COMPLEMENT SYSTEMS IN THE SKIN

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The complement system may play an important role in the pathogenesis of certain skin diseases, including the vesiculobullous skin diseases (pemphigus, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, and herpes gestationis) and cutaneous forms of lupus erythematosus and vasculitis. In the present report, complement studies in pemphigus, bullous pemphigoid, and herpes gestationis will be presented. In addition, recent evidence for immune complex formation in some of these diseases will be summarized.

PEMPHIGUS

Previous studies have established that autoantibodies are present in the serum of patients with active pemphigus using indirect immunofluorescent (IF) staining [1-3]. These antibodies react specifically with an intercellular substance (ICS) of skin and mucosa, and they react precisely at the site of the primary histopathologic lesion.

By direct IF staining, ICS deposition of IgG has been present in virtually all skin lesions tested to date [2-4]. Similar C3 deposition has been demonstrable mainly in skin lesions from patients prior to initiation of corticosteroid therapy [5,6]. C1q and C4 deposition, in addition to C3, has also been demonstrated in ICS areas of early pemphigus lesions, suggestive of classical pathway activation [7,8].

Besides deposition of C1q, C4, and C3, we have recently demonstrated similar ICS deposition of Factor B [8]. In contrast to other complement components, properdin has been seen in only a few lesions and then only around a few acantholytic cells. Factor B deposition, therefore, may best be explained by the "C3b feedback" mechanism following classical pathway activation.

We have also reported that total hemolytic complement was decreased in blister fluids of pemphigus vulgaris patients when compared to serum complement levels [9]. Hemolytic C1, C4, C2, C3, and C5, determined in serum and blister fluids from two patients, were not measurable in one blister fluid and were extremely low in the second. Factor B, measured immunochromically, was absent from both of these blister fluids.

Pemphigus blister fluids also have exhibited anticomplementary activity when tested with normal human serum [9,10]. Addition of one blister fluid to normal human serum resulted in inhibition of hemolytic C1, C2, C3, and C5 (classical pathway) and both C3 and Factor B conversion.

Complement activation locally, therefore, may be important in the pathogenesis of pemphigus.

BULLOUS PEMPHIGOID

Complement activation also may be important in the pathogenesis of bullous pemphigoid, a disease characterized by subepidermal bulla formation and autoantibodies to the basement membrane zone (BMZ) as demonstrated by indirect IF staining [3,11,12]. These antibodies also react precisely with their corresponding histopathologic site, which may explain the subepidermal location of the bulla.

Direct IF staining of bullous pemphigoid lesions has consistently demonstrated BMZ deposition of IgG and C3 in virtually all skin specimens examined [4,13]. Provost and Tomasi [14] first reported that factors associated with the alternative pathway are present in bullous pemphigoid lesions. In this respect they reported deposition of both properdin and Factor B, in addition to C1q, C4, and C3 deposition. They have recently extended these observations [15] and we have been able to confirm their findings [16].

By in vitro complement staining methods, we had reported that most serologically positive bullous pemphigoid sera fix C3 to the BMZ [17]. Recently we have extended those studies showing that bullous pemphigoid antibodies will fix C1q and C4 in addition to C3 [18], findings which suggest that these antibodies activate the classical complement pathway.

Blister fluids of most serologically positive bullous pemphigoid patients have reduced levels of total hemolytic complement when compared to serum levels and other serum and blister fluid proteins [10,19]. Serologically negative cases, on the other hand, had blister fluid complement levels approaching serum levels. With the exception of the two terminal components, C8 and C9, individual complement components appear to be decreased in blister fluids with low total complement levels [19]. C3 and Factor B conversion is
also readily apparent in these blister fluids but not in serum. Heat-stable chemotactic activity has also been identified in bullous pemphigoid blister fluids [20].

As in pemphigus, local complement activation may be important in the pathogenesis of bullous pemphigoid.

**IMMUNE COMPLEX STUDIES**

Using sucrose density gradient ultracentrifugation methods and hemolytic complement assays, we found that the pemphigus blister fluid anticomplementary activity had an S value of over 19 [21]. Significant anticomplementary activity was also present in 3 of 5 bullous pemphigoid blister fluids tested by these same methods. This activity was also present in the more rapidly sedimenting gradient fractions. None of the control blister fluids, including cantharidin-induced blisters, suction-induced blisters, and blister fluids from a few patients with other bullous diseases, contained such activity.

Six of 10 pemphigus sera tested have also demonstrated similar anticomplementary activity, although in this case the sedimentation values were between 12 and 19 [21]. Two of 5 bullous pemphigoid sera also contained some anticomplementary activity which corresponded in sedimentation to the blister fluid activity. Activity in the blister fluids was always greater than in the corresponding sera.

As with pemphigus blister fluid alone, addition of positive gradient fractions of both pemphigus and bullous pemphigoid blister fluids to fresh normal human serum resulted in consumption of both hemolytic C1 and C3. When these positive gradient fractions were added to guinea-pig serum genetically deficient in the 4th component of complement, no consumption of hemolytic C3 was noted.

We have also recently developed a radioassay employing 125I-labeled Clq as described by Nydegger et al [22]. After incubating test sera with [125I]Clq, the radioactivity present in a 1.5% polyethylene glycol precipitate is counted and compared to a standard curve prepared with heat-aggregated IgG. Of 110 serum samples from 31 patients with active pemphigus tested thus far, 25 samples from 10 patients showed a significantly elevated binding of [125I]Clq [23]. In contrast, sera from 30 normal donors exhibited consistently low levels of Clq precipitation. Studies of sera and blister fluids from patients with bullous pemphigoid are presently in progress.

**HERPES GESTATIONIS**

An uncommon vesiculobullous dermatosis of pregnancy and the postpartum period, herpes gestationis has recently been added to the list of bullous skin diseases with specific immunopathologic findings. IF studies of two such patients were reported by Provost and Tomasi [14]. One patient's skin lesion showed basement membrane deposition of C3, C5, and properdin without similar deposition of Clq and immunoglobulins. The second patient demonstrated only C3 deposition. BMZ antibodies were not present in the serum of either patient, but a heat-labile humoral factor, capable of precipitating C3 on normal skin base- membrane, was present. The presence of this factor, therefore, may be of some value in the diagnosis of herpes gestationis.

A patient with herpes gestationis who had IF findings similar to those of bullous pemphigoid was recently described by Bushkell, Jordan, and Goltz [24]. This patient had circulating IgG antibodies to the BMZ and deposition of IgG and Clq in skin lesions in addition to properdin and C3. Findings in this patient suggest that herpes gestationis may be more closely related to bullous pemphigoid than originally suspected.

**REFERENCES**