1977 YEAR BOOK OF DERMATOLOGY

MALKINSON / PEARSON

The YEAR BOOK of

Dermatology

1977

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ADVANCES IN THE DIAGNOSIS AND TREATMENT OF BLISTERING DISEASES: A SELECTIVE REVIEW

ROGER W. PEARSON, M.D.

Introduction

In 1969 Braun-Falco[1] presented an outstanding review of the pathology of blister formation. Since that time much new information has accumulated. Whereas blistering diseases constitute only a small fraction of the problems seen in dermatologic practice, they pose some of the most challenging clinical problems the dermatologist must face. Interest in blistering diseases has been heightened in recent years by the occurrence of many significant advances in diagnosis and treatment but beyond that, blistering diseases have a special ability to intrigue, mystify and confound dermatologist and lay person alike. There seems little doubt that the most remarkable progress in the study of blistering diseases has been in the field of immunology. Many new findings in the pathology of these diseases have been aided (and sometimes confused) by the emergence of routine electron microscopy; improvements in the treatment of many of these conditions also represent major accomplishments. This review aims to critically evaluate selected observations where sufficient data have accumulated for discussion purposes.

Pemphigus

General

The changing clinical status of pemphigus has become apparent to all who manage patients with this disease. Once a nearly certain killer, pemphigus is now tamed. However, even with the control of the disease the physician's responsibility is little diminished. Great vigilance is now required to avoid unnecessary morbidity or deaths from complications of treatment or intercurrent disease, and the physician must be fully aware of diagnostic refinements in order to best judge appropriate management.

In a study of 58 patients with pemphigus, Krain[2] found an overall 5-year survival rate of 81.5%. Forty-nine of his patients had pemphigus vulgaris. The age of onset ranged from 12 to 79 years, with 5 cases beginning in the 2d decade. The author noted that 14 patients (29%) had had exposure to various solvents before the development of pemphigus. Three patients had carcinoma preceding pemphigus. Sixty percent had oral onset and all but 3 had oral lesions at some time during the course

of their disease. Of 9 deaths, 4 were due to causes related to the disease or its treatment. All 9 deaths were in patients over age 50. Thirty-seven living patients have had disease from 3 months to 14 years. Six were free of lesions and taking no treatment. Of 5 adolescents, all had attained control of their disease and only 1 required steroid maintenance.

Of 8 patients with pemphigus foliaceus with disease duration of from 3 to 17 years, 2 died of causes unrelated to pemphigus or its treatment. A single patient with pemphigus erythematosus who had no evidence of lupus erythematosus died 6 months after onset of treatment from complications of steroid therapy. Of the 18 patients with pemphigus vulgaris having chemical, viral or fungal exposure, 7 had HL-A 10 and 7 had HL-A W5 antigens. The author could not confirm Ryan's earlier finding that mortality was correlated with severity of the disease and the dosage of steroid used.[3] Overall, 45 of 58 patients had steroid complications. These were most severe in patients over age 50 years. Cyclophosphamide used as adjunctive therapy in 11 cases was felt to have had a significant effect on lowering mortality rates. In these patients the hemorrhagic cystitis of cyclophosphamide therapy was prevented by high water intake.

In a general study of etiologic factors in pemphigus, Beutner and Chorzelski[4] found that whereas adult (over age 20) patients were distributed evenly between the sexes, in the group under age 20, only 2 of 13 patients were males and in the group aged 2½–20 years, pemphigus foliaceus and pemphigus erythematosus were common (6 of 13). Minor physical injury was felt to be a more significant inducing factor in pemphigus foliaceus (4 of 15) than in pemphigus vulgaris (5 of 198). Two of 234 patients had relatives with pemphigus and 1 had a relative with bullous pemphigoid.

