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Spectrum of Autoimmune Bullous Diseases in Northern Greece. A 4-year Retrospective Study and Review of the Literature

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ABSTRACT Bullous Diseases Unit at the 2nd Department of Dermatology and Venereology, Aristotle University of Thessaloniki was founded with the aim to provide the optimal diagnostic approach and treatment of patients with autoimmune bullous diseases (AIBD). We processed all AIBD files of patients diagnosed from 2011 to 2014 in order to record all epidemiological data and therapeutic manipulations during monitoring. 57 patients were diagnosed with intraepidermal and 62 with subepidermal bullous diseases. There were 51 cases (89%) of pemphigus vulgaris (PV) and 6 (11%) of pemphigus foliaceus (PF), whereas 45 (73%) patients were diagnosed with bullous pemphigoid (BP), 9 (14%) with mucous membrane pemphigoid (MMP), 3 (5%) with pemphigoid gestationis (PG), 3 (5%) with linear IgA dermatosis (LAD), 1 (2%) with epidermolysis bullosa aquisita (EBA), and 1 patient with an undefined subepidermal AIBD. The mean age of patients within the pemphigus spectrum was 57 years. In the pemphigoid spectrum, the mean age was 72 years. Comorbidities were reported with increasing frequency, as well as treatment options other than systemic corticosteroids, such as adjuvant immunosuppressive agents, which were used to achieve complete remission.
This is a report from a tertiary AIBD Referral Center in northern Greece. Our data from a 4-year period contribute to the completion of the global geographic incidence map of AIBD.

KEY WORDS: autoimmune bullous diseases, pemphigus, bullous pemphigoid

INTRODUCTION

Bullous dermatoses include a series of potentially life-threatening autoimmune clinical entities characterized by bullae and erosions of the mucous membranes and skin (1). They are classified into two groups based on the level of formation of bullae: the intraepidermal and subepidermal bullous diseases.

Intraepidermal bullous diseases are caused by the production of autoantibodies against components of the desmosomes. Destruction of the intercellular bridges causes detachment and separation of keratinocytes in the spinous layer of the epidermis, leading to the formation of intraepidermal blisters, which easily rupture and result in painful erosions (2). Subepidermal bullous diseases are caused by the production of autoantibodies against components of the dermoepidermal junction, ultimately resulting in the formation of subepidermal blisters (3).

Acta Dermatovenerol Croat
2017;25(3):195-201

The diagnostic approach that confirms the clinical suspicion and determines each clinical subtype includes: a) histopathological analysis of a fresh (<24 h) vesicle or 1/3 of the peripheral portion of a blister and 2/3 perilesional skin; b) direct immunofluorescence microscopy (DIF) of perilesional skin (up to 1 cm from a fresh lesion, even though the skin is seemingly healthy); c) indirect immunofluorescence microscopy (IIF); d) serological detection of specific serum autoantibodies (Dsg1, Dsg3, BP180, BP230) by commercially available enzyme-linked immunosorbent assay (ELISA) kits; and e) immunoblotting that specifies the identity and molecular weight of target antigens (4-6). Confirmation of diagnosis is an important determinant of any therapeutic decision.

Systemic corticosteroids are considered the first-line therapy in the majority of cases in order to achieve clinical disease control and are maintained through the consolidation phase in decreasing doses, to maintain remission. In case of refractory disease or contraindications to corticosteroids, immunosuppressive adjuvants are administered (azathioprine, mycophenolate mofetil, cyclophosphamide, mycophenolic acid, dapsone, methotrexate, sulfonamides, tetracycline, anti-CD20 or anti-IgE monoclonal antibody, intravenous immunoglobulins, immunoadsorption, and plasma exchange) (7,8).

