CASE REPORT

Bronchiolitis Obliterans Associated With Paraneoplastic Pemphigus: a Paraneoplastic Autoimmune Multiorgan Syndrome

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INTRODUCTION: Paraneoplastic pemphigus is a mucocutaneous disease characterized by well defined clinical and immunopathological features associated with neoplasia. Recent evidence of bronchial epithelium involvement has led to the suggestion that this process is a paraneoplastic autoimmune multiorgan syndrome.

CLINICAL OBSERVATION: We report the case of a patient with lichenoid eruptions on the skin and mucous membranes who later developed progressive dyspnea. With a suspected diagnosis of paraneoplastic autoimmune multiorgan syndrome, the following diagnostic tests were performed: histology and immunofluorescence of the skin, oral mucosa, and bronchial epithelium; indirect immunofluorescence of serum; pulmonary function tests; and evaluation for an occult neoplasm.

Findings of pathology and immunofluorescence confirmed the suspected diagnosis. The computed thoracoabdominal tomography revealed signs of bronchiolitis and the presence of a retroperitoneal tumor.

CONCLUSIONS: Awareness of the mucocutaneous manifestations of paraneoplastic autoimmune multiorgan syndrome, and confirmation of this diagnosis by simple laboratory techniques can facilitate the early detection of occult neoplasia and forestall respiratory involvement.

Key words: Paraneoplastic pemphigus. Paraneoplastic autoimmune multiorgan syndrome. Bronchiolitis obliterans.

Introduction

In 1990, Anhalt et al described a mucocutaneous disease with well defined clinical and immunopathological features associated with a neoplastic process, generally of the lymphoid type. They named the process paraneoplastic pemphigus. Since then, the study of new cases has provided a greater understanding of the diverse facets of this syndrome and of the possibility of late involvement of the respiratory system, in which cases the prognosis is death. More recently, it has been suggested that paraneoplastic pemphigus is the mucocutaneous expression of a paraneoplastic autoimmune multiorgan syndrome (PAMS).

We report the case of a woman with the cutaneous, mucosal, and respiratory symptoms of PAMS confirmed by immunopathological studies associated with a retroperitoneal spindle cell tumor.

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Case Description

The patient was a 46-year-old woman with no relevant history who in July 1999 presented with oral lesions that were diagnosed and treated as candidiasis. In light of their persistence, a biopsy was carried out in September 1999. The lesions were diagnosed as lichen planus, and oral corticosteroids were prescribed. Two months later the oral lesions had worsened, and the patient had developed lesions of the genital, pharyngeal, and conjunctival mucosa in addition to skin lesions on the trunk. The results of a skin biopsy were consistent with a diagnosis of pemphigus vulgaris. Direct immunofluorescence (DIF) revealed antibody deposits in the intercellular spaces and basement membrane. The results of indirect immunofluorescence (IIF) were negative. Treatment with a combination of prednisone 125 mg/day and azathioprine 100 mg/day taken orally was started. The skin lesions improved on treatment but the oral lesions persisted.

In March 2000, while receiving prednisone 70 mg/day and azathioprine 100 mg/day, the patient developed a dry cough and exertional dyspnea. The result of an intradermal allergy test was negative, and chest computed tomography revealed no abnormalities. The patient was treated with inhaled bronchodilators, zafirlukast, and oral corticosteroids. Despite treatment, the dyspnea continued to worsen, and the patient eventually required domiciliary oxygen therapy.

In April 2002, because of the persistence of the oral lesions, the patient consulted the dermatology department of the Hospital Clinic. The following symptoms were found in the course of the dermatological examination: erosive lesions in the jugal mucosa, the palate, and the tongue (Figure 1); a whitish reticulated lichenoid pattern on the lips; erythematous maculopapules; and residual lichenoid pigmentation on the trunk.

With a suspected diagnosis of PAMS the following diagnostic tests were carried out: biopsies of skin and oral mucosa, DIF and IIF, study of respiratory involvement, and evaluation for an occult neoplasm.

