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Dermatological Autoimmune Diseases and the Multiple Autoimmune Syndromes

By

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Table II. *Conditions found in various combinations in multiple autoimmune syndromes*

Type I	Pemphigus Autoimmune thyroid disease
Type II	Chronic active hepatitis Lupus erythematosus Pemphigus Bullous pemphigoid Autoimmune haemolytic anaemia Idiopathic thrombocytopenic purpura Alopecia areata Addison's disease
Type III	Acquired primary hypogonadism Hypophysitis Rheumatoid arthritis Primary biliary cirrhosis Relapsing polychondritis Multiple sclerosis Chronic active hepatitis Ulcerative colitis Scleroderma

purpura in 2 cases (13, 21). The association of V with alopecia areata is remarkable and was reported 3 times (15, 20, 24); two were associated with ulcerative colitis (15, 24). V was described in combination with myasthenia gravis in 3 MAS (11, 12, 15).

Thus, V appears to occur in type III of the classification of the MAS. All the conditions forming combinations of two or more autoimmune conditions related to V belong to this type.

Alopecia areata

Alopecia areata (AA) is a common dermatological disease whose origin is suspected to be autoimmune (25). The association of AA and autoimmune diseases has been demonstrated on various occasions (Table IV). In addition, an increased frequency of circulating organ-specific auto-antibodies and anti-nuclear antibodies has been demonstrated by some authors (26, 27, 28). Nevertheless, AA belongs to the MAS in 4 cases only (15, 20, 24, 29). When combined with other autoimmune diseases to form a MAS, AA occurs in men only. In two cases the association vitiligo-AA-ulcerative colitis was described (15, 24), in which ulcerative colitis was the first condition to appear. These observations suggest that a careful follow-up is needed in a male patient with ulcerative colitis, whose second development is AA. This could provide the early detection of a new condition liable to appear.

More interesting is the association AA-vitiligo-lichen planus, reported three times (15, 20, 24), twice occurring with ulcerative colitis and once with localized scleroderma (20). In these three cases, the MAS occurred in men aged from 38 to 47 years.

Considering all the conditions reported associated with AA to form a MAS, it appears that the combinations of AA and vitiligo, AA and myasthenia gravis, or AA and ulcerative colitis belong to type III of the classification, while the unique association of AA with bullous pemphigoid and rheumatoid arthritis (29) seems to constitute a type II MAS. Nevertheless, the number of such reports is insufficient to distinguish a preferential grouping of autoimmune disorders with AA.

Pemphigus

Skin diseases of the pemphigus (P) group are considered to have an autoimmune basis (30). The association of P with one of the various autoimmune diseases has already been described by some investigators (Table V). Among them, the remarkable combination involving P and myasthenia gravis and/or thymoma has been recently reviewed by Cruz et al. who studied 35 cases (31). The authors showed a male preponderance (sex ratio 2:1); the patients' ages ranged from 28 to 75 years. In the majority of cases, P occurred after thymectomy or thymic irradiation. Among the various hypotheses for such a double combination, the role of common auto-antibodies directed against thymus myoepithelial and malpighian cells has been suggested (32, 33, 34), as well as a deficiency of the specific suppressor T-lymphocyte function (35). In 3 out of the 4 observations (31, 36, 37, 38),

Table III. *Clinical associations of vitiligo*

Pernicious anaemia (8)
Hypoparathyroidism (3)
Lupus erythematosus (49)
Autoimmune thyroid disease (23)
Diabetes mellitus (23)
Myasthenia gravis (15)
Rheumatoid arthritis (11)
Autoimmune haemolytic anaemia (18)
Scleroderma (50)
Alopecia areata (24)
Idiopathic thrombocytopenic purpura (21)
Ulcerative colitis (15)
Addison's disease (6)
Mixed connective tissue disease (21)
Relapsing polychondritis (19)

Table IV. *Clinical associations of alopecia areata*

Vitiligo (24)
Ulcerative colitis (24)
Autoimmune thyroid disease (51)
Addison's disease (52)
Pernicious anaemia (53)
Diabetes mellitus (52)
Rheumatoid arthritis (29)
Localized scleroderma (20)

concerning the association of both P and myasthenia gravis with another autoimmune disease, the third disorder was constituted by features of lupus erythematosus (31, 36, 37). The concurrent existence of features of P and lupus erythematosus would have suggested a diagnosis of the Senear-Usher syndrome (39). However, Chorzelski et al. demonstrated that P erythematosus could be considered due to the coexistence of both P and lupus erythematosus (40).

