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Clinical experience of a specialized urticaria outpatient clinic from a Portuguese UCARE

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Key words

Antihistamines; chronic urticaria; omalizumab; treatment; UCARE.

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Impact statement

Patients with chronic spontaneous urticaria, particularly severe cases, should be referred to urticaria specialists who have more diagnostic and treatment options at their disposal, offering a high degree of specialisation in terms of research and clinical patient care.

Summary

Background. *Chronic urticaria (CU) is a frequent disease, with a prevalence of at least 1%. It is characterized by pruritic wheals, angioedema or both for a period longer than 6 weeks.* ***Objective.*** *Identify the demographic, clinical, laboratory and therapeutic profile of patients treated in a Portuguese Urticaria Center of Reference and Excellence (UCARE) and compare it with international series.* ***Methods.*** *Retrospective analysis of database of patients observed in a specialized urticaria outpatient clinic, from January 2017 through September 2019, of a UCARE center in Portugal. Demographic and clinical features, laboratory findings and pharmacological treatment were obtained from the records. Descriptive analyses were performed for all variables. Chi square and fisher's exact tests were applied to analyze the independence of variables and the fit of distribution. P-value < 0.05 was considered significant.* ***Results.*** *During this period, 477 patients were observed, of whom 429 (90%) were diagnosed with chronic urticaria. Mean age (years) at the onset of symptoms was 43.7 (standard deviation (SD) 17.6, range 6-88) and at diagnosis 46.7 (SD 17.8, range 6-88) resulting in an average diagnostic delay of 3 years (range 0-25). Median follow-up period since first attendance in the specialized outpatient clinic was 1.7 years (interquartile range (IQR) 0.79, range 0.1-2.75). Concerning the whole group of CU patients, 347 (81%) had chronic spontaneous urticaria (CSU) – 79% female, 39 (9%) had isolated chronic inducible urticaria (CIndU) and 43 (10%) had CSU with CIndU. Autologous serum skin test (ASST) was done in 76 patients (positive in 24 (32%)) and basophil activation test (BAT) was done in 38 (positive in 13 (34%)). At the moment of study, 204 (48%) of CU patients were medicated with a second-generation H1-antihistamine (sgAH) daily (first-line therapy), 99 (23%) with sgAH up to four times the standard dose (second-line therapy) and 126 (29%) with omalizumab (third-line therapy). Additionally, 7 (2%) patients were completing a short course of systemic corticosteroids for management of disease exacerbation. Disease control was achieved in 316 of CSU patients (81%).* ***Conclusions****. Referral to a specialized urticaria outpatient clinic is important for a proper assessment of the disease and adequately symptom control.*

Introduction

Chronic urticaria is a frequent disease, estimated to affect at least 1% of the general population, and characterized by the appearance of pruritic wheals, angioedema or both that persist for more than 6 weeks (1, 2). A distinction is made between chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) (2, 3). In CSU symptoms are spontaneous and not associated with a specific trigger, as opposed to CIndU, in which urticarial symptoms only occur after exposure to definite external triggers, but not spontaneously (3). The triggers that lead to the urticarial signs and symptoms in CIndU patients are mainly physical or chemical stimuli. The former included pressure (in delayed pressure urticaria), radiation (in solar urticaria), friction (in symptomatic dermographism), temperature (in cold and heat urticaria), and vibration (in vibratory angioedema). Chemical triggers of CIndU reactions are water (in aquagenic urticaria), raised body temperature (in cholinergic urticaria), and other urticariogenic chemical compounds (in contact urticaria) (4, 5).

The second-generation H1-antihistamines (sgAH) are the first-line symptomatic treatment of patients with chronic urticaria. Up to 50% of the patients will not respond to licensed doses of sgAH. However, even at higher doses, there is a subgroup of patients refractory to the sgAH treatment and further treatment is frequently necessary (6). Omalizumab is an anti-IgE monoclonal antibody, approved for the treatment of CSU, that has radically changed the management of the patients without good response to sgAH, allowing to reach complete responses in a high percentage of patients (2). Omalizumab has also been shown to be effective and safe in the treatment of CIndU patients (3). It is, however, not approved for this indication, at least not in patients with sole CIndU.

Despite recent advances such as the global harmonization of chronic urticaria classification and nomenclature, novel diagnostic tools and instruments, and better treatment options, chronic urticaria can be a challenging condition for patients and their treating physicians. Urticaria Centers of Reference and Excellence (UCARE) have a strong network of urticaria specialists and, by promoting urticaria research, harmonize and improve urticaria management globally, helping to improve the management of this condition (7). Data regarding the demographic, clinical, laboratory and therapeutic characteristics of patients observed in UCAREs is valuable. It allows comparisons between published series in order to understand the similarities and differences between different centers and countries. Nevertheless, it has not been yet described in Portugal. We aimed to fill this knowledge gap by describing these features in a significant number of patients followed in a UCARE in Lisbon (Portugal) and compare it with international series.