The biopsy revealed an inflammatory lichenoid infiltrate in the mucous membrane, an intraepidermal blister, vacuolization of the basement membrane, and necrotic keratinocytes in the skin. DIF of skin and oral mucosa revealed deposits of class G immunoglobulins (IgG) in the intercellular spaces and granular deposits of C3 in the basement membrane. IIF detected IgG antibodies (titers of 1:320), which reacted intensely with monkey esophagus and rat bladder epithelium. A gynecological examination revealed a cyst on the right ovary and a fibrocystic mastopathy. Lung function testing evidenced an obstructive defect, with forced expiratory volume in 1 second of 560 mL (21% of predicted).

Bronchoscopic examination revealed poorly defined, whitish pseudomembranes, and diffuse inflammation of the mucous membrane in both sides of the bronchial tree.

Bronchial and transbronchial biopsies revealed slight inflammatory changes and the presence of acantholysis in the basement layers of the epithelium (Figure 2A). DIF detected IgG deposits on the cell surfaces (Figure 2B) and C3 deposits in the epithelial basement membrane of the central and peripheral bronchi.

High resolution chest computed tomography showed bronchial thickening and dilation, but no changes affecting the pulmonary structures in the expiratory phase that would indicate air trapping. All of these findings were suggestive of bronchiolitis obliterans.

Abdominal computed tomography detected a retroperitoneal mass (6×8×7.5 cm) located between the pancreas and the kidney. The mass was highly vascularized and had areas of calcification and necrosis.

The results of general blood, immunological, lymphocyte population, and bone marrow aspirate analyses were normal.

In May 2002, the tumor was excised. Pathology of the excised mass revealed a well-encapsulated tumor composed of a spindle cell mesenchymal proliferation with no atypical cells, scant mitosis, and a more abundant presence of lymphocytes in the peripheral zones of the tumor. The sample from the excised mass showed deposits of class G immunoglobulins on the cell surface and in the basement membrane of the bronchial epithelium.
tested positive for vimentin and negative for dendritic cell markers and desmin. All of the above results strongly suggested a low-grade mesenchymal tumor. After the tumor was excised, corticosteroid therapy was tapered off gradually until December 2002, when it was stopped altogether. The skin lesions have disappeared, the oral lesions have improved, the dyspnea on slight exertion persists, but there has been a slight improvement in lung function (forced expiratory volume at 1 second of 26%) The antibody titers have decreased (1:20). The patient has been proposed as a candidate for a lung transplant.

Discussion

Paraneoplastic pemphigus is not a new disease. Cases have been reported with a diagnosis of lichen planus, erythema multiforme, or pemphigus vulgaris with atypical characteristics in association with a neoplastic process (frequently lymphoid). These were deemed to be paraneoplastic processes. While most have not been documented, in some cases it has been possible to demonstrate retrospectively that they were paraneoplastic pemphigus.

Approximately 80% of cases are associated with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and Castleman’s tumor. An association with sarcomas, thymomas, and Waldenström’s disease occurs less often, and only in exceptional cases is it found in conjunction with more common tumors, such as lung or breast cancer. It is rare in childhood, when it is always associated with Castleman’s disease.

Anhalt et al defined 5 criteria for the diagnosis of paraneoplastic pemphigus:

1. **Clinical**: the constant presence of painful mucosal erosions unresponsive to conventional treatments. When the skin is affected, this can take diverse forms. The existence of an occult or confirmed neoplasm.

2. **Histology**: intraepithelial acantholysis (less obvious than in the classical forms of pemphigus), isolated keratinocyte necrosis, and basal vacuolization.

3. **DIF of the perilesional tissue**: presence of IgG deposits in the intercellular spaces similar to those observed in pemphigus, although weaker and more focal. The combination of C3 in the basement membrane and intercellular IgG is quite characteristic.

4. **IIF**: antibodies that bind to the intercellular spaces not only when stratified monkey esophagus epithelium or human skin is used as a substrate, which occurs with pemphigus, but also when other epithelial tissues and non-epithelial tissues are used, such as skeletal muscle and myocardial plaque. The most intense and characteristic IIF reactions are observed with the transitional epithelium of the urinary tract.

5. **Immunoprecipitation**: when extracts of human keratinocytes are used, the serum of these patients immunoprecipitates a complex of 4 polypeptides with molecular weights of 250, 230, 210, and 190 kd. They are all plakin, a group of proteins found in the intracellular plaque of desmosomes and hemidesmosomes. Occasionally, an additional immunoprecipitation band of 170 kd has been identified.