The Bullous Diseases Unit at the 2nd Department of Dermatology and Venereology of the Aristotle University of Thessaloniki operates at Papageorgiou General Hospital as a center for diagnosis, treatment, and monitoring of patients with autoimmune bullous diseases from northern Greece. It conducts a comprehensive diagnostic approach to patients in collaboration with the Laboratories of Immunology and Molecular Biology, which lays the foundation for further individualized therapeutic management of this spectrum of diseases. In the context of long-term monitoring of patients, all therapeutic manipulations aim to achieve complete disease remission and good general health. The purpose of this study was to record epidemiological data, medical history, laboratory profiles, and therapeutic manipulations during monitoring.

PATIENTS AND METHODS

For this retrospective study, we studied the files of 119 patients (N=119), who presented at our Bullous Diseases Unit in Papageorgiou General Hospital between January 2011 and December 2014. Diagnosis was confirmed by laboratory tests, and all patients met 2 necessary input criteria:

o Histopathology

o Immunoassay (direct immunofluorescence microscopy) documenting the diagnosis "intraepidermal or subepidermal bullous disease".

A complete immunoassay approach (indirect immunofluorescence microscopy, ELISA) was performed in all patients but remained an optional input criterion, whereas immunoblotting was a selective method with ancillary contribution to the diagnosis. All patient sera were screened for the presence of specific IgG autoantibodies (Dsg1, Dsg3, BP180, BP230) using commercially available ELISA kits according to the manufacturer's instructions (Euroimmun AG, Lübeck, Germany).

We studied patient files retrospectively and recorded the following data: sex, ethnicity, date of birth, place of residence, date and patient age at the time of diagnosis of any bullous disease, clinical subtype of the disease, histopathology reports, titer of disease-specific serum autoantibodies, therapeutic agents (drug, dosage, route of administration, date of treatment initiation, treatment duration, date of treatment discontinuation, side-effects), patient compliance, eruption of new lesions throughout monitoring and relapses (number, date of recurrence, months from diagnosis, dosage at recurrence, corticosteroid dose to achieve disease control).

RESULTS

Over the study period, of the total 119 patients, 57 (48%) were diagnosed with intraepidermal and 62 (52%) with subepidermal bullous disease. All types of AIBD were observed: there were 51 cases (89%) of pemphigus vulgaris (PV) and 6 (11%) of pemphigus foliaceus (PF), whereas 45 (73%) patients were diagnosed with bullous pemphigoid (BP), 9 (14%) with mucous membrane pemphigoid (MMP), 3 (5%) with pemphigoid gestationis (PG), 3 (5%) with linear IgA dermatosis (LAD), 1 (2%) with epidermolysis bullosa acquisita (EBA), and 1 patient with an undefined subepidermal AIBD. No case of IgA-pemphigus (IGAP) or paraneoplastic pemphigus (PNP) was found. Table 1 shows frequencies of the spectrum of intraepidermal and subepidermal bullous diseases, sex ratio, mean age, and age range. There were 32 men and 25 women in the pemphigus group with a male to female ratio of 1.27:1; ages ranged from 29 to 84 years, and mean age was 57 years. The pemphigoid group consisted of 28 men and 34 women, the male to female ratio was 1:1.2, while the mean age was 72 years and the range 4 to 90 years.

The study also recorded a number of comorbidities from patient personal medical histories. Table 2 depicts the comorbidities most commonly observed

Acta Dermatovenerol Croat
2017;25(3):195-201

in our patients. In patients from the pemphigus group, there was an increased incidence of diseases associated with metabolic syndrome (hypertension, coronary disease – acute myocardial infarction – angioplasty, dyslipidemia, diabetes mellitus) and osteoporosis. According to the literature, comorbidities in patients with intraepidermal bullous dermatoses are mainly attributed to the simultaneous presence of a second autoimmune disorder. In particular, associations with myasthenia gravis, thymoma, systemic lupus erythematosus, psoriasis etc. have been recorded, a fact that makes a close and regular monitoring of these patients essential (9). In our study, we also observed many comorbidities in the pemphigoid group, mainly attributed to the elevated mean age of patients. Nearly half of patients (48%) suffered from three or more chronic diseases at the time of diagnosis. Incidence of diabetes mellitus in our study was 38.7%, while in similar studies the incidence did not exceed 20% of BP patients. A possible correlation with antidiabetic medications cannot be excluded, as it is considered to be a putative trigger (9). Additionally, although strong associations have been observed between specific neurological diseases and the later development of BP, in our study only 5 out of 45 patients diagnosed with BP suffered from dementia or Parkinson's disease (10).