Methods

The study was retrospective, based on the analysis of database of patients followed in the specialized urticaria outpatient clinic of a UCARE, Hospital Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, in Portugal, from January 2017 to September 2019. This specialized Unit receives patients referred by other colleagues either working in hospitals or primary care units.

The diagnosis and etiology of chronic urticaria were defined by a detailed clinical history and classified using the national (8) and international European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) guidelines (2).

Other diagnosis, apart from chronic urticaria, as chronic pruritus, atopic dermatitis, prurigo strophulus, contact dermatitis, acute urticaria and hereditary angioedema were not included in the analysis.

Demographic and clinical characteristics were recorded: age and gender clinical data, urticaria subtypes (CSU, CIndU, CSU+CIndU), atopic comorbidities, time between the onset of symptoms and the diagnosis and follow-up period since first attendance in the specialized outpatient clinic.

Since we are a specialized urticaria outpatient clinic, the patients referenced usually have a more severe and/or long-lasting urticaria. Therefore, in patients with CSU, in addition to basic tests including differential blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), thyroid laboratory tests (TSH, free T4 (FT4) and thyroid autoantibodies (TAA)), namely thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (anti-TG), were requested, as well as antinuclear antibodies (ANA), D-dimers (DD) and urea breath test to determine the diagnosis of *Helicobacter pylori* (*H. pylori*) infection, especially in patients with long-standing and/or uncontrolled disease.

The patients with only CIndU were submitted to diagnostic tests adapted to each subtype, for identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses.

The autologous serum skin test (ASST) is an *in vivo* test which assesses autoreactivity. Autoreactivity does not define autoimmune urticaria but may be an indication of mast cell activating autoantibodies in ASST positive CU patients (9). It was performed in patients with suspicion of autoimmune-related urticaria. The ASST and the basophil activation test (BAT) were done in patients with urticaria refractory to standardized dose anti-H1 treatment that tolerated discontinuation of these drugs for 5 days before testing and weren't doing any systemic corticosteroids for at least 2 weeks prior to the tests (9, 10). Therefore, in patients who were unable to suspend these drugs, it was not possible to perform the ASST.

The ASST was performed as recommended and described by the 2009 EAACI/GA²LEN task force consensus report on the ASST in urticaria. Wheal responses were measured at 30 min, and the ASST response was taken to be positive when the red serum induced wheal had a diameter at least 1.5 mm greater than the negative control (9). In BAT, briefly, blood from healthy donors was centri-

fuged and the buffy coat collected and resuspended in stimulation buffer containing IL-3. Donor basophils were added to each tube, and double staining was performed with anti-CCR3-PE and anti-CD63-FITC monoclonal antibodies (Bühlmann, Switzerland) and incubated at 37 °C for 15 minutes. Afterwards, the erythrocytes were lysed for 10 min at room temperature, and the samples were washed twice prior to analyzing them in a flow cytometer. Data were analyzed with FlowJo Tree Star software (Ashland, OR, USA). The test was considered positive when more than 5% of the total basophils were CD63 positive (10, 11). The disease activity and response to treatment was assessed by the Urticaria Activity Score 7 (UAS7), a validated diary-based Patient Report Outcome measure that assesses wheal number and itch severity scores, as described by the 2018 EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria (2). The UAS7 was calculated as the sum score of 7 days (minimum 0, maximum 42). Its values were assigned to five score ranges, reflecting urticaria-free to severe disease activity, as follows: UAS7 = 28-42 − severe activity CSU; UAS7 = 16-27 − moderate activity CSU; UAS7 = 7-15 – mild activity CSU; UAS7 = 1-6 – well-controlled CSU; UAS7 = 0 – urticaria-free (2, 12). It was used in all medical visits, but for the purposes of the study, it was considered the last value before the moment of analysis. Recommended treatment algorithm for urticaria includes 4 therapeutic steps: 1st line – sgAH standard dose; 2nd line – sgAH up to four times the standard dose; 3rd line – omalizumab; and 4th line – cyclosporine (2). It was also collected information about other types of medication used to manage disease exacerbations, namely oral corticosteroids.

Therapeutic modalities concerning the whole group of CU patients were characterized and were discriminated between CU subtypes (isolated CSU, CSU with CIndU and isolated CIndU). These apply only to treatment at the time of the analysis; no follow up or treatment modifications are described in this study.

Statistics

Descriptive analyses (frequency, percentage, mean, standard deviation, minimum and maximum values) were carried out for demographic and clinical variables. Chi-square test was used to analyze the fit of distribution and chi-square test/fisher's exact test to determine the statistical difference in qualitative variables. All statistical analyses were carried out using GraphPad Prism version 8.4.3 (GraphPad Software, Inc., CA, US). Significance was achieved with P-values < 0.05.

