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A Monocentric Retrospective Observational Study of Comorbidities in Patients Affected by Autoimmune Bullous Diseases

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Abstract. *Background/Aim: Autoimmune bullous diseases (AIBDs) of the skin and mucosae include a heterogeneous group of chronic diseases, which could be associated with various comorbidities. The purpose of this study was to evaluate the comorbidity profiles of patients affected by AIBDs, who referred to the Dermatological Clinic of Padua from December 2015 to June 2018. Patients and Methods: A monocentric retrospective observational study was conducted on 157 patients with diagnosis of AIBDs. Patients' comorbidities were investigated during the periodic visits of follow-up and through the analysis of computerized medical records. Results: Among the 157 patients, 40 (25.5%) were diagnosed with PV, 15 (9.6%) with PF, and 102 (64.9%) with BP. Nine different comorbidities were observed, but only two of these were statistically significantly associated with BP: type 2 diabetes (p=0.0142) and neuropsychiatric disorders (p=0.015). Conclusion: BP is statistically significantly associated with type 2 diabetes mellitus and neuropsychiatric diseases. The correlation with neuropsychiatric pathologies is interesting for the possible bidirectional role in their etiology. The association with type 2 diabetes mellitus could suggest more caution in the administration of systemic corticosteroids, especially in elderly patients.*

The high prevalence of autoimmune bullous diseases (AIBDs) among elderly and multimorbid patients, prompted several authors to study the link of AIBDs with other diseases.

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Diabetes mellitus, hypertension, infections, neoplasms, cardiovascular diseases, neuropsychiatric disorders and other autoimmune diseases are the comorbidities most frequently linked to AIBDs, although the most significant associations have been observed in patients with bullous pemphigoid (BP) (1).

The presence of comorbidities in patients with AIBDs is relevant not only for the outcome, but also for the overall evaluation of the therapy and patient management. Indeed, comorbidities such as diabetes mellitus, hypertension, chronic infections and malignancies must be considered when systemic therapies are evaluated. For example, patients whose comorbidities preclude systemic corticosteroids (*i.e.* elderly patients with uncontrolled diabetes or hypertension), should be treated with topical drugs or steroid sparing agents, like antibiotics or systemic immunosuppressants (2).

Another issue concerning the comorbidities, is their correlation or not with the therapies previously administered to treat the AIBDs: in different studies, type 2 diabetes, hyperlipidemia, hypertension, infections, osteoporosis and adrenal insufficiency, were related to the specific therapy chosen to treat these patients (3). In particular, a strong correlation has been observed between systemic corticosteroids and type 2 diabetes, hypertension, osteoporosis and insomnia (4).

Patients and Methods

Trial design. A monocentric retrospective observational study was conducted on 157 patients affected by AIBDs who referred to the Dermatological Clinic of Padua from December 2015 to June 2018. Investigation on the comorbidities was realized through the analysis of computerized medical records or by directly interviewing patients during their periodic follow-up at the Dermatological Clinic.

The following data were recorded: age at diagnosis, sex, therapy and concomitant medications, comorbidities (neurological and psychiatric disorders, hypertension, diabetes mellitus, thyroid dysfunction, psoriasis, history of neoplasms and venous thromboembolism, other skin and mucosal diseases).

The diagnosis of additional diseases was based on a reliable medical history or medical documentation that included the appropriate test results. Patients allowed the collection of further information

regarding the evolution of their AIBD, such as the number of remissions and exacerbations, the QOL (quality of life) and the adverse effects due to the dermatological therapy.