Another example of the preferential grouping of P with two other conditions is shown by the double combination rheumatoid arthritis—Sjögren's syndrome (41, 42). The two publications dealing with these examples do not contain features that could suggest a possible pathophysiological mechanism.

At the present time it is not possible to attribute P to only one of the types of the classification. Nevertheless, in spite of the rare observations of MAS constituted with P, P seems to belong preferentially to types II and III and exceptionally to type I.

Bullous pemphigoid

Bullous pemphigoid (BP) is an autoimmune blistering dermatologic disease occasionally reported associated with other autoimmune disorders (43, 44) (Table VI). To our knowledge, only 2 MAS formed with BP have been published (29, 45). Both these reports describe a

Table V. *Clinical associations of pemphigus*

Autoimmune thyroid disease (54)
Bullous pemphigoid (55)
Multiple sclerosis (56)
Lupus erythematosus (57)
Sjögren's syndrome (58)
Pernicious anaemia (59)
Myasthenia gravis and/or thymoma (60)
Rheumatoid arthritis (42)
Polymyositis (38)
Giant cell myocarditis (38)
Dermatitis herpetiformis (61)

Table VI. *Clinical associations of bullous pemphigoid*

Pemphigus (62)
Rheumatoid arthritis (63)
Lupus erythematosus (64)
Polymyositis (65)
Pernicious anaemia (66)
Ulcerative colitis (67)
Multiple sclerosis (68, 69)
Dermatitis herpetiformis (70)
Diabetes mellitus (71)
Alopecia areata (29)
Myasthenia gravis (72)
Primary biliary cirrhosis (17)
Autoimmune thyroid disease (29)
Vitiligo (17)

preferential combination of BP with rheumatoid arthritis and autoimmune thyroid disease. Rheumatoid arthritis was the first condition to appear in one case (29) and autoimmune thyroid disease was the first in the other case (45). BP was the last disease to occur in both cases.

BP is one of the conditions liable to occur in association with type II diseases. However, the lack of sufficient reported cases does not enable us to assign with certainty BP to type II.

Dermatitis herpetiformis

Among the cutaneous autoimmune diseases, dermatitis herpetiformis (DH) is undoubtedly the one whose place is best defined in type III. Most of the conditions occasionally reported in association with DH belong to this type (Table VII). Moreover, the only MAS reported in the literature concerned the triple combination: DH—pernicious anaemia—thyrotoxicosis in a 48-year-old woman (46). Thyroid abnormalities as well as the frequent presence of antigastric parietal cell auto-antibodies in the course of DH have been well documented in the literature (47, 48). A MAS with two conditions belonging to type III, with

Table VII. *Clinical associations of dermatitis herpetiformis*

Autoimmune thyroid disease (73)
Pernicious anaemia (74)
Relapsing polychondritis (75)
Addison's disease (76)
Vitiligo (77)
Primary biliary cirrhosis (78)
Diabetes mellitus (79, 80)

DH, probably represents the grouping of autoimmune disorders associated with the increased incidence of the HLA B8/DR3 haplotype seen in DH.

COMMENT

The association of autoimmune pathologies with cutaneous diseases has received little attention, except for their association by twos. Isolated case reports have been relied upon in the past for data regarding a new described association. However, it would appear that the authors who have reported a new association were usually unaware of similar previously published cases. The absence of an indexed key word for the associations of autoimmune diseases in the same patient could explain such omissions.

Moreover, it is certain that many associations have not been published due to the fact that it was thought at the time that these isolated cases were only of punctual interest. Our analysis of 91 reported cases (4) demonstrated that the publication of well-documented MAS could contribute to a better understanding of the predisposing factors and the pathophysiological mechanisms of autoimmunity in humans. It also confirms the key role of dermatological symptoms in identifying a MAS and thus helping to prevent the occurrence of a new condition in patients previously affected by two others.

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