A number of clinical associations in pemphigus have been noted. Benveniste et al.[5] noted onset of pemphigus in 5 patients with rheumatoid arthritis who were being treated with D-penicillamine and, interestingly, found no antibodies in 40 asymptomatic patients being treated with the same drug. There is the distinct possibility that in this group of patients rheumatoid arthritis itself was a cofactor in susceptibility to pemphigus. The association of pemphigus and myasthenia gravis has been studied in detail.[6,7] One patient had myasthenia gravis with thymoma.[7] After thymectomy, cobalt treatment was given for 1 month. Five months later, after 3 days of heavy ultraviolet light exposure, generalized pemphigus of the eosinophilic spongiosis type developed rapidly. Retrospectively, pemphigus antibodies were found in the serum before the appearance of clinical pemphigus. Later, antistriated muscle and antithymus antibodies were also found. These findings suggest that direct and indirect immunofluorescence studies of skin should be done routinely in patients with myasthenia gravis in the hope of subclinical pemphigus being discovered. Pemphigus has been reported in patients under treatment with penicillamine[8,9] and other drugs, such as phenylbutazone, irgapyrn[10] and rifampin,[11] also have been suspected of having triggered the disease. Pemphigus has also been reported in association with addisonian pernicious anemia[12]

and Hodgkin's disease.[13] In the latter disease the authors felt that depressed cell-mediated immunity predisposed their patients to pemphigus. Roenigk and Castrovinci described a patient with mycosis fungoides and a generalized bullous eruption showing histologic changes of pemphigus foliaceus, but with negative immunofluorescence findings.[14] The correct classification of this case remains in doubt. It could have been pemphigus foliaceus with undetectable antibodies at the time tested, or perhaps an extensive form of transient acantholytic dermatosis, type 2. The term "mycosis fungoides bullosa" should only be used if the bullous lesions are due directly to the mycosis fungoides lesions or have a pathogenic mechanism unique to mycosis fungoides.

A previously little-recognized clinical phenomenon in pemphigus, so-called eosinophilic spongiosis or acantholytic herpetiform dermatitis, is discussed in the section on dermatitis herpetiformis in this article because of clinical similarities between the two conditions.

Possible induction of pemphigus by burns was discussed by Chorzelski et al.,[15] who presented a patient showing recurrent blistering at a burn site, followed 10 months later by generalized pemphigus foliaceus. Circulating antiepidermal antibodies are well known to develop transiently after some burns.[15,16] These antibodies are not fixed to the skin in vivo, however, but like true pemphigus antibodies, they cannot be absorbed by blood-group antigen.[17] Isoagglutinins may be localized intercellularly in the epidermis but they may be readily detected because they can be absorbed completely by blood-group antigen.

The status of HL-A antigens in pemphigus is not yet clear. In contrast to Krain,[18] Katz et al.[19] found an increased percentage of HL-A13 in pemphigus patients. These authors also showed that HL-A antiserum did not react with pemphigus antigen.

Pathology and Immunopathology

The most provocative studies on the pathogenic mechanism of pemphigus were conducted by Michel and Ko[20] and Schlitz and Michel.[21] These authors showed that IgG pemphigus serum incubated with normal human skin resulted in superbasilar acantholysis. In their in vitro system, complement was not required for acantholysis to occur. This does not prove that complement is not involved in the pathogenic mechanism in vivo. These observations have been confirmed by Barnett el al.[22] Sams and Jordon[23] were unsuccessful in an attempt to induce pemphigus in monkeys by intravenous injection of pemphigus serum although antibody was bound to the intercellular region of the epidermis. Wood et al.,[24] however, were able to show pemphigus-like lesions in monkey mucosa after local injection of pemphigus foliaceus serum. The level of acantholysis was variable.

In an attempt to develop an experimental model for pemphigus, Grob and Inderbitzin[25,26] prepared anti-rabbit esophagus antibodies that localized in the intercellular area. After trauma, pemphigus-like lesions developed. Ablin,[27] using a similar system, showed that local injection of anti-rabbit esophagus serum would induce subepidermal blisters. The significance of these observations is not yet clear. Takiga-

wa and Immamura[28] prepared rabbit anti-guinea pig epidermis antibodies that bind to different sites than pemphigus antibodies.