Ethical issues

The clinical part of the study as well as laboratory tests were carried out as part of the clinical routine of the urticaria specialized outpatient clinic. Patients gave an informed consent to the use of their clinical data in an anonymous form. All patients were treated according to ethical standards established in the Declaration of Helsinki.

Results

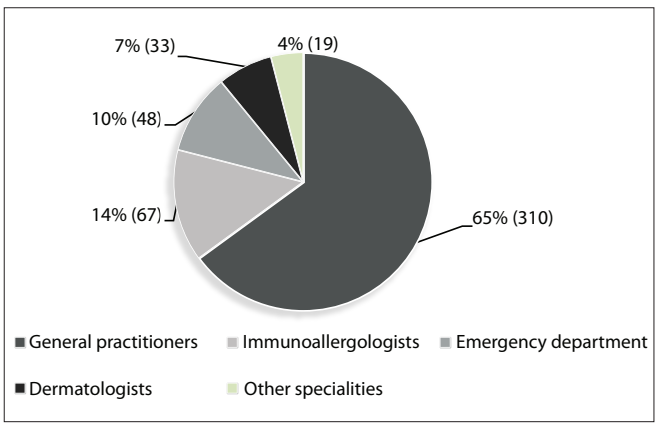
During the study period (January 2017 to September 2019), 477 patients were observed, of whom 310 (65%) were referred by the general practitioner, 67 (14%) by other immunoallergologists, 48 (10%) by the emergency department, 33 (7%) by dermatologists and 19 (4%) by other specialties, specifically internal medicine (8), rheumatology (n = 5), pediatrics (n = 3), hematology (n = 2) and nephrology (n = 1) (**figure 1**). Of the total of these patients, 429 (90%) were diagnosed with chronic urticaria (CU). Of the remaining 48 patients, 24 had other diagnosis (namely chronic pruritus (n = 13), atopic dermatitis (n = 8), prurigo strophulus (n = 2) and contact dermatitis (n = 1)), 19 had acute urticaria and 5 had hereditary angioedema. These patients were excluded for this analysis.

In the group of CU patients, mean age at the onset of symptoms was 43.7 years (standard deviation (SD) 17.6, range 6-88) and at diagnosis 46.7 years (SD 17.8, range 6-88), resulting in an average diagnostic delay of 3 years (range 0-25). Median follow-up period since first attendance in the specialized outpatient clinic was 1.7 years (interquartile range (IQR) 0.79, range 0.1-2.75). Before diagnosis, at our consultation or previously, 129 (30%) patients had symptoms for less than one year, 206 (48%) for 1-5 years and 94 (22%) for more than five years (**table I**).

More than half of these patients, 236 (55%), had history of atopic disease, with a predominance of allergic respiratory disease, namely 142 (60%) patients with allergic rhinitis and 50 (21%) with asthma (**table I**).

Concerning the subtypes of CU patients, 347 (81%) had chronic spontaneous urticaria (CSU), of whom 247 (79%) were female, 39 (9%) had isolated chronic inducible urticaria (CIndU) and 43 (10%) had CSU with CIndU (p < 0.0001). Of the patients with only CIndU, nearly half of them (42%, 16 patients) had cold urticaria, whereas the minority presented with solar urticaria (5%, 2 patients) and heat urticaria (2%, 1 patient) (p = 0.001).

Figure 1 *- Referral sources to urticaria outpatient clinic.*



Forty-three (10%) patients presented CSU with CIndU associated, the majority of which had delayed pressure urticaria (71%, 31 patients), followed by symptomatic dermographism (13%, 6 patients) ($p < 0.0001$) (**table II**). The represented P-values refer to the differences in the proportions of chronic urticaria subtypes and were obtained by chi-square goodness-of-fit test.

A laboratory profile, including thyroid laboratory tests, was requested for all patients, nevertheless 53 did not yet perform them. Of the 376 that performed the laboratory profile, 30 (8%) presented alterations in TSH and FT4, compatible with hypothyroidism in 19 (5%) and hyperthyroidism in 3 (1%). Forty-one (11%) had positive thyroid autoantibodies. All the group with hypothyroidism started daily levothyroxine sodium replacement. The clinical response of urticaria to levothyroxine sodium treatment was good in 7 (37%) patients in which urticaria became total controlled and partial in 3 (16%); conversely, 9 (47%) patients showed no improvement in clinical score ($p = 0.23$). Nevertheless, these nine patients demonstrated normalization of thyroid function after 4-6 weeks of levothyroxine sodium treatment. The patients with hyperthyroidism were medicated with anti-thyroid drugs. The clinical response of urticaria was evaluated until the normalization of thyroid function after treatment with anti-thyroid drugs. Although thyroid hormone levels were normalized after 6-8 weeks of treatment, none of the three patients showed any improvement of their respective urticaria.

