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CLINICAL AND EPIDEMIOLOGICAL FEATURES OF TRUE ACANTHOLYTIC PEMPHIGUS IN AZERBAIJAN

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The purpose of the study was to assess the epidemiological condition and clinical course of true acantholytic pemphigus in Azerbaijan. 554 patients with true acantholytic pemphigus were involved in observation. We analyzed the dynamics in morbidity (coverage of a period from 1999 to 2011). It was found that there was a steady increase in the morbidity since 1999, and since 2006 the rate of disease growth has formed 6-year cycle. The course of the disease has changed, it has become more severe and resistant to the therapy. The number of patients with true acantholytic pemphigus increased in persons under 40 years of age (where there was a twofold predominance of women). The prevalence of common forms over limited, a reduction in the period of mucosal lesions, rejuvenation of the disease's formation, resistance of the disease to the therapy (a twofold increase in the dose of glucocorticoids) make it possible to make judgments about the change in the course of the disease.

Key words: true acantholytic pemphigus, epidemiology, resistance to therapy, morbidity.

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КЛІНІКО-ЕПІДЕМІОЛОГІЧНІ ОСОБЛИВОСТІ СПРАВЖНЬОЇ АКАНТОЛІТИЧНОЇ ПУХИРЧАТКИ В АЗЕРБАЙДЖАНІ

Метою дослідження була оцінка епідеміологічного стану та клінічного перебігу справжньої акантолітичної пухирчатки в Азербайджані. Під наглядом перебувало 554 хворих на справжню акантолітичну пухирчатку. Проведено аналіз динаміки захворюваності (охоплення періоду з 1999 по 2011 рр.). Встановлено, що з 1999 р. спостерігається стійке зростання захворюваності, а з 2006 р. темпи зростання захворюваності сформували 6-річний цикл. Змінився перебіг захворювання, він став більш важким і резистентним до терапії. Збільшилася кількість хворих на справжню акантолітичну пухирчатку серед осіб молодше 40 років (серед яких спостерігалося дворазове переважання жінок). Переважання поширених форм над обмеженими, скорочення періоду ураження слизових оболонок, омолодження формування захворювання, резистентність захворювання до терапії, що проводиться (збільшення дози глюкокортикоїдів в два рази) дозволяють судити про зміну перебігу захворювання.

Ключові слова: справжня акантолітична пухирчатка, епідеміологія, резистентність до терапії, захворюваність.

Currently, true acantholytic pemphigus (TAP) is considered a severe autoimmune disease, which, in the absence of timely adequate therapy, can develop into autoaggression with a possible fatal outcome [4, 5, 13].

Pemphigus is an epidemiologically heterogeneous group of autoimmune bullous diseases. The incidence of pemphigus varies greatly between different populations, and in recent years the first non–HLA genes associated with pemphigus have been identified. In addition, various comorbidities have been described in this variant, including other autoimmune diseases, hematological malignancies and psoriasis. Evidence of the impact of COVID-19 on this patient population has also emerged, making this issue a focus for specialists across disciplines [1, 7, 9].

TAP is a disease characterized by a chronic wave-like course, the development of blisters on unchanged skin and mucous membranes, which tend to generalize and merge. According to the literature, there are 0.1–0.5 cases of TAP per 100,000 people, with a higher frequency among Indians and people of Jewish nationality, and in Europe these data fluctuated between 0.05–0.39 per 100,000 people [5].

Although the pathogenetic chains are not clear completely, steric hindrance and signaling have been proposed as the major overarching pathological mechanisms that drive loss of intercellular contacts of keratinocytes. Both mechanisms are believed to be involved, but not strictly independent of each other, and the exact chronology of events as well as contribution of each remains unknown [2, 3].

Clinical manifestations of skin lesions in patients with TAP have been well studied, described and classified, which is reflected in articles and monographs by many authors. Pemphigus in mucosal tissues may be found in the conjunctiva, nasal mucosa, larynx, pharynx, esophagus, genitals. When present in the cervix, pemphigus may cause a diagnostic problem by confounding Pap smear results, which may reveal false dysplastic changes. Within several months after mucosal lesions the skin lesions appear, usually on the face, trunk, groin, scalp, and axillae. In common cases, blisters do not cover the palms and soles. Blisters may heal without scarring, but may result in pigment changes. One of the common symptoms is alopecia [4, 11, 14].

Pemphigus is a blistering disorder that initially presents on the oral mucosa in 80 % of cases. The blisters in mouth often rupture, leaving painful erosions. Skin lesions in common cases appear in patients with pemphigus with several months after the onset of the first oral blisters. Vesicles, erosions, or bullae may appear on erythematous or normal-appearing skin, that is manifested by Nikolsky's sign [15].