Hashimoto and Lever,[29] in careful electron microscopic studies, found the earliest events in acantholysis in pemphigus to be loss of intercellular cement. Hashimoto et al.[30] later made the interesting observation that pemphigus antibodies and concanavallin A bind to the same sites on the glycocalyx of human epidermis, but that concanavallin A, in addition, binds to the basement membrane and the pericollagen of the papillary dermis. Fritsch et al.[31] investigated the glycocalyx of guinea pig epidermal cells with the use of enzymes and ultrastructural staining with ruthenium red. They showed that trypsin, phospholypase C and lysozyme were unable to alter the glycocalyx, but that hyaluronidase and neuramidinase partially removed the coating. They also showed that the glycocalyx is rapidly reconstituted by epidermal cells. The significance of these various studies on the glycocalyx is that if pemphigus involves an attack on the glycocalyx initiated by pemphigus antibodies with or without the participation of the complement system, it is possible to hypothesize that if the attack on the glycocalyx is low grade, the glycocalyx would be reconstituted at a rate adequate for the tissue to remain intact. Only when the repair mechanism was overwhelmed by a massive buildup of the attack system or the epidermal integrity was weakened by stress (e.g., ultraviolet light, mechanical trauma) would the overall equilibrium fail and the attack system predominate, resulting in clinical disease.

To date, reasonable hypotheses to explain the differences in pathogenic mechanism between pemphigus vulgaris and pemphigus foliaceus have not been developed. Perhaps it should not be dismissed as mere coincidence that staphylococcal-induced scalded skin syndrome (SSSS) pathologically involves the same layers as pemphigus foliaceus. Possibly the substrate attacked by the respective pathogenic mechanisms is the same; if so, it is tempting to suggest that the products of Odland bodies ("membrane-coating granules," "keratinosomes") might be involved. However, it has already been shown that pemphigus vulgaris antibodies do not bind at the same sites as the staphylococcal acantholytic toxin.[32] This may only indicate that the site of initial attack is different. At some point the pathogenic mechanisms of SSSS and pemphigus foliaceus may coincide.

Since Beutner and Jordon[33] first demonstrated antibodies localizing to the intercellular space in pemphigus, an extensive literature on immunofluorescence studies has accumulated. The data to 1970 have been summarized by Beutner et al.[34] On direct immunofluorescence staining, intercellular antibodies are found in nearly all cases of pemphigus.[35] IgG antibodies are most often present, although IgA (especially in oral lesions) or IgM antibodies, or both, may also be found.[35] On indirect staining, titers of antibodies tend to reflect clinical activity of the disease.[36, 37] Generally, intercellular antibodies are found at all levels of the epidermis, but some patients with pemphigus foliaceus apparently have circulating antibodies preferentially localizing to the upper epidermal layers.[38] Patients with pemphigus foliaceus and pemphigus erythematosus sometimes may have associated base-

ment membrane antibodies and some of these patients have lupus erythematosus.[39, 40] Ultrastructural studies have shown that pemphigus antibodies are localized only to the intercellular region of the epidermis.[41, 42] The localization coincides with the glycocalyx. Early studies of complement fixation in pemphigus were somewhat contradictory,[43, 44] but more recent investigations have clearly demonstrated that by direct immunofluorescence C3 is found in nearly all untreated pemphigus lesions. C1q and C4 are frequently present, indicating activation of the classical pathway. Factor B and properdin may also be found, however, suggesting that the alternate pathway may be activated also.[45] By in vitro techniques, pemphigus serum has not been shown to fix complement.[44] Pemphigus blister fluid, presumably reflecting the naturally operating pathogenic mechanism, usually shows striking anticomplementary activity.[46] Immune complexes may also form in pemphigus serum,[47] but the relationship to the lesions of pemphigus has not yet been shown. As noted previously, in the in vitro pemphigus model, complement is not needed.