In what concerns other laboratory parameters, ANA were positive in 42 (11%) patients and increased values of CRP in 31 (8%), ESR in 46 (12%) and d-dimers in 35 (9%). When considering each of these results and the patients with UAS7 > 15 (131 patients, 35%) at time of blood sampling, which translates a moderate to severe disease activity, we have verified that ANA were positive in 35 (83%) of these patients and increased values of CRP were observed in 26 (84%), ESR in 40 (87%) and d-dimers in 18 (51%), respectively. On the other hand, UAS7 > 15 was found in 96 (29%) ANA negative patients, 105 (30%) patients with normal values of CRP, 91 (28%) patients with normal values of ESR and 113 (33%) patients with normal levels of d-dimers. When comparing these variables, we verified that ANA positive

Table I *- Demographic and clinical characterization of chronic urticaria patients.*

Characteristics	**CU patients (n = 429)**
Gender, n (%)	
Male	94 (22%)
Female	335 (78%)
Mean age, years (range)	
At the onset of symptoms	43.7 (6-88)
At diagnosis	46.7 (6-88)
Average diagnostic delay	3 (0-25)
Time of disease before diagnosis, n (%)	
< 1 year	129 (30%)
1-2 years	99 (23%)
2-5 years	107 (25%)
> 5 years	94 (22%)
Median follow-up period in the outpatient clinic, years (range)	1.7 (0.1-2.75)
Atopic comorbidities, n (%)	236 (55%)
Allergic rhinitis	142 (60%)
Asthma	50 (21%)
Drug allergy	21 (9%)
Food allergy	14 (6%)
Atopic dermatitis	9 (4%)
Autoimmunity tests, n positive result/total (%)	
Autologous serum skin test	24/76 (32%)
Basophil activation test	13/38 (34%)
Helicobacter pylori infection, n positive result/total (%)	110/291 (45%)
Eradication, n (%)	96 (87%)
Reported improvement, n (%)	57 (59%)
UAS7 < 6, n (%)	316 (81%)

CU: chronic urticaria; UAS: urticaria activity score.

Table II *- Chronic urticaria diagnosis of studied population according to the EAACI/GA²LEN/EDF/WAO guidelines.*

Chronic Urticaria subtypes	CU patients (n = 429), n (%)
Isolated chronic spontaneous urticaria	347 (81%)
Chronic inducible urticaria	39 (9%)
Cold urticaria	16 (42%)
Cholinergic urticaria	9 (23%)
Symptomatic dermographism	8 (21%)
Delayed pressure urticaria	3 (7%)
Solar urticaria	2 (5%)
Heat urticaria	1 (2%)
Chronic spontaneous urticaria + Chronic inducible urticaria	43 (10%)
Delayed pressure urticaria	31 (71%)
Symptomatic dermographism	6 (13%)
Cold urticaria	3 (8%)
Cholinergic urticaria	2 (5%)
Delayed pressure urticaria + Symptomatic dermographism	1 (3%)

All data are presented as frequencies and percentages. The chi-square goodness-of-fit test indicated that the differences in the proportions of chronic urticaria subtypes diagnosed in the study were statistically significant ($p \leq 0.001$). CU: chronic urticaria.

patients demonstrated a statistically significant more severe disease than ANA negative patients ($p < 0.0001$), as well as patients with elevated values of CRP ($p < 0.0001$), ESR ($p < 0.0001$) and d-dimers ($p = 0.04$) than patients with normal levels, respectively. Seventy-six patients underwent ASST which was positive in 24 (32%) and 38 underwent BAT which was positive in 13 (34%). Of the patients who demonstrated a positive ASST, 18 (75%) presented UAS7 > 15 at time of blood sampling, in contrast with 3 (7%) ASST negative patients ($p < 0.0001$). When analyzing BAT positive patients, 11 (85%) presented UAS7 > 15, as opposed to 5 (20%) BAT negative patients ($p = 0.0003$).

In our CSU population, non-steroidal anti-inflammatory drugs (NSAIDs) trigger urticaria in 27 (7%) patients. When considering this population and UAS7 values > 15 we have found that 21 (78%) NSAID-intolerant CSU patients presented it, as opposed to 53 (15%) NSAID-tolerant CSU patients ($p < 0.0001$). *Helicobacter* (*H. pylori*) infection was tested in 291 patients and identified in 110 (45%). With the first therapeutic attempt, eradication was achieved in 96 of those patients (87%) and 57 (59%) reported urticaria improvement ($p = 0.07$) (**table I**).

