PARANEOPLASTIC PEMPHIGUS ASSOCIATED WITH A HYPOPHARYNX SQUAMOUS CELL CARCINOMA. CASE REPORT

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ABSTRACT

Introduction: Paraneoplastic pemphigus (PNP) is a rare autoimmune disease of the skin associated with neoplasm. It is mostly associated with lymphoproliferative disorders (nearly 84% of all cases are found in hematologic neoplasms). The underlying pathogenesis is believed to be triggered by altered immune system in response to underlying neoplasm. The manifestations can predate, occur at the same time or after the diagnosis of cancer. Males between 40 and 70 years are most frequently affected. The prognosis of PNP is generally poor, and the disease is often fatal. The occurrence of PNP with squamous cell carcinoma is rare.

Case presentation: We present the case of a 67-year-old male with squamous cell carcinoma of the hypopharynx associated with PNP. The patient treatment performed was external beam radiotherapy, concomitant with chemotherapy. A skin biopsy was performed and it revealed pemphigoid lesions.

Conclusions: This kind of case is rare because the PNP is rarely associated with a hypopharynx carcinoma and also because the particularities regarding diagnosis and challenging treatment. After the oncological treatment, the evolution was favorable, with amelioration of symptomatology, pemphigoid lesions and tumor regression. Unfortunately, the patient was not present at the visit 6 months after treatment, being lost to follow-up.

Keywords: paraneoplastic pemphigus, rare, hypopharynx squamous cell carcinoma.

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Introduction

Paraneoplastic syndromes (PNS) are a clinical spectrum of manifestations of neoplasms, and maybe the first manifestations of malignancy, also being responsible of the most prominent symptoms\textsuperscript{(1,2)}. PNS can precede, be concomitant with a malignancy or follow the neoplasm. It is mandatory to differentiate these syndromes from false-PNS; the PNS’s symptoms may be directly related to the invasion of the normal tissue by the tumor or by secondary lesions\textsuperscript{(1,3)}. The exact mechanism of the PNS associated with underlying malignancy is not well known but it was suggested that malignant cells use many ways to produce components of PNS. Neoplastic cells can produce enzymes, fetal proteins, hormones, and cytokines, can stimulate antibody production and metabolize steroids. All of these products can determine manifestation of PNS\textsuperscript{(1,4)}. 
The most frequent dermatological PNS are: Acantosis nigricans, Eruptive seborrheic keratosis, Erythema gyratum repens, and paraneoplastic Pemphigus (PNP).

PNP is a rare autoimmune, blistering disease, associated with an underlying malignant disease, especially lymphomatoid and hematologic, (e.g. B-cell lymphoma, chronic lymphocytic leukemia, Castleman’s disease, Waldenström’s macroglobulinemia, and thymoma). PNP is characterized by intraepithelial lesions at teguments and mucous level and is developed following the interaction between genetic predisposition and some exogenous factors.

PNP is usually associated with auto-antibodies from tumor cells against the desmosomal and hemidesmosomal components of epithelium. PNP has the highest prevalence in 45-70-year-old patients but can also occur on adolescents and children. Unfortunately, PNP is often resistant to treatment. The prognosis is poor with high mortality rates, depending on the nature of the underlying disease.

PNP can be frequently associated with various hematologic tumors such as lymphoma and leukemia, and non-hematologic tumors such as carcinoma, sarcoma, and melanoma, although very rarely.

We present a case of a PNP associated with a hypopharynx squamous cell carcinoma because of the rarity of such cases showing the amelioration of pemphigoid skin lesions during the specific oncologic treatment.

**Case report**

We present the case of a 67-year-old man who presented to the Otolaryngology department with dyspnea and dysphonia. The patient was a heavy smoker and chronic alcohol consumer for more than 30 years. He was also a former worker in an environment with industrial exhaust emissions, in the metallurgical industry. The personal pathological history included high blood pressure and diabetes mellitus.

On the clinical examination the patient presented vesicles with clear liquid and painful sores on the trunk, arms and legs, that had appeared a few weeks earlier. Otolaryngeal examination revealed a vegetant tumor mass that narrowed the glottic space and caused respiratory insufficiency (figure 1).

