Background: Paraneoplastic pemphigus was first described in 1990 in 5 patients with extensive mucocutaneous erosions, a distinct set of autoantibodies, and underlying neoplasia. Since then, patients described have been middle-aged, have suffered from prognostically unfavorable malignant neoplasms, and have responded poorly to immunosuppressive agents.

Observation: A 16-year-old boy was examined with extensive oral erosions, halitosis that interfered with his quality of life, and rapid weight loss. The suspected clinical diagnosis of paraneoplastic pemphigus was confirmed by histopathological, immunofluorescence, and biochemical (eg, immunoblotting and immunoprecipitation) findings as well as by the demonstration of an inflammatory myofibroblastic tumor of the left retroclavicular region.

Despite administration of corticosteroids, followed by excision of the neoplasm, clinical symptoms improved only slightly, and autoantibody titers decreased only marginally. We therefore initiated an immunoapheresis regimen with the use of sheep anti–human-IgG bead-formed agarose gel (Sepharose; Pharmacia Biotech Comp, Vienna, Austria), which led to the disappearance of circulating autoantibodies and the patient’s recovery.

Conclusion: Immunoapheresis may represent a novel therapeutic option for patients with paraneoplastic pemphigus who show little improvement after curative treatment of their neoplasms.

Arch Dermatol. 1998;134:706-710

PARANEOPLASTIC pemphigus (PNP), a rare blistering disease, is characterized by distinctive clinical symptoms (eg, extensive oral involvement) and a typical set of tissue-bound and circulating autoantibodies. These autoantibodies can be visualized on rodent urinary bladder by indirect immunofluorescence techniques, precipitate a unique complex of proteins from carbon 14–labeled human keratinocytes, and are pathogenic after passive transfer.¹

Neoplasms associated with PNP include lymphoid malignant neoplasms, poorly differentiated sarcomas, and benign neoplasms such as Castleman tumors and thymomas.²,³ Treatment of PNP is challenging. Immunosuppressive regimens are reportedly not very effective,⁴ and curative treatment of the underlying neoplasm is often not feasible.⁵

In this report, we describe a patient with PNP whose clinical and immunological symptoms persisted despite systemic immunosuppression and excision of an inflammatory myofibroblastic tumor of the upper mediastinum. Given that apheresis methods now exist for the selective removal of IgG antibodies, we initiated immunoapheresis to clear our patient’s serum of autoantibodies. The efficacy of this treatment was evidenced by the disappearance of circulating PNP-associated autoantibodies and reepithelialization of the oral mucosa.

REPORT OF A CASE

A 16-year-old white boy with an otherwise unremarkable medical history was admitted to our department because of an erosive process of the oral mucosa that had begun 2 months earlier and had been diagnosed as primary herpes simplex infection (Figure 1). Despite acyclovir treatment, his condition worsened, and he lost 8 kg of body weight during the following 6 weeks, probably because of discomfort when eating.

On admission, the patient exhibited extensive denuded areas of the buccal mucosa, hard and soft palate, posterior pharynx, and tongue with halitosis that interfered with his quality of life. The submandibular lymph nodes were en-
MATERIALS AND METHODS

Histopathological and immunohistological studies were performed on skin biopsy specimens of lesional oral mucosa and uninvolved retroauricular skin as well as on the excised tumor specimen.

IMMUNOFLUORESCENCE

For direct immunofluorescence, cryostat skin sections mounted on gelatin-coated glass slides were consecutively stained by fluorescein isothiocyanate–labeled goat anti–human IgG, IgM, IgA, C3, and fibrin antibodies (INCASTAR Corp, Stillwater, Minn) as previously described. For indirect immunofluorescence, sections of monkey esophagus and rat bladder were exposed to patient serum diluted with phosphate-buffered saline for 30 minutes, washed, and incubated with either fluorescein isothiocyanate–goat anti–human IgG (ATAB Atlantic Antibodies; INCSTAR Corp) or fluorescein isothiocyanate–mouse anti–human IgG1, IgG2, IgG3, and IgG4 (Zymed Laboratories Inc, San Francisco, Calif). After washing, slides were examined with an epifluorescence microscope (Zeiss Axioshot; Carl Zeiss, Jena, Germany).

IMMUNOBLOTTING

Epidermal sheets were homogenized, boiled, and centrifuged as described previously. Proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes. Strips were blocked, incubated with the patient's serum, washed, and incubated with alkaline phosphatase–conjugated anti–human IgG (Promega Corp, Madison, Wis). Controls included serum samples from healthy volunteers and from a patient with verified PNP. The enzymatic reaction was visualized by bromochloroindoly/nitrobluetetrazolium phosphatase (BCIP/NBT Membrane Phosphatase Substrate System; Kirkegaard and Perry Laboratories Inc, Gaithersburg, Md).