At the moment of the study, 204 (48%) of CU patients were medicated with a second-generation H1-antihistamine (sgAH) daily, 99 (23%) with sgAH up to four times the standard dose, 126 (29%) with omalizumab and none with cyclosporine. Additionally, 7 (2%) patients were completing a 10-day short course of systemic corticosteroids (20 mg oral prednisolone) for management of a disease exacerbation at the time of data analysis. Of these, all of them were under sgAH four times the standard dose and five of them also under omalizumab. They were all controlled (UAS7 < 6) before this exacerbation.

Discrimination of therapeutic modalities in CU subtypes (isolated CSU, CSU with CIndU and isolated CIndU) are represented in **table III**. It was observed a statistically proven major use of sgAH daily in the group of patients with isolated CInDU and a trend to upgrade treatment (updosing sgAH or adding omalizumab) in CSU patients with or without CInDU associated ($p < 0.0001$).

UAS7 in the four weeks prior to the study date was < 6 in 316 of CSU patients, which translates a disease control of 81% (**table II**). When considering uniquely the group of CSU patients under treatment with omalizumab, disease control was accomplished in 107 patients (89%).

Discussion

In our study, we have described a large cohort of patients with CU (n = 429) followed-up at a specialized urticaria outpatient clinic of a UCARE, in a period of time of 2 years and 9 months. Demographic, clinical, laboratory and therapeutic profile of these patients were reported.

We have verified that the majority of these patients (n = 310, 65%) were referred by general practitioners. Subsequently, 67 patients (14%) were referred by other immunoallergologists. These 67 patients were referred because they failed to achieve control with sgAH treatment and needed evaluation in a specialized urticaria consultation to start third-line therapy, not everywhere available. As observed, in our population, more than half of the patients were referred by general practitioners directly, rather than other immunoallergologists. We assume this might be due to the fact that, in our country, they represent the primary health care and frequently the first medical contact, regardless of the severity of the disease, allowing direct referral to our specialized outpa-

Table III *- Discrimination of pharmacological treatment in chronic urticaria subtypes (isolated CSU, isolated CIndU and CSU+CIndU).*

Pharmacological treatment	CSU patients (n = 347)	CIndU patients (n = 39)	CSU+CIndU patients (n = 43)	P-value
SgAH 1/day, n (%)	163 (47%)	29 (74%)	12 (28%)	< 0.0001*
SgAH 2 to 4 times the standard dose	83 (24%)	4 (10%)	12 (28%)	
Omalizumab	101 (29%)	6 (16%)	19 (44%)	
Cyclosporine	0 (0)	0 (0)	0 (0)	

CSU: chronic spontaneous urticaria; CIndU: isolated chronic inducible urticaria; sgAH: second-generation H1-antihistamine. *Chi-square test; value for all the comparisons in the table.

tient clinic. Furthermore, as previously mentioned and below explained, patients may also be referred to our outpatient clinic by the emergency department, other hospitals or other specialties. Despite it, we have verified that sometimes these patients do not have a severe disease. Emergency department (n = 48, 10%) and dermatology consultations (n = 33, 7%), were also a common origin of these patients, but the data also reported a referral of colleagues from other specialties, namely internal medicine, rheumatology, pediatrics, hematology and nephrology. The wide variety of specialties through which these patients were referred shows a significant portion of physician visits due to urticaria and thus its importance in everyday practice among many specialties.

Nearly all of the evaluated patients had CSU (n = 390, 91%), of whom 43 (10%) had CIndU associated.

Maurer *et al.* descriptively compared some of these aspects among CU patients in many countries residing in Europe (EU) and Central and South America (C/SA). Among patients with CSU, CIndU was a comorbid disease in 30% of C/SA patients but only 22% of EU patients (13). Our findings show a slight lower percentage of CIndU compared with the European patients mentioned in this report. We presume that it might have been a significant lesser referral of patients with isolated CIndU, taking into consideration the high percentage of referral of patients to our center by other specialties and a probable minor awareness of CIndU disease, either by doctors or by patients who do not seek medical attention.

As previously described, 39 (9%) of CU patients had isolated CIndU, namely 16 (42%) cold urticaria, 9 (23%) cholinergic urticaria, 8 (21%) symptomatic dermographism, 3 (7%) delayed pressure urticaria, 2 (5%) solar urticaria and 1 (2%) heat urticaria. CIndU is characterized by itchy wheals, flare-type skin reactions, and/or angioedema induced by external physical factors. Our findings are similar to a report of Abajian and colleagues, who estimated the prevalence of CIndU is 13.1-14.9% among patients with chronic urticaria (14).

The demographic characteristics of our cohort, namely median age and a predominance of the female gender in CSU patients, are in line with other studies, including the Portuguese AWARE Study and consequently with German and Scandinavian AWARE patients (15, 16). This consistently reported female predominance is not explained, neither mechanistically nor clinically (15).

