reacting antitumor antibody may be responsible for the syndrome. The disease may have a protracted course owing to a small occult neoplasm that may only become apparent at autopsy [5, 16–18].

Serum and cerebrospinal fluid autoantibodies have recently been identified for several neurological paraneoplastic syndromes [2, 18]. In some mucocutaneous lesions, the presence of immunoglobulins and complement in the basement membrane assumes a tumor-mediated immune response [2, 19]. Additionally, antineuronal autoantibodies have been identified for a number of paraneoplastic neurological syndromes [2, 18].

Overview of clinical syndromes related to primary head and neck cancer

Because of their complexity and variety, the clinical presentations of the paraneoplastic syndromes may vary greatly and may not be characteristic of a specific organic system. Several clinical manifestations may be observed, each one specifically simulating the more common benign conditions. However, they can be categorized under the following headings.

Paraneoplastic endocrine syndromes

Identification of paraneoplastic endocrine syndromes is important because they cause symptoms which are frequently tractable. The pathogenesis of paraneoplastic endocrine syndromes results from aberrant production of protein hormones, hormone precursors, or hormone-like substances by tumors. Generally, cancers, except those arising in organs with physiological steroidogenesis, do not synthesize steroid hormones.

The *syndrome of inappropriate antidiuretic hormone production* (SIADH, or Schwartz–Bartter syndrome) is a well-recognized form of paraneoplastic syndrome that may accompany head and neck malignancies. Key features of SIADH include serum hypo-osmolality; an unexpectedly high urinary specific gravity; an absence of edema or dehydration; normal adrenal, thyroid, and renal function; hyponatremia; and an elevation of plasma vasopressin [2]. SIADH is characterized by excessive blood levels or actions of vasopressin associated with hyponatremia without edema. The inability to excrete dilute urine implies a subsequent retention of the ingested fluids with expansion of the extracellular fluid volume without edema. Hyponatremia is due to both sodium dilutions in a larger extracellular fluid volume, and its higher urinary excretion caused by a decreased reabsorption in the proximal renal tubular tract because of the increased extracellular fluid volume [2].

This syndrome may precede the presentation of the cancer by a few weeks or months. The first two cases of this syndrome associated with squamous cell carcinoma of the larynx were described in 1976 by Moses et al. [20]. Other cases associated with squamous cell carcinoma of the larynx and hypopharynx were subsequently reported by various authors [21–24]. In 1979, Trotoux et al. [25] described Schwartz–Bartter syndrome in a 61 year-old man that led to the detection of a small cell carcinoma of the subglottic region. Recently Maxwell and Witterick [26] reported a case of SIADH in a patient with metastatic supraglottic cancer. In 1989, Takeuchi et al. [27] reported a case of small cell neuroendocrine carcinoma of the larynx in a 53-year-old man. The tumor was associated with SIADH, and hyponatremia persisted until the patient's death, despite the administration of salt. In 1995, Myers and Kessimian [28] described a patient with small cell neuroendocrine carcinoma of the larynx who had clinical complications of SIADH. Careful patient evaluation identified only the laryngeal neoplasm as the cause of SIADH and excluded any other potential causes (pulmonary neoplastic or non-neoplastic diseases, central nervous system lesions, drugs).

In 1994, al Ahwal et al. [29] reported a case of olfactory neuroblastoma in a 27-year-old man who initially presented with SIADH manifesting as nausea, vomiting, hyponatremia, and a serum osmolality of 225 mmol/kg. No lower limb edema was present. After a few weeks, a neoplastic lesion of the right maxillary sinus was discovered. A recent review of the literature revealed nine cases of olfactory neuroblastoma associated with SIADH [10, 30] and one case of sinonasal neuroendocrine carcinoma in association with SIADH [10].

Talmi et al. [31] presented the largest series to date of head and neck cancer patients with SIADH, a report of 43 patients drawn from a review of the University of Iowa Tumor Registry. This retrospective review identified a 3% incidence of SIADH among 1,436 patients with head and neck cancers and included an examination of relevant laboratory values and exclusion of other causes of hypo-osmolality and hyponatremia for each patient.