However, regularly received information from various regions of the Republic of Azerbaijan on the increase in morbidity in the last decade, information on the complexity of differentiation of diseases, resistance to therapy of some forms (paraneoplastic, herpetiform) of true pemphigus dictates the need to develop new provisions in the current clinical and epidemiological situation.

The purpose of the study was to assess the epidemiological patterns and clinical features of true acantholytic pemphigus in Azerbaijan.

Materials and methods. For this purpose, an analysis of 554 patients with TAP who were under our observation over a 13-year period (from 1999 to 2011) was conducted at the Department of Dermatovenerology of the Azerbaijan Medical University.

The epidemiological situation was evaluated according to data collected during the period mentioned above.

Clinical manifestation, onset and duration of mucosal lesions, response on therapy were assessed. In addition, the gender and age features of patients enrolled were taken into account.

The diagnosis of TAP was confirmed based on clinical, histopathologic, and laboratory studies. The biopsy of skin lesions and histopathologic measurements were performed. Detection of specific serum IgG using enzyme-linked immunosorbent assay (ELISA) testing was performed. Histology examination helped to confirm acantholysis.

In addition, routine tests, such as complete blood count, a metabolic panel, antinuclear antibody (ANA), and a urinalysis were carried out.

Statistical processing of the obtained data was carried out using the analysis of the results using Microsoft Excel-2010 (Statistica 7.0) spreadsheet programs, generated in accordance with the objectives of the studies. Nonparametric methods of calculations and comparisons were used. The mean (M) and standard error of the mean (m) were calculated. The reliability of intergroup differences was established by calculating the Mann–Whitney U–criterion, as it does not require checking the sample for normality. Differences were considered reliable at $p<0.05$.

Results of the study and their discussion. Analyzing the epidemiological situation, we found that there was a steady increase in the incidence rate. Thus, from 1999 to 2011, 554 patients were registered (an average of 42.6±6.3 cases per year). However, starting in 2006, the number of cases of the disease increased by 2.5 times compared to the previous 6–year period (369 versus 185), and amounted to an average of 61.5±8.32 cases per year versus 26.4±1.84 for the period 1999–2005 ($p<0.001$). The peak of the incidence was in 2011 and amounted to 90 patients per year (Fig. 1).

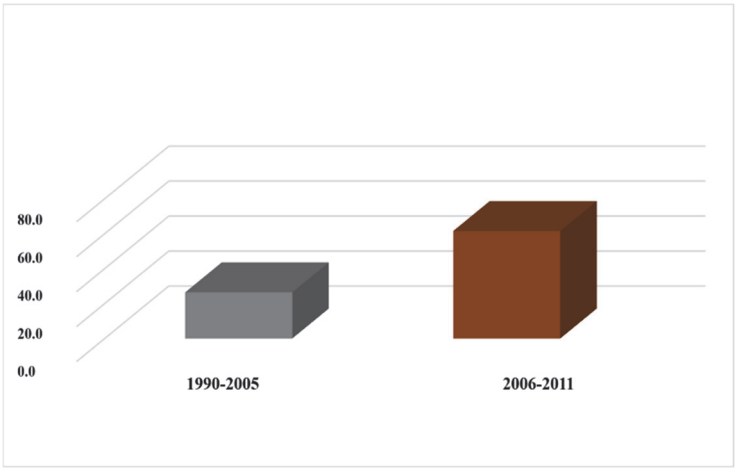

Fig. 1. Average number of pemphigus cases in the Republic of Azerbaijan for the periods 1999–2005; 2006–2011.

According to our data, the incidence of TAP in Azerbaijan currently amounts to 0.8–1.0 patients per 100,000 population.

An assessment of the gender distribution of patients showed that in the group of patients aged 40 to 60 years (n=485, average age 48.6±5.3 years) there was a slight predominance of women, by 2 % (247 women and 238 men). This ratio changed sharply in the group of patients under 40 years (n=69, average age 26.5±4.1 years) and amounted to 46 women (66.7 %) and 23 men (33.3 %), where a twofold excess of women was found ($p<0.001$).

When analyzing the ratio of different forms of TAP, it was found that of the 4 main clinical forms, 96.4 % of cases (534 patients) were the vulgar form of pemphigus and only 3.6 % of cases (20 patients) were the other clinical forms. The onset of the process with mucosal damage in the vulgar form of pemphigus was noted in 98.9 % (528 patients). In the majority of our patients with the vulgar form of

pemphigus, after damage to the mucous membrane (within 1–3 months), skin rashes quickly increased and were widespread in 90 % (500 patients), limited rashes were present in only 10 % (55 patients).

