

Gender approach in pemphigus patients: a comparative study in the Dermatology Department of Rabat (Morocco)

Farah El Hadadi (MD)¹, Line Mezni (MD)¹, Mariame Meziane (Prof)¹, Nadia Ismaili (Prof)¹, Laila Benzekri (Prof)¹, Karima Senouci (Prof)¹

(1) Department of Dermatology, Mohammed V University in Rabat, Ibn Sina University Hospital-Rabat, Morocco

INTRODUCTION

Pemphigus is the most frequent chronic autoimmune bullous condition in the eastern European Jewish and Mediterranean descent. The disease involves the skin and mucous membranes of the stratified squamous epithelium. It is the first leading cause of hospitalization in our department with 15 newly diagnosed cases per year. Few studies have been published to see whether there is a significant gender influence on disease presentation, severity activity score and evolution.

MATERIALS & METHODS

We performed a comparative analysis of 129 male and 173 Moroccan female pemphigus patients seen at the Dermatology Department of Ibn Sina University of Rabat between 1990-2020. Files were retrospectively analyzed, and the following epidemiological and clinical data were retrieved from the medical records: age at diagnosis, mean duration of disease, history of autoimmune conditions, clinical subtypes, cutaneous and oral involvement and the evolution. The Softwares Excel and Statistical Package for the Social Sciences (SPSS Inc, version 15.0 for Windows) were used for data entry and analysis. Normally distributed numerical data was summarized by its mean values and standard deviation.

RESULTS

There was no significant difference in terms of age of disease's onset (52,24±14 in women VS 54,05±15 in men), the mean duration of the disease before diagnosis in both cases was (13 months). The association with autoimmune diseases was more frequent in women (9 patients with thyroid dysfunction, 5 cases with diabetes type 1, 5 rheumatoid polyarthritis, 2 systemic lupus, 1 autoimmune hepatitis, 1 Gougerot-Sjogren, 1 vitiligo, 1 autoimmune sclerosing cholangitis) VS 2 males with diabetes type 1 and 1 vitiligo. As for the clinical subtypes we noticed that pemphigus herpetiformis was more frequent in women (8 cases VS 1 men), but also pemphigus vegetans (17 female VS 10 male) and pemphigus vulgaris (75 women VS 50 men), the mucosal involvement with no cutaneous lesions was more frequent in women (12 cases) VS 3 male, the PDAI was more severe in women (135 cases) VS men (96 cases).

The association with autoimmune diseases was more frequent in women (9 patients with thyroid dysfunction, 5 cases with diabetes type 1, 5 rheumatoid polyarthritis, 2 systemic lupus, 1 autoimmune hepatitis, 1 Gougerot-Sjogren, 1 vitiligo, 1 autoimmune sclerosing cholangitis) VS 2 males with diabetes type 1 and 1 vitiligo. As for the clinical subtypes we noticed that pemphigus herpetiformis was more frequent in women (8 cases VS 1 men), but also pemphigus vegetans (17 female VS 10 male) and pemphigus vulgaris (75 women VS 50 men), the mucosal involvement with no cutaneous lesions was more frequent in women (12 cases) VS 3 male, the PDAI was more severe in women (135 cases) VS men (96 cases). In both cases, the main protocol used was oral steroids in 55%, a combination of steroids and other sparing agents in 45%, the most immunosuppressive therapy used was the azathioprine in 91.6% the use of rituximab as a first line therapy in 8%. In terms of evolution: a complete remission was noticed in: 48% female VS 38% men, there was no difference in term of time of recovery (80 days in women VS 73 days in men). Relapses and mortality weren't statically different in women (30% for relapses and 16 case's death) VS men (28% relapses and 17 case's death). Females tend to relapse 49 months after a complete remission while males after 52 months.

DISCUSSION

The mechanism of acantholysis (loss of keratinocyte cell adhesion) in pemphigus is increasingly decoded and is mainly due to an autoimmune mechanism (production of antibodies against desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1), desmocollins (Dsc) and plakins) [1]. However, several studies suggested that environmental factors may play a crucial role in the pathogenesis such as: exposure to pesticides, excessive intake of allium group (Garlic, onion...), Herpes simplex virus infection and a prevalence bias toward females [2]. In fact, it was found that females have a higher absolute number of CD4+ T lymphocytes than men and produce more Th1 cytokines; for example, after vaccination [3]. The gender specific auto immunity can be explained by hormonal, immunological, microbiome, and genetic theories (specific genes encoded on the X chromosome). Sex hormones (estrogens, progesterone) are reported to affect antigen presentation, lymphocyte activation, cytokine gene expression, and/or homing of immune cells with a severe activity disease during pregnancy and relapses in the postpartum period while testosterone has a protective effect on the immune system [4] [5].



(a) *Pemphigus vegetans* in a 45-year-old Moroccan female patient, phototype IV: please note the erosions and vegetations in the genital area



(b) *Pemphigus vulgaris* in a 52 year-old-patient, phototype IV with muco-cutaneous involvement.



(c) *Pemphigus vulgaris* in a 64-year-old patient: blisters and erosions of the trunk.

CONCLUSION

We conclude that gender can influence the clinical phenotype of pemphigus patients: Pemphigus herpetiformis, vegetans and mucosal involvement are more frequent in women. The association of multiple autoimmune disease are also more frequent in females. Our data shows that there is no difference in terms of evolution or prognosis. The main limitations of our study are the

“one center study”, the retrospective design, the absence of dosage of the Desmoglein antibodies and the genetic analysis (HLA type). Further multicenter studies are therefore necessary to explain the role of genetic and hormonal factors in the immune dysregulation among pemphigus patients

REFERENCES

1. Witte M, Zillikens D, Schmidt E. Diagnosis of Autoimmune Blistering Diseases. *Front Med.* 2018; 2;5:296.
2. Brenner S, Tur E, Shapiro J, Ruocco V et al. Pemphigus vulgaris: environmental factors. Occupational, behavioral, medical, and qualitative food frequency questionnaire. *Int J Dermatol.* 2001;40(9):562-9.
3. Amadori A, Zamarchi R, De Silvestro G et al. Genetic control of the CD4/CD8 T-cell ratio in humans. *Nat Med.* 1995; 1(12):1279-83.
4. Ahmed SA, Penhale WJ. The influence of testosterone on the development of autoimmune thyroiditis in thymectomized and irradiated rats. *Clin Exp Immunol.* 1982;48(2):367-374.
5. Whitacre CC. Sex differences in autoimmune disease. *Nat Immunol.* 2001 Sep;2(9):777-80.