In a review of the literature Ferlito et al. [2] collected 70 cases of SIADH-associated malignancies of the head and neck. The most common site of occurrence was the oral cavity, with 29 detected cases (29 of 70 or 41.43%). In 13 patients the larynx was involved (13 of 70 or 18.57%), while nasopharyngeal malignancies were found in nine cases (9 of 70 or 12.86%). In seven cases (7 of 70 or 10.00%) the cancer was localized in the hypopharyngeal area, and in five cases (5 of 70 or 7.14%) the lesion involved the nasal cavity. Other regions of involvement were the maxillary sinus (two cases), parapharyngeal space (two cases), salivary glands (two cases), and oropharynx (one case). The histologic tumor type most frequently present in this series was squamous cell carcinoma, with 55 out of 70 cases (78.57%); however, other tumor types, such as olfactory neuroblastoma, adenoid cystic carcinoma, small cell neuroendocrine carcinoma, undifferentiated carcinoma, and sarcoma, were found [2]. One patient with a B cell lymphoma of the nasopharynx and another patient with small cell carcinoma of the tonsil were also reported [32, 33].

Cushing syndrome, accompanied by very high plasma ACTH levels, hypokalemia and increased serum and urine cortisol concentrations, is a common example of an endocrine disorder linked to a malignancy. This is related to the ectopic production of ACTH or ACTH-like molecules from many tumors. Ectopic ACTH syndrome in association with a squamous cell carcinoma of the larynx was reported by Imura et al. [34] in 1975. The authors described a Japanese patient, a 66-year-old man, who underwent surgical excision of the larynx for squamous cell carcinoma. One year later, he developed hyperadrenocorticism, and postmortem examination revealed metastases to the liver and other organs. Bioassayable and immunoassayable ACTH, as well as bioassayable melanocyte-stimulating hormone, were detected in the metastatic tumor tissue [34]. In 1985, Bishop et al. [35] reported the first case of laryngeal small cell neuroendocrine carcinoma associated with ectopic ACTH syndrome. The cell cytoplasm of the primary tumor was immunoreactive for ACTH, gastrin-releasing polypeptide, neuron-specific enolase, β-endorphin, calcitonin, and keratin, by indirect immunoperoxidase techniques. Lieberum et al. [11] reported a case of recurrent nasal paraganglioma, which started to produce ACTH after a period of ten years and resulted in Cushing's syndrome. Resection of the tumor normalized ACTH and cortisol secretion. In 1996, Tan et al. [36] reported a case of nasopharyngeal carcinoma associated with Cushing syndrome. In 2005, Barbosa et al. [37] reported 10 cases of medullary carcinoma associated with Cushing syndrome.

Squamous cell carcinoma of the head and neck is a rare cause of humoral *hypercalcemia* of malignant origin through an ill-understood hormonal mechanism. This paraneoplastic syndrome is usually one of the presenting symptoms of the disease and is a poor prognostic sign as it correlates with advanced disease. It is the most common paraneoplastic syndrome in patients with cancer of the head and neck and occurs in approximately 10% of all advanced malignancies [9]. Clinical signs of mild hypercalcemia include dehydration, anorexia, nausea, vomiting, constipation, ileus, fatigue, and mental confusion. Severe hypercalcemia is considered a medical emergency [3]. Non-metastatic hypercalcemia is not uncommon in patients with laryngeal malignancies [38]. In 2003, Iwase et al. [39] reported hypercalcemia in 12 of the 242 patients (5%) with oral squamous cell carcinoma. Another interesting report described a case of squamous cell carcinoma of the oral cavity that presumably elaborated parathyroid hormone-related peptide (PTH-rP) and caused hypercalcemia only after radiotherapy and chemotherapy [40].

5-Fluorouracil and cysplatinum are often temporarily effective in controlling hypercalcemia in patients with squamous cell carcinoma [9]. Gallium nitrate has also been used successfully to treat hypercalcemia of malignant tumors.