Statistical analysis. For the statistical analysis, comorbidities were grouped as follows:
- Type 2 diabetes mellitus;
- Hypertension;
- Heart disease (for example, coronary heart disease, cardiac arrhythmia and congestive heart failure);
- Neuropsychiatric diseases [dementia, stroke, Parkinson's disease, Alzheimer's disease, psychosis, anxiety, depression, epilepsy and amyotrophic lateral sclerosis (ALS)];
- Malignancies;
- Autoimmune diseases (Hashimoto's thyroiditis, Basedow-Graves' disease, rheumatoid arthritis, psoriasis, type 1 diabetes mellitus, Crohn's disease);
- Obstructive respiratory diseases [asthma, chronic obstructive pulmonary disease (COPD)];
- Osteoporosis;
- Kidney disease (*e.g.*, chronic kidney disease, lupus nephritis and nephrotic syndrome);

The association between comorbidities and AIBDs was evaluated with the Fisher exact test.

The results of the analysis are expressed as the absolute number and the relative percentage of subjects of each AIBD affected by a specific comorbidity, and the value of statistical significance "*p*" (*p*-value, probability value). The results were considered statistically significant when $p<0.05$.

The data were analyzed with the SAS 9.4 program (SAS Institute Inc., Cary, NC, USA) for Windows.

Results

In this study, 157 patients were included: 102 (64.9%) with BP, 40 (25.5%) with pemphigus vulgaris (PV) and 15 (9.6%) with pemphigus foliaceus (PF).

In the subgroup of BP there were 46 (45.1%) males and 56 (54.9%) females. The mean age was 77.2 years (range=26-98 years) and the majority (88.2%) was older than 60 years old.

In the subgroup of PV, the number of males and females was equivalent (20:20). The mean age was 62 years (range=34-85 years).

In the subgroup of PF, there were 9 females (60%) and 6 males (40%). The mean age was 68.1 years (range=46-88 years).

Thus, PV and PF patients were younger than BP patients (mean age of 62 years and 68.1 years *versus* 77.2 years, respectively).

Nine different comorbidities were observed: type 2 diabetes mellitus, hypertension, cardiovascular diseases, neuropsychiatric disorders, malignancies, autoimmune diseases, obstructive respiratory diseases, osteoporosis and kidney diseases (Table I).

Because of the low number of patients with PV and PF, statistical analysis was performed only for patients with BP. Two comorbidities were significantly associated with BP: type 2 diabetes mellitus (14.7%; $p=0.0142$) and neuropsychiatric disorders (19.6%; $p=0.015$) (Table II).

With regard to the association between AIBDs and neuropsychiatric disorders, 37.5% of patients (9/24) were affected by mood disorders or psychosis, and used antidepressant drugs (*i.e.* trazodone, paroxetine, duloxetine and venlafaxine), antipsychotics (*i.e.* valproate, quetiapine, haloperidol) and benzodiazepines.

The mean age of patients with BP and neurological diseases was higher than the mean age of patients with BP without neurological diseases (83.4 years *versus* 75.9 years, respectively). The most frequent neurological comorbidities in BP patients were mood disorders (8 patients, 7.84%), followed by epilepsy (3 patients, 2.94%), Parkinson's disease (2 patients, 1.96%), Alzheimer's disease (2 patients, 1.96%) and stroke (2 patients, 1.96%).

With regard to the association between type 2 diabetes mellitus and BP, the possible role of DPP-4 inhibitors in the onset of the BP was studied in detail. Among the 102 patients with BP, 15 (14.71%) had a previous diagnosis of type 2 diabetes mellitus, of whom 5 (4.9%) were treated with DPP-4 inhibitors, in particular linagliptin (3 patients) and vildagliptin (2 patients).

Discussion

Among the 157 selected patients of our study diagnosed of AIBDs, 64.9% (102/157) were affected by BP, 25.5% (40/157) by PV and 9.6% (15/157) by PF. Results were obtained only for patients with BP, given the limitations deriving from a small sample size of patients with PV and PF. About the nine comorbidities detected, we observed several patients with different autoimmune disorders, hypertension, cardiovascular diseases and neoplasms, but only type 2 diabetes mellitus and neuropsychiatric diseases were reported as significantly associated with BP.

