Paraneoplastic Autoimmune Multiorgan Syndrome (Paraneoplastic Pemphigus) in a Child: Case Report and Review of the Literature

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ABSTRACT. Paraneoplastic autoimmune multiorgan syndrome, also known as paraneoplastic pemphigus, has been observed only rarely among children. We describe a 10-year-old boy with typical clinical and histologic findings of paraneoplastic pemphigus associated with Castleman’s disease. His disease was refractory to resection of the tumor and aggressive combination immunosuppressive therapies. The patient died 1 year after presentation, as a result of complications of bronchiolitis obliterans. This case is unusual because of the young age of the patient. Pediatrics 2004;114:513–516. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0436; paraneoplastic pemphigus, paraneoplastic autoimmune multiorgan syndrome, child, Castleman’s tumor.

P araneoplastic autoimmune multiorgan syndrome (PAMS) (paraneoplastic pemphigus) encompasses a multitude of mucocutaneous and systemic findings. Mucocutaneous involvement in paraneoplastic pemphigus is prominent, with painful erosive lesions involving the oral, nasal, upper gastrointestinal, respiratory, ocular, and genital epithelium.1 Cutaneous manifestations are variable and often consist of polymorphous inflammatory macules, papules, and plaques. Histopathologic examinations classically reveal acantholysis, intraepidermal blister formation, and immunoreactant deposition along the basement membrane and within epithelial intercellular spaces. Associated neoplasia is a requisite finding of PAMS but may be occult at the onset of cutaneous lesions. Patients with PAMS frequently have significant pulmonary involvement, which accounts for the high mortality rate.

The occurrence of PAMS in childhood has been reported infrequently. When PAMS occurs among children, however, Castleman’s disease is the most common underlying neoplasm, with progressive bronchiolitis obliterans resulting in pulmonary destruction and death. We report the case of a 10-year-old child who developed a diffuse mucocutaneous eruption that was clinically and immunopathologically consistent with PAMS. Systemic evaluation revealed a retroperitoneal Castleman’s tumor.

CASE REPORT

A 10-year-old, previously healthy, white boy presented with a 2-month history of a papular eruption of the trunk, conjunctivitis, erosive stomatitis, proximal nail fold inflammation, and dyspnea. Prior evaluation included a positive mycoplasma titer and a skin biopsy that was interpreted as indicating erythema multiforme/Stevens-Johnson syndrome. The mucocutaneous lesions were resistant to systemic corticosteroid treatment. The patient was referred to our institution because of progressive symptoms.

System review results included fever, cough for 6 to 8 weeks, fatigue, constipation, and weight loss, with poor food intake attributable to painful oral ulcers. The physical examination revealed a thin boy with perioral cyanosis and resting tachypnea. A facial examination revealed bilateral exudative bulbar and palpebral conjunctivitis, nasal septal erosions with crust, gray erythematous desquamation of the tongue and gums, and erosive erythema of the interdigital gingiva (Figs 1 and 2). Erythematous plaques were present on both palms, with erythema and edema of the distal digits and dystrophic nail changes (Fig 3). In addition, an erythematous plaque with focal erosion was present on the glans penis. Pustules were present on the knees and ankles. Right and left upper quadrant tenderness and fullness were noted in the abdominal examination. The initial differential diagnosis included Reiter’s syndrome, Behcet’s disease, lupus erythematosus, dermatomyositis, and PAMS.

Laboratory investigations revealed a normal complete blood count, normal erythrocyte sedimentation rate (8 mm/hour), and negative titers for antinuclear antibody (Hep-2), anti-double-stranded DNA, anti-SSA/Ro, anti-SSB/La, anti-Smith, anti-U1-ribonucleoprotein, anti-Jo-1, cytoplasmic anti-neutrophil cytoplasmic antibody, perinuclear anti-neutrophil cytoplasmic antibody, antiscardiolipin antibodies, cryoglobulins, HLA-B27, and HLA-B5. Urinalysis results were normal. Chest radiograph results were initially normal.

Histopathologic examinations of cutaneous biopsies demonstrated interface vascular dermatitis with minimal acantholysis, a slight increase in connective tissue mucin, and focal basement membrane thickening. The stratum corneum was compact and parakeratotic. A specimen obtained after corticosteroid therapy showed vascular interface dermatitis with ulceration, acantholysis, abscess formation, and underlying vasculitis. No direct immunofluorescence was observed for immunoglobulin (Ig) G, IgA, IgM, or complement component 3 (C3). Indirect immunofluorescence assays showed intercellular and dermal/epidermal staining for IgG and C3 on monkey bladder (Fig 4). Paraneoplastic pemphigus was diagnosed on the basis of clinical and histopathologic findings. A neoplasm was not evident at that time.