Pemphigus-like antibodies may be found in the serum of patients with burns,[16, 17] and isoagglutinins may show similar binding.[17] Patients taking sulfamethoxypyridazine with or without a cutaneous eruption may have pemphigus-like antibodies in their serum.[48] According to Fellner et al.,[49] many patients with maculopapular penicillin eruptions (and especially ampicillin eruptions) have pemphigus-like circulating and fixed antibodies. Pemphigus-like antibodies have also been reported in toxic epidermal necrolysis,[16] dermatitis herpetiformis[50] and benign mucous membrane pemphigoid.[51, 52] They have also been found regularly in the benign mucous membrane pemphigoid-like syndrome induced by practolol[53] and in dermatophyte infections.[54] Antilymphocyte serum may contain pemphigus-like antibodies.[16] In addition to the experimental production of pemphigus-like antibodies already noted, they have been produced by immunization of rabbits with human wart tissue.[55]

Shu and Beutner[56] have studied antigens of rabbit and human esophagus reacting with pemphigus serum. Rabbit pemphigus antigens are soluble in 70% ethanol but not in water; the human antigen is saline extractable. The human antigen is a protein of molecular weight of approximately 68,000.

Treatment

Of relatively recent reports, Ryan's review on the treatment of pemphigus is the most discouraging.[57] Of 40 patients with pemphigus vulgaris, 18 died of the disease or of treatment complications. Ryan felt that the higher steroid doses previously recommended by Lever and White[58] were not justified by improved results over moderate-dosage regimens.

In 1972, Lever reported impressive results using methotrexate and prednisone in pemphigus vulgaris.[59] Of 12 patients treated with prednisone alone, 8 were living, and 5 had been free of lesions from 23 to

117 months despite receiving no treatment. The other 3 were on small maintenance doses of prednisone (5–10 mg/day) and had been on such treatment from 3 to 8 years. One of these 3 was free of lesions, 1 had a small number of oral lesions and 1 had a few cutaneous lesions. Six of the 8 living patients had been treated with initial high-dose prednisone and the other 2, with intermediate-dose treatment. Two of the 4 deaths were from myocardial infarctions and 2 from complications of prednisone therapy (both intra-abdominal abscesses). In both of the latter cases, intermediate-dose treatment (20–80 mg) had been given before high-dose treatment (120–180 mg/day). Of 15 patients treated with initial high prednisone dosage and subsequently with methotrexate, all were living. Three were free of lesions and receiving no treatment. One of these was a patient who had had 11 courses of high-dose treatment and was receiving 45 mg prednisone as a maintenance dose before methotrexate was instituted. Three patients were free of lesions but receiving maintenance methotrexate intramuscularly. One of the 3 was receiving 25 mg prednisone 3 days per week. Nine patients had active lesions. Three were receiving methotrexate alone, and 6 also were receiving prednisone 3 days per week. Nine patients were treated with methotrexate alone from the beginning of treatment. All had initially relatively mild disease. Two were free of lesions; only 1 of these was off treatment (for 1 month). They had received methotrexate for 30 and 29 months, respectively. Of the other 7 with some lesions, 6 had received prednisone intermittently at high or moderate dosage during "breakthrough" periods. None of the 9 patients was ever hospitalized and there were no serious side reactions. On evaluation of his own data, for severe pemphigus vulgaris Lever recommended oral prednisone, 180–300 mg daily for 6–8 weeks to suppress the disease, then 40 mg/day for 1 week. Intramuscular Methotrexate was then added and the prednisone dose was reduced further. Methotrexate was never given with high-dose prednisone. For early, relatively mild pemphigus vulgaris, Lever suggested methotrexate, 25–50 mg/week intramuscularly with or without small doses of prednisone.