Bullous pemphigoid is the most common form of AIBDs and affects a range of the population generally older than the other AIBDs. In these patients, old age and immunosuppressive therapy are important triggering factors in the onset of new pathologies or in the worsening of pre-existing pathologies. In particular, cardiovascular diseases result the most frequent comorbidities (70%), followed by CNS disorders (37%), type 2 diabetes (15%) and malignant tumors (14%) (5). In their study, Kremer *et al*. have shown that arterial hypertension was the most frequent comorbidity in patients with BP (64% of patients, $p=0.04$) (6). Conversely, the use of some antihypertensive drugs (*e.g.* loop diuretics) was described as a possible triggering factor in the pathogenesis of BP (7). Several theories have been proposed regarding the link between drugs and the development of BP: drugs could act as haptens or could cause a dysregulation of the immune system modifying the function of suppressor T-cells (8). Furthermore, BP, like

Table I. *Comorbidities observed in the 157 patients affected by autoimmune bullous diseases (AIBDs), grouped in (PV) pemphigus vulgaris, pemphigus foliaceus (PF) and bullous pemphigoied (BP).*

Comorbidities in AIBDs	PV (n°, %)	PF (n°, %)	BP (n°, %)	Total (n°, %)
Type 2 diabetes mellitus	0	2 (13.3%)	15(14.7%)	17 (10.8%)
Hypertension	11 (27.5%)	2 (13.3%)	29 (28.4%)	42 (26.7%)
Cardiovascular diseases	10 (25%)	6 (40%)	17 (16.6%)	33 (21%)
Neuropsychiatric disorders	1 (2.5%)	3 (20%)	20 (19.6%)	24 (15.2%)
Malignancies	4 (10%)	1 (6.67%)	8 (8.8%)	13 (8.2%)
Autoimmune diseases	7 (17.5%)	1 (6.67%)	16 (15.6%)	24 (15.2%)
Obstructive respiratory diseases	2 (5%)	0	2 (1.9%)	4 (2.5%)
Osteoporosis	2 (5%)	0	6 (5.8%)	8 (5%)
Kidney diseases	0	0	7 (6.8%)	7 (4.4%)

other autoimmune diseases, is linked with an increased risk of venous thromboembolism (9-15). Chronic inflammation, through the production of pro-inflammatory cytokines, is the key element in perpetuating endothelial dysfunction, stimulating the coagulation cascade and promoting a thrombophilic state (16-19). In the light of these observations, a prophylactic anticoagulation therapy, especially in patients with other pro-thrombotic risk factors, may be indicated (9).

Our study also indicated that there is a statistically significant correlation between BP and type 2 diabetes mellitus (p=0.0142): among the 102 patients with BP, 15 (14.71%) had a previous or subsequent diagnosis of type 2 diabetes mellitus. The cases in which BP preceded the diagnosis of type 2 diabetes mellitus may be related to the treatment with systemic corticosteroids, to which the majority of these patients are subjected. Several studies have shown that patients with BP treated with systemic corticosteroids had more complications than those treated with topical corticosteroids (20). Furthermore, it has been observed that the incidence of serious side effects (*e.g.* septicemia, diabetes mellitus, psychiatric disorders) increases according to corticosteroids dosage (21).

Nevertheless, type 2 diabetes mellitus could also precede the diagnosis of BP. In these cases, the link between these pathologies is not easy to understand, except for those patients previously treated with dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), a quite recent class of hypoglycemic oral drugs frequently used in older diabetic patients and known to cause adverse skin reactions (22, 23). The mechanisms underlying the association of DPP-4 inhibitors with BP are still not clear. DPP-4 is an immune system's important enzyme, whose activity is altered in some autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel diseases. Thus, in our study, the cases in which type 2 diabetes mellitus precedes the diagnosis of BP are difficult to interpret except for those patients (5/15) previously treated with DPP4-inhibitors. Furthermore, our results are consistent with the most recent studies, according to which BP occurs more frequently in patients treated with vildagliptin, linagliptin and teneligliptin compared to other gliptins (24-28). Some studies suggest that BP associated with the use of DPP4-inhibitors could be clinically and immunologically distinct from the conventional BP, due to the absence of the characteristic eosinophilic inflammatory infiltrate in the subepidermal blisters (25) and because of the frequent negativity of anti-BP180-NC16A antibodies (26).