Carcinoid (carcinoidosis or argentaffinosis) is a syndrome of four main clinical components including; skin flushing, usually localized in the face and upper trunk, episodic watery diarrhea, manifestations of carcinoid heart disease, and wheezing. Less common changes include dermatitis and episodes of depression. Few patients display all the symptoms. The majority of typical and atypical carcinoids of the larynx reported in the literature has been non-functional and therefore did not lead to clinical syndromes [7, 41, 42]. Five cases of laryngeal carcinoid tumors (one typical and four atypical carcinoid) associated with a carcinoid syndrome have been reported [43–47].

Jackson et al. [8] described a paraneoplastic syndrome in cases of glomus tumors of the skull base operated upon. High circulating levels of cholecystokinin after resection of these tumors may be responsible for the unexplained phenomenon of prolonged postoperative *ileus*.

Scholl et al. [48] reported a case of a squamous cell carcinoma of the maxilla producing beta human chorionic gonadotropin (*ectopic production of β-HCG*).

Paraneoplastic cutaneous or dermatologic syndromes

A wide variety of cutaneous syndromes are associated with malignancies. The spectrum ranges from erythrodermia to the grave peripheral ischemic manifestations [32, 49].

Acanthosis nigricans is the most frequent paraneoplastic lesion of the skin. It is a cutaneous paraneoplastic syndrome characterized by the presence of symmetric, light or dark brown areas of hyperpigmentation with orthokeratosis, hyperkeratosis, exaggerated skin markings, and warty lesions, particularly involving the intertriginous and flexural areas, especially the axilla, posterior neck, anogenital region, umbilicus, and areola. However, widespread involvement of the hands, feet, and mucosal membranes has also been seen. This process has been described in association with squamous cell carcinoma of the larynx and hypopharynx [50, 51].

Dermatomyositis is an idiopathic inflammatory disease affecting the skin and skeletal muscle, causing widespread degenerative and inflammatory changes. The disease is characterized clinically by, progressive proximal, symmetrical muscle weakness and skin lesions. Its cause is unknown. Approximately 15–20%

of cases are associated with underlying malignancies, most commonly carcinomas of the lung, breast, stomach, ovary, and kidney. Dermatomyositis has also been reported in association with laryngeal carcinoma [52, 53]. The association between dermatomyositis and malignancy of the pharynx is rare among the Caucasian population but not uncommon among Far Eastern and North African populations. However, Botsios et al. [54, 55] reported two cases of Caucasian Italian patients with dermatomyositis associated, respectively, with nasopharyngeal [54, 55] and tonsillar carcinomas [54]. In addition, urticarial vasculitis with dermatomyositis and polymyositis was described in association with nasopharyngeal carcinoma. The lesions of urticarial vasculitis were initially photodistributed, indicating photosensitivity. The patient was treated with systemic steroids, chemotherapy, and radiation therapy. The tumor and urticarial vasculitis completely resolved, and the myositis improved [56]. The autoimmune basis of dermatomyositis was confirmed by the presence of a lymphoplasma cellular infiltrate of the muscular interstices and by the presence of muscle necrosis revealed by increased serum levels of creatine kinase and increased erythrocyte sedimentation rate.

Bazex's syndrome (also termed Bazex's acrokeratosis paraneoplastica, acrokeratosis paraneoplastica, acrokeratosis Bazex) was described in 1965 [57] as a paraneoplastic process associated with a carcinoma of the pyriform sinus. The initial reports came mainly from the European literature, and from French authors in particular, but the lesion is now reported with increasing frequency all over the world [58]. Clinically, it is characterized by erythematous squamous cutaneous plaques that spread centripetally—as a psoriasiform cutaneous eruption—with a predilection for the extremities (ears, nose, fingers, and toes) and, less frequently, the elbows, knees, and trunk. Sometimes, even vesicles, bullae and scabs have been described, particularly on the fingers, hands, and feet. The distribution of the cutaneous manifestations is generally symmetric.