The patients were diagnosed with three years of average time of disease and after being observed/treated by several specialists (as about 22% presented symptoms for more than five years), demonstrating the complexity in appropriate diagnosis and management of this disease.

Regarding allergic co-morbidities, our results are concordant with others, who have reported associations between CU and atopic conditions, such as atopic dermatitis, allergic rhinitis and asthma, even though in our study in a lower percentage. Nassif *et al.* reported that more than 90% of CU patients had a personal history of atopic disease (17). In our study it was documented in 55%. Two recent cross-sectional studies of 11,217 and 12,185 patients, respectively, observed significant associations of CU with asthma, atopic dermatitis and allergic rhinitis (18, 19). Accumulating evidence shows that CU and atopic conditions are associated with aberrant immune function. Its association may reflect aberrant crosstalk between T-helper cells and mast cells (20), even though there are studies which do not support these conjectures (21). We assume that the interrelationships between these conditions are possibly complex and require further study.

In terms of laboratory findings, we found alterations in TSH and T4, compatible with hypothyroidism in 19 (5%) and hyperthyroidism in 3 (1%). Kolkhir *et al.* performed a systematic review and found hypothyroidism in 0-42.6% and hyperthyroidism in 0-17.6% of CSU patients. In this review, it was also reported that in CSU hypothyroidism is more common than hyperthyroidism (22), which is in line with our findings. In our population, thyroid autoantibodies serum levels were high in 11% (n = 41) patients, similar with a review of 24 studies and ≥ 100 patients that demonstrated that the frequency of elevated IgG thyroid autoantibodies varied from 3.7% to 37.1% (23).

Forty-one (11%) had positive thyroid autoantibodies. Of the group of patients with hypothyroidism they all started daily levothyroxine sodium replacement. The clinical response of urticaria to levothyroxine sodium treatment was good in 7 (37%) patients in which urticaria became total and partial controlled in 3 (16%). Nine (47%) patients showed no improvement in clinical score, even though they demonstrated normalization of thyroid function after 4-6 weeks of levothyroxine sodium treatment. The patients with hyperthyroidism (n = 3, 1%) were

under anti-thyroid drugs. None of the three patients showed any improvement of their respective urticaria, although thyroid hormone levels were normalized after 6-8 weeks of treatment.
According to the systematic review of Kolkhir and colleagues, in some studies treatment of hypothyroidism and hyperthyroidism led to improvement or remission of CSU in 28% and 67% of patients, respectively. However, in other, neither replacement treatment with levothyroxine nor anti-thyroid drugs had effect on improving urticaria control. The data on the efficacy of treatment with thyroid drugs including levothyroxine in CSU are not consistent. Conflicting evidence may be explained by the various confounding factors and limitations such as the small numbers of patients included in some studies and the absence of appropriate controls (22).
In what concerns other laboratory parameters, ANA were positive in 42 (11%) patients, CRP in 31 (8%), ESR in 46 (12%) and d-dimers in 35 (9%).
Antinuclear antibodies (ANA) are a group of autoantibodies directed against corresponding antigens in the nucleus and are found in many patients with systemic or organ-specific autoimmune disorders. According to Viswanathan and colleagues the percentage of CSU patients having a positive test for ANAs (titer more than 1:160) is approximately 29% (24). In our setting, positive ANA is observed in 12%. Costa and colleagues showed that the presence of ANA has been identified in patients with CU in percentages ranging from 0 to 29%. It is also referred that percentages varying between 22.6% and 84.6% are also found in apparently healthy patients or with other pathologies (8). Although measuring ANA serves as a nonspecific marker of systemic autoimmunity in rheumatologic disorders, its relationship with CSU is poorly understood. Nevertheless, Viswanathan and colleagues established association between the presence of ANA and the severity of urticaria (24). We have found, in our population, positive ANA patients had a significant more severe disease, when compared to patients with negative ANA.
ESR, CRP or d-dimer levels have been shown to be high in CSU and might correlate with disease activity as evidenced in several studies from different centers (25). In our study, we have verified that patients with elevated values of these laboratory parameters demonstrated, respectively, a statistically significant more severe disease, than patients with normal values. However, the problem remains as whether these substances are specific enough for urticaria, as they can often be elevated in many other diseases that are often co-morbid in CSU patients or even an underlying cause of the CSU (*e.g.*, chronic infections, autoimmune disorders) (26).
Based on these premises and the actual literature, we assume that the referred biomarkers are particularly useful as biomarkers of disease activity, but as they are related to inflammatory and coagulation, their interpretation in CSU must always be done with caution.
The pathogenesis of CU is complex and not yet fully understood. However, central to our current understanding of this unpredictable disease is the activation and subsequent degranulation of mast cells in the skin (2).
The degranulation of mast cells in CU can be due to different mechanisms in different patients (27). CSU is considered to be an autoimmune disorder (type I and type II) in 50% of all cases (28). Reviewing literature, up to 45% of patients with CU have IgG autoantibodies directed against either IgE (5-10%) or FcεRI (35-40%). These IgG autoantibodies can bind to and cross-link FcεRI on mast cells and basophils, resulting in their activation. This is classified to be type IIb autoimmunity in CSU. In contrast to this, type I autoimmunity in CSU is characterized by the finding of IgE autoantibodies against thyroid antigens such as thyroid peroxidase (TPO) and/or auto-allergens. This autoimmune characteristic of the disease is now regularly assessed by physicians, by means of the ASST, to aid in specific diagnosis of autoimmune-related urticaria (29). Recently, Schoepke *et al.*, in the PURIST study, also suggested the inclusion of the Basophil Histamine Release Assay (BHRA) or the BAT in the diagnostic work up of CSU patients which may allow for the identification of autoimmune CSU patients in clinical practice (30).
In our cohort seventy-six patients underwent ASST which was positive in 24 (32%) and 38 underwent BAT which was positive in 13 (34%); of these, 7 patients had both ASST and BAT positive.
In a recent metanalysis of studies in Asian patients, it was observed a higher UAS7 and high risk of angioedema in ASST positive patients, suggesting an association of test positivity and disease severity (31). Furthermore, there is also evidence showing that BAT with or without the combination of ASST can identify patients with more severe CSU (32, 33). These studies are in conformity with our results which revealed that ASST positive patients and BAT positive patients demonstrated a statistically significant more severe disease than ASST and BAT negative patients, respectively. Mast cell degranulation in CSU may also result from infection-associated signals and other unknown mechanisms. In addition to these, various other non-immunological factors can prime or trigger mast cells to induce inflammatory reactions, including different drugs such as NSAIDs (34). Also, a substantial proportion, up to 40%, of patients with CSU experience exacerbations when exposed to NSAIDs (35). In the studied sample we have verified NSAIDs were a trigger to urticaria in 27 (7%) patients. Sánchez-Borges *et al.* have observed that patients with aspirin exacerbated cutaneous disease experience more severe disease when compared with CSU patients who are tolerant to NSAIDs (35). Shin *et al.* observed that patients with NSAIDS-induced urticaria have a more severe and chronic disease (36). In our population we have also demonstrated a statistically significant more severe disease in NSAID-intolerant CSU patients when compared to NSAID-tolerant CSU patients ($p < 0.0001$).
In recent years, there has been emerging literature suggesting that *H. pylori* could be involved in the pathogenesis of CU