Hematological and biochemical parameters have been in normal limits. Chest X-ray examination showed an accentuated interstitial of the lung and mitral configuration of the heart. In May 2016, the Computed Tomography (CT) examination of the cervical area revealed an inhomogeneous, iodophilic tumor mass in the right infraglottic space of the larynx measuring 39/39/55 mm, extending towards the right carotid space, with erosion of the thyroid cartilage multiple bilateral cervical lymph nodes highly iodophilic inhomogeneous, the biggest measuring being of 30 mm.

The biopsy sampled from the hypopharynx showed the low grade squamous cell carcinoma. An emergency tracheostomy was performed in May 2016 and the patient was redirected to the Oncology-Radiotherapy department where, in June 2016, clinically presented bubble with clear liquid, erosions, and ulcerations on the anterior and posterior trunk, thigh, arms and legs; right cervical adenopathy of 4/3 cm, and mobile respect profound plans, painless at palpation; left cervical adenopathy of 3/2 cm, suppurative secretion round the tracheal cannula from which was sampled for bacteriological examination. The evaluation of distance lesions did not reveal any visceral metastasis.

The diagnose was hypopharynx tumor with extension in the larynx and erosion of the thyroid cartilage, cT4aN2cM0.

Hematological and biochemical constants were within normal limits, excepting GGT=69U/L, and Urea=45mg/dl.

The Oncological Committee recommended external beam radiotherapy with concomitant chemotherapy. The skin biopsy showed moderate and superficial orthokeratotic hyperkeratosis, and unequal epiderma, with atrophic zones and presence of intraepidermal bullous with serous eosinophilic content, in which were identified rare neutrophils and acantholytic cells.
At epidermal level, spongiosis and numerous cleavage spaces situated suprabasal were noticed. Superficial derma presented moderate, inflammatory, chronic perivascular infiltrate (figure 2a-f).

Histopathological (HP) examination revealed pemphigus lesions, which were interpreted in the clinical context of hypopharynx squamous cell carcinoma (also with HP confirmation) as paraneoplastic syndrome.

The patient performed conventional external beam radiotherapy (EBRT) with 60Co, in TD=70Gy/35 fr./8 weeks, dose/fr.= 2Gy daily, and concomitantly chemotherapy (CMT) with Cisplatin 100 mg/m2 days 1, 22 and 43, with good compliance; hematological and biochemical parameters being in normal limits, excepting leucocytes, L=3800/mm³, corrected with corticotherapy. Antalgic second line treatment was administered. The patient also received symptomatic treatment with corticoids, proton pump inhibitors, and antibiotic treatment according to the antibiogram. The prolonged treatment time was due to the grade 3 radiodermatitis.

At the end of the oncological treatment an improvement of the skin pemphigoid lesions was observed (figures 3a and 3b).

Figure 3: (a) and (b). Clinical images showing improvement of the skin pemphigoid lesions on the left arm.

Otolaryngeal examination at two months post-treatment indicated a 75% reduction of the tumor mass. At the 6 months post-treatment visit, the patient was not present, being lost to follow-up.

Discussions

PNP is a rare autoimmune skin disease that is always associated with a neoplasm. Usually, oral,
skin, and mucosal lesions are the earliest manifestations shown by PNP patients. The pathogenesis of PNP is not yet completely understood, although some immunological aspects have been recently clarified\(^\text{[12]}\).

PNP was first described as a distinct entity in 1990 by Dr. Anhalt, since then more than 200 cases being reported\(^\text{[19]}\), and about 450 cases have been reported in the literature between 1990 and 2011\(^\text{[14,15]}\).

PNP is a rare life-threatening, autoimmune blistering disease, associated with an underlying malignant disease, especially lymphomatoid and hematologic, (eg. B-cell lymphoma, chronic lymphocytic leukemia, Castleman’s disease, Waldenstrom’s macroglobulinemia, and thymoma)\(^\text{[6,7,11,16,17]}\). There is no consensus regarding the diagnostic criteria for PNP\(^\text{[10]}\). According to Anhalt et al., characteristic clinic appearance, histopathology, detection of tissue bound, circulating autoantibodies via direct immunofluorescence, and indirect immunofluorescence might represent a set of criteria\(^\text{[11,12,18,19,20]}\).