Bazex's acrokeratosis is the most frequent paraneoplastic syndrome associated with cancer of the larynx and hypopharynx [57, 59–71]. Exceptionally, an association of different paraneoplastic cutaneous syndromes (Bazex's syndrome, hyperpigmentation, acquired ichthyosis, and pruritus) has been reported in a patient with laryngeal cancer [59]. Additionally, Ali et al. [12] reported a case of flexural Bazex syndrome with tonsillar adenocarcinoma. How this cutaneous syndrome develops in response to an underlying malignancy is unknown. Possible mechanisms include cross-reactivity between skin antigens and the tumor, or the secretion of growth factors by the tumor [58].

Sweet's syndrome (acute febrile neutrophilic dermatosis) was originally described by Robert Douglas Sweet, a British dermatologist, in 1964 [72]. It may occur as a cutaneous paraneoplastic syndrome. It has been associated mainly with hematologic disorders such as leukemia and with solid tumors [73]. The clinical characteristics included pyrexia, neutrophilia, anemia, painful erythematous cutaneous plaques, and nodules, mainly localized on the upper extremities, face, and neck. The absence of fever or neutrophilia does not rule out the possibility of Sweet's syndrome in patients with solid tumors [73]. Exceptionally, Sweet's syndrome may occur in association with a squamous cell carcinoma of the pyriform sinus [73]. A complete malignancy workup is indicated in patients after the onset of Sweet's syndrome skin lesions, because an unsuspected primary or recurrent cancer may be detected. Corticosteroid therapy is the treatment of choice. All the manifestations of Sweet's syndrome improved dramatically with corticosteroid therapy, regardless of the response of the associated neoplasm to tumor-directed therapy [73]. Potassium iodide or colchicine have also proven to be effective therapeutic alternatives.

Acral ischemia and digital necrosis of multiple fingertips have been described as a paraneoplastic syndrome. Buch et al. [49] reported a 72-year-old male patient with severe acral ischemia and multiple necroses on several fingertips. Symptoms evolved under palliative chemotherapy for inoperable metachronous squamous cell carcinoma of the tonsil following a history of two simultaneous carcinomas of the alveolar crest. Digital ischemia was combined with severe pain, similar to Raynaud's syndrome.

Pruritus is rare in patients with a laryngeal malignancy. In a letter to the editor, Rantuccio [74] described one patient with "idiopathic" pruritus who subsequently developed cancer of the larynx. Paraneoplastic pruritus has been reported in patients with hematologic malignancies, particularly Hodgkin's lymphoma, and with solid tumors. Pruritus may result from hypereosinophilia [74, 75]. Herpes zoster, ichthyosis, flushes, alopecia, or hypertrichosis also may be observed. Flushes may be present in patients with acute leukemias and carcinoids that secrete vasoactive substances, mainly prostaglandins. Immune system depression, which may be observed in most patients with cancer, often is responsible for the reactivation of latent varicella-zoster virus in the sensory ganglia.

Additionally, some clinical descriptions assumed to be paraneoplastic were very rarely reported in association with malignancies of head and neck region and include *pemphigus* [76–81], *tylosis* (palmarum et

plantarum) [82], *yellow nail syndrome* [83], *necrolytic migratory erythema* [84], and *Bowen's disease* [85].

Paraneoplastic hematologic syndromes

Paraneoplastic hematologic syndromes may occur in many neoplasms, but have only occasionally been observed in association with head and neck cancer. Symptoms related to myelemia or anemia, thrombocytopenia, thrombocytosis or leukocytosis, may result from many types of cancer including squamous cell carcinoma of the tongue and nasopharynx and spreading medullary thyroid cancer [14, 86]. Erythrocytosis results from an increase of erythropoietin that results from hypoxia. On the other hand anemia which may be the presenting symptom of several neoplasms may results from chronic hemorrhages from ulcerated tumors, altered intestinal absorption of vitamin B, and increased destruction or insufficient production of red blood cells. Thrombocytopenia, in some cases, also may be caused by autoantibodies, however the causes of thrombocytosis still are unknown.