IMMUNOPRECIPITATION

Cellular extracts of carbon 14 metabolically labeled normal human keratinocytes were prepared as described. After preabsorption with normal human serum and protein A–bearing staphylococci (Pierce Chemical Company, Rockford, Ill), the particle-free extracts were incubated with the patient's serum or, for control purposes, serum from healthy volunteers or a patient with verified PNP. Antigen–antibody complexes were precipitated with staphylococcal protein G–bead-formed agarose gel (Protein G, Insolubilized on Sepharose 4B Fast Flow; Sigma Chemical Co, St Louis, Mo). After washing, pellets were boiled in sodium dodecyl sulfate–Tris hydrochloride buffer and separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. The precipitated antigens were visualized by autoradiography.

IMMUNOSPECIFIC IgG APHERESIS (IMMUNOADSORPTION)

Blood was drawn from an antecubital vein at a flow rate of 70 to 100 mL/min. Coagulation was prevented with heparin (input rate of 20 U/min; not exceeding 5000 U per treatment) and anticoagulant citrate dextrose, formula A (ACD-A; Baxter, Munich, Germany). The ratio of citrate to whole blood flow was kept at 1:2.

For primary plasma separation, an autopheresis-C therapeutic plasma system (TPS; Baxter, Deerfield, Ill) was used. The functional separation unit of the device is the Plasmacell C, a rotating cylindrical membrane in a plastic casing. It is capable of rapid and highly efficient plasma separation with a blood processing volume of only 7 mL. With this method, a sole peripheral venous approach was possible.

The IgG apheresis was performed in an automated double-needle, continuous flow operation in which the therapeutic plasma system was connected with an adsorption–desorption automate (Baxter) controlling the flow of plasma and regeneration solutions.

Individual IgG immunoabsorption columns (Ig-Therasorb; Baxter) contained 130 mL of bead-formed agarose gel–coupled sheep anti–human IgG with a binding capacity of approximately 4.0 g. Each adsorption cycle consisted of simultaneous loading and unloading procedures. Each treatment session consisted of 18 cycles (mean plasma desorbed, 7200 mL; mean duration, 4.5 hours).

To avoid antibody resynthesis, pooled human IgG (Endobulin Pro-TIM; Immuno Aktiengesellschaft, Vienna, Austria) was infused once weekly at a dose of 0.3 g/kg of body weight. The IgG apheresis sessions were performed twice to 3 times weekly for 4 weeks until circulating antibodies completely disappeared.

larged bilaterally. Ophthalmologic and ear, nose, and throat examination did not show any lesions of the conjunctivas or the larynx, and the genital region was also unaffected. Results of routine laboratory studies were all within normal limits except for a slight leukocytosis (white blood cell count, 13.1 × 10^9/L) with relative lymphopenia, including a substantial depletion of CD4+ lymphocytes (count, 0.16 × 10^9/L). Screening for human immunodeficiency virus was repeatedly negative.

Differential diagnosis included diseases of the pemphigus group, ie, pemphigus vulgaris and PNP, as well as erythema multiforme. Histopathological examination showed typical signs of pemphigus, eg, suprabasal acantholysis. The additional findings of individual keratinocyte necrosis and a vacuolar-interface dermatitis were suggestive of PNP. This diagnosis was confirmed by (1) direct immunofluorescence showing less pronounced staining for IgG than for C3 deposits within the intercellular spaces of the epidermis–mucosal epithelium and along the dermoeidermal junction; (2) the indirect immunofluorescence demonstration of circulating autoantibodies against epithelial cell surfaces of both monkey esophagus and rat urinary bladder up to titers of 320 and 80, respectively; IgG subtyping disclosed predominant IgG1 staining of all epidermis–mucosal cell layers, and IgG2 and IgG3 staining of the basal keratinocytes; (3) immunoblotting experiments on extracts of normal human skin showing antibodies directed against polypeptides of
According to the text, the patient's serum was shown to precipitate four of the five characterized PNP-associated antigens of 250 kd (desmoplakin 1), 230 kd, 210 kd (desmoplakin 2), and 190 kd, but not of 170 kd from epidermal extracts (Figure 2, right). It should be noted that the 200-kd band was not only detected by our patient's serum but occasionally also by otherwise nonreactive serum from normal healthy volunteers (not shown). This 200-kd band therefore cannot be considered specific for paraneoplastic pemphigus.

Before the diagnosis of PNP had been definitively established, the patient had received 2 weeks of a standard pemphigus therapy, ie, 100 mg of methylprednisolone daily orally, without improvement. After PNP was biochemically proved and the neoplasm detected, the corticosteroid dose was slowly tapered during the next 4 weeks to an alternate-day regimen of 40 mg/20 mg, not only because of the planned surgical procedure but also in view of the reportedly poor efficacy of high-dose corticosteroids in patients with PNP.

During the 3 postoperative weeks, the mucosal lesions slightly improved while the corticosteroid dose was gradually reduced to 20 mg/10 mg on alternate days. Another 2 weeks later, his condition had worsened again, with a serum antibody titer of 160.