According to Vikram et al., PNP is a clinically and immunopathologically distinct mucocutaneous blistering dermatosis and a severe form of autoimmune multiorgan syndrome generally associated with poor therapeutic outcome and high mortality\(^\text{[16]}\).

Although very rare, PNP can be associated with various non-hematologic malignancies such as carcinoma, sarcoma, and melanoma. From 163 PNP cases reported during a period of 13 years only 13 cases were carcinomas\(^\text{[22]}\). The association with solid tumors is infrequent but the association with the head and neck carcinomas is extremely rare; only one case of PNP associated with squamous cell carcinoma of the tongue was described\(^\text{[17]}\). No case of PNP associated with larynx squamous cell carcinoma was reported.

Regarding genetic characteristics, it has been reported that PNP is associated with the DRB1*03 allele and HLA-Cw*14 alleles\(^\text{[13]}\).

Clinically, PNP is extremely polymorphous, being characterized by severe mucosal erosions and various cutaneous lesions\(^\text{[13,17]}\). PNP might be the first clinical manifestation of neoplasm and oral and skin lesions may be the earliest manifestations\(^\text{[13,15,22]}\).

Pathological results are connected with clinical features, indicating different pathological characteristics depending on the examined lesions\(^\text{[20]}\).

When blisters are present, suprabasal acantholysis with sparse inflammatory infiltrates is usually evident on skin biopsy\(^\text{[11,23]}\), while interface and lichenoid dermatitis are usually detected if inflammatory maculopapular lesions are present\(^\text{[23,24]}\).

The prognosis of PNP is often very poor and the mortality rate is high due to complications of immunosuppressive regimens such as sepsis, gastrointestinal bleeding due to high dose of corticosteroids, or bronchiolitis obliterans\(^\text{[25]}\). The prognosis depends also on the nature of the underlying disease. PNP associated with malignancy can be severe and unresponsive to treatment\(^\text{[11]}\). PNP most frequently presents in patients between 45 and 70 years of age but it can also occur in children and adolescents\(^\text{[10]}\). The diagnosis is made based on clinical, histological, and immunofluorescence findings. The prognosis of PNP is poor and the mortality rate is high due to complications and resistance to treatment and it can be a frequent cause of death rather than the malignancy itself. The specific treatment has not yet been well established\(^\text{[26,27]}\).

Nevertheless PNP alongside the larynx carcinoma remains a life-threatening disease due to its unknown evolution and lack of specific treatment. Radiotherapy can also be a trigger factor for the PNP\(^\text{[27,28]}\).

Patients with PNP can develop life-threatening restrictive bronchiolitis consistent with bronchiolitis obliterans. The frequency of the involvement of the respiratory system and pathological mechanisms is not known\(^\text{[11]}\).

The prognosis depends on the associated tumors. The mortality rate ranges from 75% to 90%, with respiratory failure as the main cause of death. Early diagnosis and initiation of treatment are of paramount importance\(^\text{[11,29]}\).

Fried et al. described a case of paraneoplastic pemphigus which appeared after palliative radiotherapy for large cell lymphoma\(^\text{[26,30]}\). Due to EBRT that could be a worsening agent for PNP and aware of possible complications, PNP therapy remains challenging.

The case presented in this article represents a rarity because PNP is rarely associated with a hypopharynx carcinoma and also because of the particularities regarding diagnosis and the challenging treatment. Skin histopathological (HP) examination revealed pemphigus lesions; these were interrelated in the clinical context of hypopharynx squamous cell carcinoma (also with HP confirmation) as paraneoplastic syndrome. After the onc-
logical treatment, the evolution was favorable both for the tumor and the pemphigoid lesions. Unfortunately, the patient was lost to follow-up, being absent at the visit 6 months after treatment.

Conclusions

PNP is a rare autoimmune disease of the skin associated with neoplasm but the association of PNP with hypopharynx squamous cell carcinoma is not commonly seen - and this is the rarity and the particularity of our case. After the oncological treatment, the evolution was favorable both for the tumor and for the pemphigoid lesions.

Because of its varying clinical features, PNP still represents a challenge for clinicians. Furthermore, diagnosis and management of paraneoplastic pemphigus require close collaboration between physicians, including dermatologists, oncoloists, and otorhinolaryngologists.

References


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