Trousseau's syndrome (thrombophlebitis migrans, migratory thrombophlebitis, disseminated intravascular coagulation or thromboembolism) is characterized by disseminated intravascular coagulation and is detected by laboratory tests (elevated levels of fibrin, thrombocytosis, hyperfibrinogenemia). The prevalence of this syndrome with head and neck cancers is less than 1% [87], and it has only occasionally been observed in laryngeal carcinoma [88]. An unexplained thromboembolism may indicate the presence of a malignancy before any signs or symptoms of the tumor itself become apparent [89].

In some cases, symptoms result from *neutrophilic leukemoid reactions*, which are characterized by the presence of immature white blood cells in the bloodstream, and may be accompanied by hypereosinophilia and itching. These reactions typically are observed in patients with lymphomas, however, they were also reported in association with nasopharyngeal and oropharyngeal carcinoma [13, 90]. Leukemoid reactions probably are caused by mechanical stimuli on bone marrow, resulting from bone metastases, or they may be caused by humoral stimuli resulting from neosynthesized blastic factors or factors released from the foci of tumor necrosis.

Paraneoplastic neurologic syndromes

These syndromes have been occasionally described in association with head and neck cancers.

Cerebellar degeneration or cerebellar cortex degeneration has been reported in association with laryngeal cancer [91, 92]. It is characterized by subacute symptoms of diffuse cerebellar dysfunction; vertigo, dysarthria, intention tremor, and progressive limb and truncal ataxia. Ocular disturbances, nystagmus, ocular dysmetria, and opsoclonus are also common. This syndrome may be caused by immunological cross-reactions, and antineural autoantibodies are found in about half the patients [16, 93, 94]. Paraneoplastic syndromes usually occur before the malignancy is diagnosed.

In 1998, Garcia et al. [95] reported a case of paraneoplastic *ataxia* due to laryngeal carcinoma.

In 1973, Fontanel et al. [96] described a case of *Eaton–Lambert myasthenic syndrome* in a 58-year-old man that led to the detection of a squamous cell carcinoma of the larynx. Another case of Eaton–Lambert syndrome with onset 18 months prior to detection of a squamous cell carcinoma of the larynx has been reported by Ferroir et al. [97] in 1989. Regression of the syndrome, and its total remission over 10 years following excision of the tumor, suggested a possible relationship as a paraneoplastic disorder. In 1984, Medina et al. [98] reported a case of primary small cell neuroendocrine carcinoma of the larynx associated with clinical and electromyographic evidence of the myasthenic syndrome. The upper extremities may become involved. Ocular and bulbar involvement is rare and, when present, less severe than in the case of myasthenia gravis. Deep tendon reflexes are hypoactive or absent, but sensory function is preserved. Unlike myasthenia gravis, muscle strength improves with exercise. Electromyography is essential in the diagnosis of this syndrome, and electromyographic findings differ from those observed in patients with myasthenia gravis. The electrophysiological diagnosis of Eaton–Lambert syndrome relies on the observation of a progressive increase in the amplitude by 200% or more of the compound muscle action potential evoked by repetitive supramaximal nerve stimulation. Diagnostically useful serum and cerebrospinal fluid autoantibodies have recently been identified in several neurologic paraneoplastic syndromes, including cerebellar degeneration and Eaton–Lambert myasthenic syndrome.

Encephalomyelitis was seldom observed in patients with head and neck cancer. There is large evidence in the literature that the anti-Hu antibody is a marker not only of sensory neuropathy but also of encephalomyelitis [17]. An interesting report was of a patient with paraneoplastic anti-Hu positive encephalomyelitis associated with a supraglottic squamous cell carcinoma with neck metastases [32].

Paraneoplastic osteoarticular or rheumatologic syndromes

Paraneoplastic arthropathies arise as *polyarthritis* or *polymyalgia rheumatica*, particularly in patients with myelomas, lymphomas, acute leukemia, and malignant histiocytosis. In 1992, Eggelmeijer and Macfarlane [99], described a case of polyarthritis as the presenting symptom of the occurrence and recurrence of laryngeal carcinoma. In 1999, Sandoval et al. [100] reported a case of squamous cell carcinoma of the laryngopharynx associated with polyarthritis of large and small joints and a skin rash. In one patient asymmetrical paraneoplastic polyarthritis appeared 5 months before a hypopharyngeal carcinoma was diagnosed [32]. While polymyalgia rheumatica was identified as a synchronous feature of hypopharyngeal carcinoma [101]. The pathologic mechanism for paraneoplastc polyarthritis and polymyalgia rheumatica is not known. Autoimmune cross reactivity of synovial and tumor antigens has been suggested [99].