The most highly sensitive and specific of these criteria are association with a lymphoproliferative process, positive IIF in rat bladder, and the detection by immunotransfer of antibodies to the 210 and 190 kd antigens.

Respiratory involvement and the presence of IgG deposits on the cell surfaces of bronchial epithelium were described by Fullerton et al. This combination occurs in 30% of cases and is a late complication which persists even after the tumor has been excised and in spite of immunodepressant therapy. It has been suggested that the acantholysis of the respiratory epithelium caused by the antibodies directed against the plakin proteins may cause occlusion and scarring in the distal bronchi. It has also been suggested that this is a bronchiolitis associated with an autoimmune process.

The prognosis depends on the associated neoplasm and on the presence of respiratory involvement. Cases associated with benign tumors improve or remit when the tumor is removed. Clinical cure coincides with negativatization of the IIF. In the case of malignant neoplasms, the lesions persist despite control or apparent cure of the underlying disease. The mortality rate associated with paraneoplastic pemphigus is 90% and is related to the immunodepressant therapy (sepsis, digestive hemorrhage, and multiorgan failure) and to bronchial involvement.

Various treatments have been used: corticosteroids alone or in combinations with immunodepressants such as azathioprine, cyclophosphamide, or cyclosporin; plasmapheresis; and photopheresis. The skin lesions respond relatively well while the lesions affecting the oral and bronchial mucosa are highly refractory. Lung transplant is the only therapeutic option for the progressive respiratory failure secondary to bronchiolitis. Only 1 case has been reported in the literature of a transplant patient who survived without any evidence of bronchial recurrence 2 months after the transplant.

Most patients die within 2 years of diagnosis, although some cases of prolonged survival have been reported.

Nguyen et al, who studied the effectors of humoral and cellular autoimmunity conclude that the pathophysiology of the PAMS lesions, while still poorly understood, differs from that of classic pemphigus. The fact that immunoglobulin deposits have been found in organs not clinically or histologically affected suggests to these authors that such antibodies are not pathogenic but may be serological markers of the disease. They emphasized the importance of the inflammatory lesions (normally absent in pemphigus), from both the clinical and the histological standpoint. Analysis of the infiltrate from the lesions revealed cytotoxic reactions that damaged the basal epithelial cells. This cell damage exposes intracellular antigens to recognition by autoreactive T cells, thereby triggering the activation
and production of autoantibodies against desmosome and hemidesmosome proteins. This would suggest that the autoimmune process is propagated by way of epitope spreading.10 The term “paraneoplastic pemphigus” has historical value but may be a source of confusion, since the term “pemphigus” is traditionally associated with blisters and erosive lesions and this may lead physicians to rule out this entity as a possible diagnosis when it manifests itself as some other kind of lesion, which is often the case. Furthermore, pemphigus never affects the bronchial epithelium. The phenotypical variability of the patients and the different pathophysiology of the process suggest that a more appropriate name should be used, the proposed term being PAMS. Paraneoplastic pemphigus would be its mucocutaneous expression.3

Mucocutaneous symptoms precede the diagnosis of a neoplasm in a third of cases. Clinical suspicion of the diagnosis and consequent confirmation by immunofluorescence would make early detection of an occult neoplasm possible, forestalling later respiratory involvement, for which the prognosis is death. In the case of specific bronchial involvement, a lung transplant should be considered within the shortest period possible, since there is no other effective treatment, and the high mortality rate associated with this disease is related to immunodepressant treatment.

Although we did not perform enzyme-linked immunosorbent assay or immunoprecipitation studies, we believe that this was a typical case of PAMS, possibly the one with the longest survival of those published in the literature in which the lung has been involved (documented by way of lung function testing, computed tomography, pathology, and DIF). The evolution of the mucocutaneous symptoms coincides with the course described in the literature. The stabilization and slight improvement in lung function are surprising. The withdrawal of immunodepressant therapy, thereby avoiding its possible adverse effects, may have had an influence on the favorable evolution of the patient’s condition.

REFERENCES