Persistent constipation and the presence of abdominal fullness prompted computed tomography (CT) evaluation of the abdomen, which showed a mass (5.5 cm × 7 cm × 9 cm) in the right lower retroperitoneal space. An open biopsy, complicated by significant bleeding, was interpreted as indicating a hemangioma. Magnetic resonance angiography was performed to delineate the
vascular nature of the mass; it revealed a large feeding vessel to
the mass, which was embolized.
Early in the disease course, the patient’s respiratory symptoms
worsened. CT evaluation of the chest demonstrated a diffuse
interstitial infiltrate. The patient was unable to undergo pulmo-
nary function testing because of the fixation of his mouth and
painful oral lesions. A clinical diagnosis of bronchiolitis obliterans
was made. The patient was treated with prednisone (50 mg daily,
2 mg/kg per day) and then intravenously administered
γ-globulin (24 g of Ig) and cyclosporine (350 mg/day). The skin findings
transiently improved, except for those for the distal phalanges.
Therapy with rituximab (monoclonal antibody against B cells) and
daclizumab (antibody against interleukin-2 receptor) was subse-
quently initiated.2,3
Four months after presentation, the patient was referred to a
nearby academic center and underwent partial resection of the
tumor. The histopathologic examination revealed a vascular vari-
ant of Castleman’s tumor. Immunohistochemical examination for
human herpesvirus 8 yielded negative results. Three months after
surgery, the patient received radiotherapy to his abdomen.
Pulmonary function testing was performed 5 months after the
initial presentation and after partial tumor resection, when the
oral lesions had improved. The studies were consistent with se-
vere restrictive and obstructive pulmonary disease with air trap-
ing. There was no bronchodilator responsiveness to the obstruc-
tive pattern.
During the disease course, the patient underwent multiple
admissions because of fever and weight loss. He developed sym-
blepharon as a result of chronic conjunctivitis, and he eventually
lost his fingernails.
Fourteen months after presentation, the patient’s lung function
had progressively deteriorated. Chest CT scans showed new de-
velopment of lower-lobe bronchiectasis, with progression of pre-
viously identified, thin-walled, cystic lesions in both lungs and
increasing areas of ground glass opacity, especially in the left
lower lobe. Bronchoalveolar lavage was performed and showed
no superficial inflammation or friability of the mucosa. Cultures
were negative for bacterial, fungal, or viral infection. Sections from
an open lung biopsy performed on the same day showed evidence
of small-airway disease, with mucostasis and an absence of respi-
atory bronchioles in the visible sections. There was also mild
cellular interstitial pneumonia, with small nonnecrotizing granu-
ломas and multinucleated giant cells present, which was likely
an incidental finding in the context of small-airway disease. Subse-
quent CT scans of the abdomen and pelvis showed a residual
tumor (2 cm × 3 cm) inferior to the right kidney in the pelvis. One
month after the lung biopsy, despite aggressive medical therapy,
end-of-life issues needed to be discussed with the patient and his
parents. The patient was discharged from the hospital with hos-
pice care and died shortly thereafter.

DISCUSSION
An association between polymorphous skin lesions, including bullae, and internal malignancies has long been recognized. However, a distinct entity, ie, PAMS (paraneoplastic pemphigus), was formally characterized by Anhalt et al1 in 1990, as an autoimmune bullous disease associated with neoplasia (often occult). The disease is typified by painful muco-
sal ulcerations and polymorphous cutaneous lesions progressing to bullae among patients with underly-
ing neoplasia. Histopathologic findings include epider-
nal necrosis, acantholysis with suprabasilar clefting, vacuolar-interface changes (sometimes lichenoid
inflammation), and exocytosis of inflammatory cells. Direct immunofluorescence assessment of perile-
rosional skin shows intercellular IgG and C3 staining similar to that found in pemphigus, with additional
staining along the dermal-epidermal junction.

Anhalt et al1 demonstrated that 4 desmosomal and hemidesmosomal protein antigens, with molecular
masses of 250 kDa (desmoplakin I), 230 kDa (bullous pemphigoid antigen I), 210 kDa, and 190 kDa, were
the targets of IgG autoantibodies. These autoantibod-
ies, when injected into mice, reproduced the disease clinically and histopathologically. Later it was dis-

Fig 1. Exudative bulbar and palpebral conjunctivitis.

Fig 2. Gray erythematous desquamation of the tongue and gums, with mild nasal septal erosions and crusting.