Jablonska et al.,[60] in a smaller series, were less enthusiastic about immunosuppressants in pemphigus. They used methotrexate in somewhat smaller dosages than Lever (25 mg/week). They noted that cutaneous lesions responded better than mucosal and also made the incidental observation that topical steroids were sometimes quite effective. Burton and Greaves treated 8 patients by using azathioprine,[61] which was chosen because of its alleged favorable therapeutic index compared with other immunosuppressive drugs. Dosage was 2.5 mg/kg daily. In 3 of 8 patients prolonged control of disease was obtained. In 1, the drug was unable to control the disease, and 4 patients were unable to tolerate the drug.

Krain et al.[62] used cyclophosphamide, 50–100 mg/day, in 5 patients with pemphigus vulgaris who had developed serious side effects from prednisone. The authors were able to reduce high maintenance doses of prednisone without serious additional side effects (transient alopecia and leukopenia were the major problems encountered). Based on his results with a single patient, Medved and Maxwell[63] felt that widely

spaced (10–21 days) doses of cyclophosphamide intravenously had a superior therapeutic index to daily dosage. Rosenberg et al.,[64] in a 20-year study of 107 patients with pemphigus treated with corticosteroids, found mortality to be increased greatly when 180 mg or more of prednisone daily was required for control. Dosage above 120 mg/day was associated with a high incidence of corticosteroid complications. Fifty-four percent of pemphigus vulgaris and pemphigus vegetans patients never required more than 120 mg prednisone daily for control.

Sulfone and sulfapyridine treatment of pemphigus has been somewhat clouded by controversy concerning diagnosis of some of the responding cases. Seah et al. described a patient who had 10 years of control with sulfapyridine of an apparent case of pemphigus foliaceus.[65] Barranco[66] controlled a case of pemphigus foliaceus and 1 case of eosinophilic spongiosis by using dapsone. Piamphongsant[67] successfully treated 2 clear-cut cases of pemphigus foliaceus and 1 of pemphigus vulgaris with dapsone. The most remarkable aspect of these reports on the use of sulfapyridine and sulfones is the rapidity of response. This suggests that sulfapyridine or sulfone acts by a different mechanism from that of prednisone or immunosuppressants in pemphigus.

Penneys et al.[68] revived the use of gold therapy for pemphigus. They treated 18 patients and were able to manage 14 successfully. Three had never had prednisone. In the follow-up study,[69] this investigative group reported that 56% of their patients were in remission without treatment, with an average of 21 months of freedom from the disease. Seven patients were receiving maintenance therapy: weekly doses (50 mg after lower test doses) until control was attained (2–3 months), then at intervals of 2 or more weeks. Most toxicity occurred during the initial control period and consisted of the nephrotic syndrome, dermatitis or agranulocytosis. The authors regarded gold as the therapy of choice for pemphigus, after initial control with corticosteroids when necessary. In vitro studies showed that aurothiomalate inhibited prostaglandin synthesis and also inhibited epidermal acid phosphatase and tryptophanyl-tRNA synthetase activity.[70]

In view of the previously discussed demonstration that pemphigus antibodies cause pemphigus-like alterations in organ cultures of human skin, plasmapheresis might also be useful adjunctive or primary therapy.

Familial Benign Chronic Pemphigus (FBCP)

Izumi et al.[71] demonstrated that lesions of FBCP may be readily induced by a variety of mechanical and chemical stimulants. Forgotten were the excellent studies in 1942 of Frank and Rein,[72] who described characteristic clinical lesions and first showed that lesions could be induced by trauma. Their name for the disease, "dyskeratoid dermatosis," did not prevail because of the priority of Hailey and Hailey[73] and others who described the clinical entity.

An interesting papular variant of FBCP was noted by Witkowski and Parish.[74] They did not state whether all affected family members had the same type of lesion. Esophageal involvement was documented