Regarding treatment with systemic steroids, the initial dose was 1-1.5 mg/kg/day prednisone equivalent for intraepidermal bullous diseases and 0.5-1 mg/kg/day prednisone equivalent for subepidermal bullous diseases. Adjuvant therapy with immunosuppressive agents was used as a therapeutic option beyond systemic corticosteroids in our group of patients in order to achieve complete disease remission. In some cases (epidermolysis bullosa aquisita, linear IgA dermatosis), dapsone was used as first-line treatment.

Adjuvant treatment with immunosuppressive and immunomodulatory agents was used during the corticosteroid tapering period (corticosteroid sparing regimens), in order to limit side-effects and complications associated with long-term corticosteroid use (>4 months) and in some recalcitrant cases. Table 3 shows all adjuvant therapeutic options and the duration of administration.

Relapse was defined as the appearance of 3 or more new lesions/month or a large lesion (>10 cm) that did not heal spontaneously within a week, or the extension of the existing lesions in a patient who has achieved control of the disease (11). Of all treated patients with intraepidermal bullous diseases, 40.0% of them presented with one relapse, 17.6% had a second relapse, and 7.0% a third and fourth relapse. A relapse of the disease was observed in 21.0% of patients with subepidermal bullous diseases, while 3.2% of them presented with a second relapse, and only 1 patient (1.6%) had a third relapse. Diagram 1 depicts the percentage of patients who experienced relapse of the disease. Among patients from the pemphigus group who had the first relapse (13 in 62 patients – 21.0%), nearly half of them, 6 patients, relapsed while being treated with 5 mg prednisone equivalent. Among the pemphigoid group, 11 patients relapsed while being

Table 1. Characteristics of 119 Greek patients with different AIBD

Clinical subtype of Autoimmune Bullous Disease	No. of cases	%	M:F ratio	Mean age, years	Age range, years
Intraepidermal Bullous Disease					
Pemphigus Vulgaris (PV)	51	89,4	1,21:1	56,7	30-84
Pemphigus Foliaceus (PF)	6	10,5	2:1	59,6	29-80
	57	100,0	1,27:1	57,0	29-84
Subepidermal Bullous Disease					
Bullous Pemphigoid (BP)	45	72,6	1:1	76,1	55-90
Mucous Membrane Pemphigoid (MMP)	9	14,5	1:1,3	66,7	48-83
Linear IgA Dermatosis (LAD)	3	4,8	1:2	51,0	4-77
Pemphigoid Gestationis (GP)	3	4,8	F	36,3	32-40
Epidermolysis Bullosa Acquisita (EBA)	1	1,6	F	70,0	70
Unidentified subepidermal disease	1	1,6	F	60,0	60
	62	100,0	1:1,2	72,0	4-90

Acta Dermatovenerol Croat
2017;25(3):195-201

Table 2. Patients' comorbidities

Comorbidities	No. of cases	Percentage %
Intraepidermal		
• Hypertension	12	21,0
• Diabetes mellitus	5	8,7
• Coronary disease – Acute Myocardial Infarction – Angioplasty	5	8,7
• Osteoporosis	5	8,7
• Dyslipidemia	4	7,0
Subepidermal		
• Hypertension	24	38,7
• Diabetes mellitus	24	38,7
• Coronary disease – Acute Myocardial Infarction – Angioplasty	10	16,0
• Atrial Fibrillation	6	9,6
• Benign Prostatic Hyperplasia	6	9,6
• Dementia – Parkinson's disease	5	8,0
• Stroke	5	8,0
• Chronic Renal Failure	5	8,0

treated with 5 mg prednisone equivalent, of a total 23 in 57 patients – 40% – who experienced a first relapse.