In 1977, Zornoza et al. [102] reported the association of *hypertrophic osteoarthropathy* (HOA) (Pierre–Marie syndrome) in patients with nasopharyngeal carcinoma. Similarly, Maalej et al. [86] reported 17 patients with nasopharyngeal carcinoma presenting with HOA. In 2001, Biswal et al. [103] reported two cases of nasopharyngeal cancer developing finger dubbing and HOA as a part of their paraneoplastic manifestation following radical radiotherapy. Other cases of HOA in patients with nasopharyngeal carcinoma have been reported by several authors [86, 104–106]. HOA, well known in the adults, is rarely encountered in children with nasopharyngeal carcinoma and may precede pulmonary symptoms by 1–18 months. However, a striking feature of HOA is the reversibility of the complaints after successful occurrence of the primary cancer [107]. Chan and Xie [108] described a case of nasopharyngeal carcinoma complicated by pseudohypertrophic osteoarthropathy due to pulmonary metastasis following radiotherapy. Mackenzie and Scherbel [53] described two cases of this syndrome associated with laryngeal cancer. The causes of HOA remain unknown, although several hypotheses have been developed including estrogen or growth hormone production by the tumor or vagal hyperactivity.

In 1988, Cabane et al. [109] reported a case of aryepiglottic fold squamous cell carcinoma associated with *pseudo-Still disease*, an inflammatory arthritis characterized by swelling, tenderness, and pain in one or more joints and by lymph node and splenic enlargement.

In 2006, Inokuchi et al. [110] described a paranasal tumor associated with paraneoplastic *osteomalacia*.

Serum fibroblast growth factor 23 (FGF-23) was measured before and after surgery. After surgery, the patient's symptoms were resolved and the serum phosphate and FGF-23 levels became normalized.

Paraneoplastic ocular syndromes

Paraneoplastic ocular syndromes are characterized by the progressive loss of function of photoreceptors with subsequent painless visual loss with night blindness, light-induced glare, photosensitivity, and peripheral and ring-like scotomas. Funduscopic examination is normal or shows arteriolar narrowing. The electroretinogram demonstrates abnormal cone and rod-mediated responses [111].

The most common paraneoplastic ocular syndromes are the *cancer-associated retinopathy* (CAR) and the *melanoma-associated retinopathy* (MAR). CAR syndrome has been mainly described in association with small cell lung cancer, secondly with gynecologic and breast cancers and, less commonly, with non-small cell lung cancer, pancreatic cancer, bladder cancer and lymphoma [112–116]. In 1992, Matsui et al. [117] reported two cases of CAR syndrome, one of which was related to cancers of prostate, bladder and larynx. CAR syndrome (and its subset "*cone dysfunction*") has also been described in relation to head and neck cancers (thymoma, tongue and laryngeal cancers) [115, 118, 119]. Patients with metastatic cutaneous melanoma or MAR may present unusual fundus lesions that be caused by autoimmunity which is part of the relevant clinical characteristics [120, 121].

Another ocular paraneoplastic syndrome associated with cancers of the head and neck region (nasopharyngeal carcinoma and thymoma) is *optic neuritis* or *optic neuropathy* [122–124]. It includes sudden bilateral visual loss, swollen optic discs, and field defects that usually occur in association with encephalomyelitis [111, 113].

Investigation and patient management

Patients with a suspected paraneoplastic disorder should undergo a complete panel of laboratory studies of blood, urine, and cerebrospinal fluid. The interpretation of the data may suggest or confirm the diagnosis of paraneoplastic syndrome, for example a diagnosis of SIADH should be considered in patients initially presenting with hyponatremia (<135 mEq/l) and a urine osmolality or a urine specific gravity higher than expected for serum osmolality (urine osmolality > 300 mmol/kg; urine specific gravity > 1.015; serum osmolality < 280 mOsm/kg).