We then decided to subject the patient’s serum to anti-IgG immunoabsorption. The patient received, in addition to the continued low-dose glucocorticosteroid regimen, 2 or 3 immunoapheresis treatments per week for a total of 4 weeks. During the course of 10 treatment sessions, we observed a gradual decline of both pretreatment and posttreatment autoantibody titers, which finally became and remained negative. Two weeks after initiation of the apheresis treatment, the clinical condition began to improve and continued to do so slowly but steadily during the next few weeks (Figure 4).

Since the original description of pemphigus paraneoplasticus in 1990 by Anhalt et al., approximately 60 additional cases have been reported. Paraneoplastic pemphigus is characterized by mucocutaneous erosions with predominant oral involvement occurring in the context of a neoplasm. Patients with PNP have circulating autoantibodies that bind to 250-kd (desmoplakin 1), 230-kd, 210-kd (desmoplakin 2), 190-kd, and occasionally other antigens.
170-kd keratinocyte antigens. The pathogenicity of these autoantibodies has been proved by injection into newborn mice, which consecutively developed cutaneous blisters; a positive Nikolsky sign; and esophageal acantholysis.1

It is not clear whether (and, if so, how) malignant or even benign tumors induce the formation of autoantibodies.3 One possible mechanism was recently revealed in patients with lung cancer who develop antibodies against tumor antigens released into the circulation by either normal metabolic turnover or tumor necrosis. These antibodies then cross-react with retinal antigens and finally lead to blindness (cancer-associated retinopathy).13,14

In the case of PNP, cellular expression of desmoplakins was demonstrated in non-Hodgkin lymphomas, Castleman tumors, and various sarcomas. Should these molecules serve as immunogens, they may conceivably induce the formation of autoantibodies cross-reacting with desmosomal structures in the skin15 and, thus, trigger the blistering eruption. On removal of the tumor, the presentation of epithelial self-antigens could restimulate the autoantibody response and, thus, perpetuate disease activity.

In our patient, the underlying disease was shown to be an inflammatory myofibroblastic tumor, also referred to as inflammatory fibrosarcoma (World Health Organization classification of soft tissue tumors).16 It usually runs a rather benign clinical course, with multifocal lesions or recurrence in only a small proportion of cases.17 Our patient’s tumor was completely excised and examined independently by several pathologists. The occurrence of blunt, focally pleomorphic spindle cells and a predominantly lymphocytic infiltrate within a collagen-rich matrix unanimously led them to the diagnosis of an inflammatory myofibroblastic tumor without definite signs of malignancy (Figure 3). As accurate staging showed no masses at distant sites, no further antitumoral therapy (chemotherapy or radiation) was performed.

Whereas PNP runs a rapidly progressive and almost invariably fatal course when associated with a malignant tumor, it usually resolves slowly but permanently after excision of a benign neoplasm. In our patient, after a period of temporary relief that followed total excision of the tumor and corticosteroid treatment, titers of autoantibodies as well as disease activity increased again. This poor response to systemic corticosteroid regimens is in keeping with reports from the literature indicating that various immunosuppressive regimens (high-dose glucocorticosteroids, azathioprine, and/or cyclosporine) are of no or little value in patients with PNP.4

Despite conflicting reports on its efficacy in pemphigus,22,23 we originally considered plasmapheresis as a possible treatment strategy but ultimately decided to use a more specific technique to deplete our patient’s serum of the pathogenic IgG1 autoantibodies, ie, immunoadsorption on anti–human IgG bead-formed agarose gel.4 Immunoadsorption is an established treatment modality in various autoantibody-mediated diseases, eg, idiopathic thrombocytopenic purpura, cryoglobulinemia, Goodpasture syndrome, lupus erythematosus, and myasthenia gravis.22

In our patient with a 4-month disease duration, 10 immunoapheresis sessions depleted his serum of PNP-specific autoantibodies and induced clinical improvement in 2 weeks. That the continued low-dose corticosteroid regimen was primarily responsible for the clinical improvement is unlikely, because high-dose administration of methylprednisolone resulted in neither unequivocal clinical nor immunological improvement. Alternatively, one could argue that disease amelioration was merely a consequence of the neoplasm’s surgical removal. Although this cannot be entirely ruled out, complete resolution of PNP lesions is reportedly seen only 6 to 18 months after excision of a benign neoplasm.23 It therefore appears that immunoapheresis greatly accelerated our patient’s healing process, presumably by lowering the titers of pathogenic autoantibodies and, perhaps, by halting autoantibody resynthesis through the postapheresis administration of high-dose immunoglobulin.24,25

We therefore suggest this method as a valuable adjunct regimen for patients with PNP in the context of benign neoplasms. Immunoadsorption methods are expensive but can be effective and quickly beneficial to the seriously impaired patient.

Accepted for publication February 25, 1998.

Serum from a patient with verified PNP was kindly provided by Grant J. Anhalt, MD, Department of Dermatology, Johns Hopkins University, Baltimore, Md.

Reprints: Heidemarie Schoen, MD, DIAID, Department of Dermatology, University of Vienna Medical School, Waehringer Guertel 18-20, A-1090 Vienna, Austria (e-mail: beatrice.volc@akh-wien.ac.at).
REFERENCES