DISCUSSION

Epidemiological studies from different countries have outlined the main features of AIBD per country (12-26).

Subepidermal bullous diseases are the most common AIBD in Western Europe (France, Germany, and Switzerland). In China, Malaysia, Iran, Kuwait, and in Mediterranean countries, studies report a predominance of intraepidermal over subepidermal AIBD, particularly in Iran with a ratio of 8:1.

The geographical distribution of pemphigus is unequal. It can be released or exacerbated by a plurality of potential risk factors (genetic, environmental, nutritional, UV radiation, trauma, pharmaceuticals). Some ethnicities, such as Jewish and Japanese, show an increased incidence of pemphigus. Countries with increased incidence are Greece (0.93/100 000/year), Tunisia (0.67/100 000/year), Bulgaria (0.47/100 000/year), Italy (0.25/100 000/year), and Turkey (0.24/100 000/year). However, the limitations of these epidemiological studies are: 1) data in most studies were recorded at least 15 to 20 years ago, 2) certain records relate to specific regions rather than the whole population of the country, and 3) the samples are small.

Geographical distribution of BP varies as well. Recent studies have shown increased incidence in the United Kingdom (43/million/year), France (21.7/million/year), Germany (13.4/million/year), and Switzerland (12.1/million/year) compared with older studies from Western Europe (6-7/million/year).

The most common pemphigus subtype in most countries is pemphigus vulgaris (PV), mainly in Europe and the USA. It is particularly dominant in Iran (92% PV, 7% PF), Kuwait (80% PV, 18% PF), Turkey (83% PV, 8% PF), and Bulgaria (77% PV, 17% PF). PF is more frequent in South Africa, Tunisia with endemic PF (36%), Brazil (rural), and other Latin American countries where the endemic form fogo selvagem dominates. PF is the most common form in Finland, while PV and PF are found with equal prevalence in Morocco.

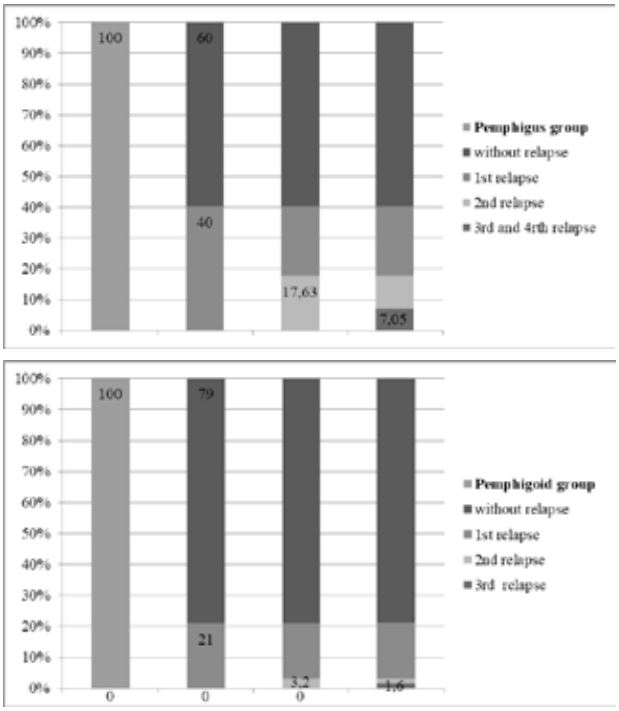
Mean age of onset of PV in Kuwait is 36 years and is similar in India, slightly higher in Iran (42 years), Turkey, Saudi Arabia, Singapore, Tunisia, and South Africa, and even higher (>50 years) in most European countries, Korea, and Japan. Pemphigoid diseases manifest over the age of 75 years in many developed