Table II. *p-Values of each comorbidities observed in the sub-group of patients with BP (bullous pemphigoid). Bold values show significance.*

Comorbidities in BP	*p*-Value
Type 2 diabetes mellitus	**0.0142**
Hypertension	0.5453
Cardiovascular diseases	0.1040
Neuropsychiatric disorders	**0.0015**
Malignancies	0.9000
Autoimmune diseases	0.6979
Obstructive respiratory diseases	1.0000
Osteoporosis	0.5436
Kidney diseases	0.2484

Literature data about the association of BP with malignancies are controversial (29): the open question is whether there is an association between these pathologies and whether they share a common pathophysiologic mechanism. Among the different theories, one of the most accredited suggests that antibodies against tumor-specific antigens cross-react with antigens of epithelial basement membrane zone (BMZ) (30). Another hypothesis suggests that cancer cells could secrete hormone-like substances able to damage epithelial BMZ, resulting in the production of anti-basement membrane antibodies. Further theories consider the role of an external agent, such as a virus, which could be carcinogenic and, at the same time, able to damage the epithelial BMZ (31). Considering that BP predominantly

affects the elderly, and that some recent reports suggest an increased risk for some solid tumors and lymphoproliferative disorders in BP, a higher frequency of malignant tumors was expected (31-33). However, other authors did not find a link between PB and malignancies (34). In our patients with BP, no association was found with malignant neoplasms (8/102, *p*-value=0.9000). Therefore, we agree with those authors who recommend screening tests only when BP is characterized by severe systemic manifestations and/or atypical presentations (*e.g.* onset in young people).

Conversely, a statistically significant association was observed between BP and neuropsychiatric disorders (p-value=0.0015). The prevalence of neuropsychiatric pathologies in our BP patients was 19.6% (20/102). The most frequent neuropsychiatric disorders observed in our study were mood disorders (*i.e.* anxiety, depression) and psychosis (40% of cases) followed by epilepsy (15%), Parkinson's disease (10%), Alzheimer's disease (10%), strokes (10%) and dementia, ALS and migraine with aura (15%). Overall, our data are in agreement with the recent studies (35-38). The mean ages of patients with BP and neurological diseases and with BP without neurological comorbidities were 83.4 years and 75.9 years, respectively. The range of age between 80 and 89 years showed the highest association with neuropsychiatric diseases. In the literature, several studies have evaluated the association between mean age of patients with BP and neurological pathologies, showing that patients with neurological comorbidities were generally older than those without (34, 39, 40). This result may be explained by the concept of immuno-senescence that is an age-related immune dysfunction with a consequent process of auto-immunization against antigens common between the CNS and epidermis (39). However, the chronological order of development of these two pathologies is unclear. The alteration of the blood-brain barrier in the course of neurological pathologies is a triggering factor for the development of an autoimmune response against antigens shared with BP (41, 42). However, the chronic inflammatory processes of BP acts like a promoter of neuronal degeneration (43, 44). Consequently, the relation between BP and neuropsychiatric disorders could be described as bidirectional.

The main limitation of this study is the small sample size of PV and PF which are rare pathologies characterized by a very low prevalence in the population. Nevertheless, we identified statistically significant associations of BP with type 2 diabetes mellitus and with neuropsychiatric diseases. The correlation with neuropsychiatric pathologies is interesting for the possible bidirectional role in their etiology. The association with type 2 diabetes mellitus could suggest more caution in the administration of systemic corticosteroids, especially in elderly patients.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

MA: conception and design of the work. GG, MA and MF: data collection. MF, GTC and MA: drafting the article. All Authors read and approved the final manuscript.

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