(37). In our study, *H. pylori* infection was tested in 291 patients and identified in 110 (45%). Eradication was achieved in 96 of those patients (87%) and 57 (52%) reported remission of urticaria, which, in our study, was not statistically significant ($p = 0.07$). Our results are in line with other studies, involving 2200 participants, with a total *H. pylori* infection rate of 44.73% (984/2200). The prevalence rate of *H. pylori* infection was 49.74% in chronic urticaria group and 40.81% in controls (38). However, the association between *H. pylori* and CSU is subject to much dispute. Several studies have shown a higher prevalence of *H. pylori* infection in chronic urticaria patients and have reported remissions of skin lesions after eradication treatment (39-41). However, other investigations supported a lack of relationship between *H. pylori* infection and CU and other studies found no correlation between *H. pylori* eradication and remission of urticarial symptoms (42).

As documented and even though *H. pylori* eradication has been recommended as part of routine chronic urticaria management by multiple authors, the evidence that *H. pylori* eradication leads to improvement of chronic urticaria outcomes is weak and conflicting (43). When analyzing our own results, we also observe that the effectiveness of *H. pylori* eradication therapy in suppressing CSU symptoms was not statistically significant. For this reason we assume that *H. pylori* eradication should be individually and carefully considered, instead of a routine recommendation. We agree with Shakouri *et al.* (43) that potential harms/burdens and benefits of this therapeutic intervention and patient values and preferences must be considered before proceeding with assessment and treatment for *H. pylori* in chronic urticaria patients.

Treatment of chronic urticaria follows a standard approach with the goal of achieving complete absence of symptoms. All patients should avoid known triggers, including certain drugs such as NSAIDs and relevant triggering stimuli in the case of CIndU. However, given that this approach only results in very few cases, symptomatic treatment is recommended for nearly all patients (2). According to the current version of the EAACI/GA²LEN/EDF/WAO chronic urticaria guideline, the non-sedative second-generation H1-antihistamines (sgAH) are the first-line therapy. If continuous treatment for 2-4 weeks does not lead to adequate control of symptoms, the guideline recommends up-dosing (up to four times the standard dose), which is much more effective than standard-dose therapy and has a similar side effect profile (3). In line with these recommendations, in our cohort, and at the moment of study, 204 (48%) patients of were medicated with sgAH daily or on-demand and 105 (24%) with sgAH two to four times the standard dose (46 patients with two H1-antihistamines, 17 with three and 42 with four).