Table 3. Adjuvant therapeutic agents and duration of treatment

Adjuvant therapy	No. of patients	Duration, months
Intraepidermal Bullous Diseases		
Azathioprine (AZA)	34	1-28
Cyclophosphamide (CTX)	11	1-29
Cyclosporine (CYA)	2	1-7
Mycophenolate mofetil (MMF)	2	1-7
Colchicine (COL)	2	2-13
Rituximab (RTX)	2	375mg/m^2/ week for 4 weeks
Subepidermal Bullous Diseases		
Azathioprine (AZA)	7	1-18
Dapsone (DDS)	6	1-18
Colchicine (COL)	3	6-12
Doxycycline (DOX)	1	1
Sulfasalazine (SSZ)	1	5

Acta Dermatovenerol Croat
2017;25(3):195-201

Diagram 1. Percentage of patients who experienced disease relapse.



countries (France 83.00 years, Portugal 79.60 years, Germany 77.3 years, United Kingdom 77.00 years), while the patients are younger in developing countries (Tunisia 67.20 years, Kuwait 65.00 years, Iran 59.40 years).

Increased incidence of AIBD in women compared with men has been reported in most countries. In contrast, AIBD are more common in men in Germany and China.

Our study is the first epidemiological imprinting of the spectrum of autoimmune bullous diseases in northern Greece. Previous published data for northern Greece included only cases with PV (27).

Direct immunofluorescence remains the gold standard in the diagnostic approach for AIBDs. Serration pattern analysis, however, is a recently described technique of direct immunofluorescence microscopy which may be useful in the differential diagnosis of subepidermal AIBD. Serration pattern analysis was not performed in our Laboratory during the time period of this study, which may have consequently led to an underestimation of patients with EBA (28). Today, with the addition of detection of specific circulating autoantibodies using ELISA techniques, diagnostic criteria are supplemented and serological monitoring of pemphigus disease activity is possible. In one recent study of our group, it has been demonstrated that the titer of autoantibodies against Dsg1 correlates strongly with the clinical status of skin lesions, whereas the titer of autoantibodies against Dsg3 may still remain high after the recession of mucosal lesions (29). ELISA techniques that are now available also became part of the diagnostic evaluation of pemphigoid diseases. Circulating antibodies target two hemidesmosomal proteins. BP230 is an intracellular glycoprotein, but circulating antibodies against this antigen do not correlate with disease activity. On the other hand, autoantibody levels against the NC16A domain of the BP180 antigen could be very helpful in monitoring disease activity and choosing the best therapeutic approach (30).

Therapeutic strategy in most countries follows the basic principles of the AIBD guidelines, and the only deviations are always related to cases that according to the clinician's discretion require a personalized therapeutic approach (7,8). Recent studies in patients with moderate disease showed that clobetasol propionate 0.05% ointment was as effective and safe as oral prednisone at 0.5 mg/kg/day (31). This particular dose of oral prednisone is under evaluation, as it seems to be safer but not less effective compared to higher doses. Recent studies have shown that the monoclonal anti-CD20 antibody rituximab (375 mg/m^2/week for 4 weeks) and anti-IgE antibody omalizumab (300 mg/4-8weeks) could be effective in pemphigus and bullous pemphigoid respectively, but further evidence is needed (32,33). It is also noteworthy that administration of rituximab, an anti-CD20 monoclonal antibody which constitutes a high cost therapy, is a common and simple practice in most central European countries, unlike the rest of southern Europe including Greece and Middle East countries, where the drug approval includes very time-consuming paperwork.

The main consideration regarding AIBDs management remains their chronic and recurrent nature. Relapses of intraepidermal AIBD seem to be more common and more difficult to manage than those of subepidermal AIBD. Finding new therapeutic targets that will relieve our patients from the short- and long-term side-effects of systemic corticosteroids is an ongoing challenge.

CONCLUSION

This is a report from a tertiary AIBD Referral Center in northern Greece. Our data from a 4-year period contribute to the completion of a global geographic incidence map of AIBD.

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