An analysis of the therapy conducted over this entire period showed that if before 2000 the dose of glucocorticoids required to stop the autoimmune process was 60–80 mg per day (on average 66.4±3.2 mg), then after 2000 it averaged 80–150 mg per day (on average 114.5±6.1 mg). The required dose increased twofold ($p<0.001$).

Thus, the data we have obtained on the growth of TAP cases in Azerbaijan indicate an unfavorable trend that changes its cyclicity over time. At the present time, the frequency of TAP occurrence in Azerbaijan, according to our data, is 2–10 times higher than the average statistical values [1, 9].

The change in the intensity of the epidemiological process may be associated with changes in both natural (meteorological) and social, territorial-population and demographic conditions, which do not correspond to the reactions of internal adaptive restructuring (genetic, endocrine-immunological systems), which may be the cause of disorders that can lead to an increase in cases of the disease [2, 12].

However, an analysis of studies by other authors suggests that such an increase in incidence cannot be considered a local phenomenon.

An increase in incidence rates is also indicated in the work of Kridin K, et al., who analyzed epidemiological data in various countries around the world [9]. In all likelihood, these data indicate a global trend towards an increase in the incidence of true pemphigus. In the Danish National Patient Registry, the prevalence of pemphigus was calculated to be 60 per million in 2006. However, in subsequent years the incidence rate increased. Thus, based on data from the largest German health insurance, the prevalence of pemphigus was estimated to be 148 per million individuals in 2014, later, the rate was reported as 95 per million [13].

There is no clear data in the available literature regarding the “rejuvenation” of the disease that was observed in our study. In the work of Jelti L, carried out in France, et al the mean age of patients was 71±11 years [6]. Ohzono A., et al, indicated that the average age in their study was 57±10 years [11]. But, compared with our contingent, these researches covered only paraneoplastic pemphigus cases were assessed.

According to literature, pemphigus can occur in any age but most prevalent among patients aged between 45 and 65 years at the time of diagnosis. Some authors reported that outside the endemic areas, where up to 30 % of patients were younger than 20 years, they noted about low prevalence of pemphigus in persons aged below 18 years: in a recent study from Germany, only 0.6 % of patients with pemphigus were minors. The mean age of presentation in PV ranges between 36.5 years in Kuwait, which is close to our results, but and 72.4 years in Bulgaria (completely opposite of the main age groups in our work) [9].

Therefore, we can talk about the tendency of growth and development of the disease in Azerbaijan even at a younger age than indicated in the data for other countries. At the same time, similar studies by other authors note that TAP is most severe in patients aged 35–40 [4, 11]. In this regard, it is logical that the rejuvenation of the disease increases the risk of a greater number of severe forms.

With regard to gender differences, our results for the female/male ratio are consistent with the indications of most authors regarding the predominance of women among patients with TAP. So, in Tunisia, pemphigus is more common in women than men by a ratio of 4 to 1 [12, 13]. Female/male ratio in France is 2:1 [6]. In some research the prevalence of pemphigus was reported as roughly the same in men and women, that differs from our data. However, the age-related differences that we identified (1:1 at the age of 40–60 years and 2:1 at a younger age-up to 40 years) have not been studied in a comparative aspect by other authors.

The management of pemphigus is challenging and often necessitates the administration of high-dose systemic corticosteroids and immunosuppressive agents [8, 10]. But recently there are many problems related to treatment.

Firstly, according to our data (more aggressive course, tendency to widespread skin lesions, etc.), the increasing torpidity to glucocorticosteroid therapy revealed in our observations, which was manifested in the need to almost double the dose in patients compared to previous observation periods, also seems logical.

Secondly, treatment of this disease poses even a harder challenge in light of the COVID-19 pandemic, given the concern about the vulnerability of pharmacologically immunosuppressed patients. Recent expert recommendations have proposed guidance for the management of patients with pemphigus during the COVID-19 pandemic [7]. Therefore, work on new solutions related to these problems should become a topic of further research.

Conclusions

Thus, based on the analysis of our own clinical observations, the following conclusion was made:

1. Starting in 2006, the number of cases of the disease increased by 2.5 times compared to the previous 6–year period (369 versus 185), and amounted to an average of 61.5±8.32 cases per year versus 26.4±1.84 for the period 1999–2005 ($p<0.001$).

2. The predominance of common forms over limited ones, an increase in the incidence in the age group up to 40 years (rejuvenation of the development of the disease), resistance of the disease to the therapy (a twofold increase in the dose of glucocorticoids) permit to express an opinion on the change in the course of the disease in the modern period.

Thus, the increase in morbidity, changes in the severity of the disease, the complexity of differentiation of diseases, resistance to therapy of true pemphigus dictate the need to develop new approaches to this pathology.

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