Fig 3. Prominent erythema and nail dystrophy of the distal digits.
covered that the 210-kDa protein was actually 2 separate 210-kDa proteins, ie, desmoplakin II and envoplakin.4 The 190-kDa protein was shown to be identical to periplakin.4 Desmoplakins I and II, envoplakin, periplakin, and bullous pemphigoid antigen I all belong to the plakin family of cytoplasmic proteins. This combination of autoantigens is unique to paraneoplastic pemphigus. Hemidesmosome1/plectin (another plakin) and an unidentified 170-kDa protein were recently shown to be additional targets in paraneoplastic pemphigus. Mahoney et al5 showed that a homologous region near the carboxy terminus of the plakins serves as the antigenic site in paraneoplastic pemphigus. Antibodies against the cell-surface proteins desmoglein 1 and desmoglein 3 are also usually present in paraneoplastic pemphigus.6 The autoantibodies cause loss of cell-cell and cell-basement membrane adhesion, resulting in acantholysis histopathologically and blistering clinically.

The pathogenesis of PAMS may be attributable to tumor-induced inhibition of tolerance to keratinocyte junctional antigens. In other words, the antitumor immune response cross-reacts with normal epithelial proteins. Another concept used to explain the disease is “epitope spreading,” in which chronic inflammation of the dermal-epidermal junction leads to exposure of new self-antigens, triggering a humoral response. In addition to this humoral response, there is evidence that a cytotoxic (CD8+ T lymphocyte response contributes to the pathogenesis by causing keratinocyte death.7 Several cases have been reported to arise during or soon after chemo-therapeutic treatment of malignancies. A recent study showed that PAMS is associated with HLA-DRB1*03.8

Intercellular staining of rodent (mouse or rat) urinary bladder transitional epithelium in indirect immunofluorescence assays is highly specific (83–98.9%) for paraneoplastic pemphigus.9,10 Bladder epithelium has a high concentration of desmosomes. This relatively inexpensive and simple test is the best diagnostic tool9 to distinguish paraneoplastic pemphigus from pemphigus vulgaris occurring coincidentally with neoplasia.11 However, immunoprecipitation or immunoblotting of antibodies may be the standard method for diagnosis.

Although PAMS is rare, it has been reported with a variety of neoplasms, including non-Hodgkin’s lymphomas, chronic lymphocytic leukemia and other lymphoid malignancies, Castleman’s disease without human herpesvirus-8, Waldenstrom’s macroglobulinemia, benign thymomas, poorly differentiated sarcomas, and carcinomas of the lung, colon, pancreas, and cervix.12–19 It is now well recognized that autoimmune mucocutaneous bullae should prompt physicians to search for occult malignancies among patients with no history of malignancy or for recurrence among patients with a known history of malignancy. If a tumor is not readily detectable, then continued surveillance is indicated. Notably, the skin lesions of paraneoplastic pemphigus do not always parallel the activity of the underlying malignancy.

The cutaneous eruption in paraneoplastic pemphigus may resemble pemphigus vulgaris, pemphigus vegetans, bullous pemphigoid, erythema multiforme major (Stevens-Johnson syndrome), toxic epidermal necrolysis, graft-versus-host disease, lichen planus pemphigoides, or lichen planus. Pustules have been described.20 Nikolsky’s sign may be positive. Patients may have hemorrhagic crusting of the lips, severe ulcerative stomatitis/gingivitis, desquamative esophagitis and tracheobronchitis, scarring conjunctivitis, and genital erosions. In fact, the variety of clinical lesions is characteristic of the disease. A recent study showed that autoantibodies are found in kidney, bladder, smooth muscle, and striated muscle, in addition to skin, upper digestive tract, and respiratory tract epithelium.21 In light of this multisystem involvement and the clinical and immunopathologic heterogeneity of this entity, Nguyen et al22 suggested the broader term PAMS.

Unfortunately, with few exceptions, paraneoplastic pemphigus has a very poor prognosis and a high
mortality rate. It is characterized by severe respiratory compromise associated with IgG deposits in the epithelium of the bronchi, as well as pulmonary epithelial acantholysis and intraepithelial cleavage. No therapy has been consistently successful. Eradication of the associated tumor is occasionally curative but not uniformly helpful. Treatment is palliative immunosuppression. Systemic corticosteroid treatment, cyclosporine, cyclophosphamide, azathioprine, gold, dapsone, thalidomide, mycophenolate mofetil, rituximab administration, intravenous Ig administration, plasmapheresis, immunopheresis, and photopheresis have been tried.2,3,22,23 These treatments are generally ineffective and usually, at best, only slightly delay the patient’s rapid demise as a result of progressive obstructive lung disease and respiratory failure or infection.

Autoimmune blistering diseases are much more common among adults and elderly subjects than among children and adolescents. Chronic bullous disease of childhood (linear IgA disease) and dermatitis herpetiformis are the autoimmune bullous diseases seen most commonly among children.24 Paraneoplastic pemphigus has been observed rarely among children.22,25–28 Mimouni et al27 recently analyzed 14 cases of paraneoplastic pemphigus among patients <18 years of age. Among those patients, Castleman’s disease, bronchiolitis obliterans, and a fatal outcome were common.

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