If sufficient improvement does not occur after 2-4 weeks of sgAH therapy at a higher-than-standard dose, omalizumab should be added to the regimen. As mentioned before, it has also been shown to be effective and safe in the treatment of CIndU patients, however, it is not yet approved for patients with isolated CIndU. If there is no success after six months of omalizumab therapy, off-label treatment with cyclosporine is recommended (3). In our population, 126 patients (29%) were under treatment with omalizumab due to being refractory to sgAHs. It is worth mentioning that in our country, and in accordance with the EAACI/GA²LEN/EDF/WAO chronic urticaria guideline (2), only patients resistant to second-line therapy (four daily sgAH) are accepted for treatment with omalizumab by the hospital pharmacy and therapy commissions. As a result, every CSU patient that started omalizumab was under sgAH four times the standard dose at that moment and might have been under systemic corticosteroid therapy at that moment or in the past. Despite that, when the patient achieves a complete response to omalizumab, the daily dose of sgAH is progressively reduced and, consequently, many patients under omalizumab therapy stop using sgAH.

A similar percentage of patients treated with omalizumab was found in the Portuguese population of AWARE study, an heterogeneous non-interventional study including patients recruited from 10 participating centers of immunoallergology and dermatology throughout Portugal, designed to evaluate the real world disease burden of CU patients' refractory to sgAHs standard dose treatment, at specialized urticaria centers (15). Also in comparison with this study, we have verified, along with the analysis of our UAS7 results (mentioned below), that, in our population, a higher percentage of disease control (81%) was achieved, corroborating the fact that our patients are adequately treated and in agreement with the latest guidelines whose goal is total control of urticaria symptoms. Moreover, when considering uniquely the group of CSU patients under treatment with omalizumab, disease control was accomplished in 107 patients (89%), which reinforces the importance of a proper assessment and the well-documented efficacy of this therapeutic option, not everywhere available.

In our population, six of the patients with isolated CIndU (16%), namely, two patients with delayed pressure urticaria, one with cold urticaria, one with heat urticaria, one with solar urticaria and one with cholinergic urticaria were medicated with omalizumab. Even though it has an off-label use in CIndU, these patients presented a severe disease refractory to sgAHs that justified trying omalizumab treatment. At the moment of study, we have verified that all but one experienced a complete/partial relief of symptoms.

The efficacy of cyclosporine has been confirmed in placebo-controlled trials and it should be used with caution due to its adverse events or used only in specific groups of patients (3). In our population sample there was no patient taking cyclosporine. Seven (2%) patients were completing a 10-day short course of systemic corticosteroids (20 mg oral prednisolone) for management of a disease exacerbation at the moment of data analysis. Of these, all of them were medicated sgAH four times the standard dose and five of them also with omalizumab. They were

all controlled (UAS7 < 6) before this exacerbation. This is in agreement with several guidelines and expert opinions which recommend a short course of oral corticosteroids only in exacerbations and, due to the risk of serious adverse events, do not recommend their long-term use (15).

When comparing with the Portuguese AWARE study about the real-life clinical practice setting in Portugal in which almost 11% of patients were taking oral corticosteroids (15), a lower percentage is described in our study.

The use of UAS helps to monitor the evolution of the disease and the efficacy of treatment. It is the best method for assessing activity given that this instrument evaluates the seven days prior to the medical visit, evaluating more accurately a disease that has a fluctuating course. We have considered the median UAS7 of the four weeks prior to the study date and concluded that it was < 6 in 316 CSU patients, which translates a disease control of 81%.

Our study has some limitations that must be considered. First, this study is retrospective, with analysis of patients' database. Some information, as results of laboratory tests, was not available for all patients (12%). Second, we didn't provide any data concerning follow-up or quality of life. Despite it, we provide helpful data regarding distribution of urticaria ethology, clinical course time, laboratory tests and pharmacological treatment of patients treated in a Urticaria Centers of Reference and Excellence.

Conclusions

A central aspect to be generally considered in the treatment approach and patient management is the individual disease severity. Given the prevalence of chronic urticaria, general practitioners or emergency medical services are frequently the first to be consulted, as observed in our cohort. For patients with mild disease, standard-dose antihistamine therapy is usually sufficient. Nevertheless, if this is not the case, patients should be referred to a specialist who typically have more diagnostic and treatment options at their disposal. UCAREs are certified by the European GA²LEN network and are characterized by a high degree of specialization in terms of research and clinical patient care.

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Conflict of interests

The authors declare that they have no conflict of interests.

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