A urinary sodium concentration of >20 mEq/l may also be suggestive of this syndrome [2].

Complete blood picture counts may demonstrate anemia. This anemia may be the result of any of several different types of cancer, or it may be the result of different benign conditions. The erythrocyte sedimentation rate usually is increased in patients with cancers and in those with infectious diseases. A microscopic study of the white blood cells is helpful for diagnosis of leukemia or lymphoma-related disorders. Hypereosinophilia frequently is observed in patients with leukomoid reactions. A platelet count must be performed in any patient with symptoms of disseminated intravascular coagulopathy.

Blood enzymes may be altered, even in healthy individuals or those who have benign conditions. Increased plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) commonly are observed in patients with malignancies of the digestive system as well as in patients with bone or muscle injuries. Protein electrophoresis of serum and cerebrospinal fluid may demonstrate alterations of albumin levels and increased beta-globulins and gamma-globulins. Gamma-globulins always are increased in patients with autoimmune disorders, whether neoplastic or not.

Tumor markers are very useful for diagnosis of cancers that are clinically silent, but most markers are not specific for determining the origin of the cancer.

Many patients with paraneoplastic disorders may have autoantibodies against several tissues of the body. Demonstration of these autoantibodies is very important to confirm the diagnosis of a paraneoplastic syndrome and distinguish it from non-neoplastic syndromes. However, most known autoantibodies are directed against nervous system structures. Anti-Hu (previously called antineuronal nuclear antibody 1 or ANNA-1) is an autoantibody detected in the serum of patients with paraneoplastic subacute sensory neuronopathy and/or encephalomyelitis.

In addition to laboratory investigations, imaging studies may be useful to detect the primary tumor in patients with paraneoplastic disorders. Computed tomography scanning and magnetic resonance imaging of the whole body allow detection of the site and the extension of the underlying primary tumor and its metastases, if present. Positron emission tomography might be an additional option for searching a primary tumor in cases of early paraneoplastic symptoms. Scintigraphy may be useful in patients with endocrine disorders related to a hormone-producing tumor. Endoscopy is useful to detect tumors of the aerodiges-

tive tract, and it also allows the examiner to obtain biopsy samples.

Because of their protean manifestations, paraneoplastic syndromes should be evaluated clinically by a coordinated team of doctors, including medical oncologists, surgeons, radiation oncologists, endocrinologists, hematologists, neurologists, and dermatologists.

Treatment varies with the type and location of the paraneoplastic disorder. Two treatment options exist; treatment of the underlying tumor—this therapeutic option is based on the usual surgery, radiation, or chemotherapy (singly or in combination). These therapeutic protocols are those that generally are applied to neoplastic disorders without the presence of paraneoplastic syndrome. The second therapeutic option is treatment of the presumptive immune-mediated disorder. It is based on immunosuppression (by intravenous immunoglobulins, steroids, or other immunosuppressive drugs or by plasma exchange). This treatment should be reserved for patients with clearly identifiable antibodies in their serum.

Clinical significance

Physicians who deal with cancer-associated syndromes should be able to differentiate the paraneoplastic syndromes from the benign disorders that mimic them. Sometimes, paraneoplastic syndromes can be more serious than the consequences of the primary tumor itself and can precede, develop in parallel, or follow the manifestations of this tumor; moreover, it can dominate the clinical picture and thus lead to errors with respect to the origin and type of the primary tumor [125].

Paraneoplastic syndromes are important because their identification allows an early diagnosis and adequate treatment of tumors, with a favorable oncologic and neurologic outcome and improved life expectancy for the patient. They often represent the only signal of a silent neoplasm; sometimes they precede the tumor itself [1, 126].

Being the biological signals in the diagnosis of cancer, paraneoplastic syndromes can lead to the diagnosis of a previously undetected malignant or benign neoplasm and they can follow the clinical course of the underlying tumor and thus be useful for monitoring its evolution [125].

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