






# Complete remission of spontaneous chronic urticaria after treatment of *Helicobacter pylori* infection: case report and literature review

Remissão total da urticária crônica espontânea após o tratamento de infecção por *Helicobacter pylori*: relato de caso e revisão de literatura

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## ABSTRACT

**Introduction:** Urticaria is a skin disorder that affects 15-20% of individuals at some stage of life. It is classified as chronic spontaneous urticaria (CSU) when the manifestations are daily or almost daily and exceed six weeks. It is of fundamental importance to research the cause of CSU for the correct treatment. **Objective:** To report the case of a patient who presented complete remission of CSU after treatment for *Helicobacter pylori* infection and with clinical and laboratory exclusion of the different causes of chronic urticaria. **Case report:** A 46-year-old woman presented CSU for 15 months, refractory to treatment with antihistamines. Different causes of chronic urticaria, such as neoplasms, autoimmune and infectious diseases, were excluded after clinical and laboratory exams. During follow-up, she revealed epigastric pain, when digestive endoscopy was required, revealing erosive gastritis and the presence of *H. pylori*. Then, the patient received treatment for *H. pylori* infection and showed complete remission of urticaria. Literature studies suggest a possible association between *H. pylori* infection and chronic urticaria, and further studies are needed. **Conclusion:** The authors believe that the diagnostic investigation of *H. pylori* infection in patients with CSU and dyspeptic manifestations is important, after excluding other causes of chronic urticaria, such as neoplasms and autoimmune and infectious diseases.

**Keywords:** Chronic urticaria, *Helicobacter pylori*, Abdominal pain

## RESUMO

**Introdução:** A urticária é um distúrbio de pele que atinge 15 a 20% dos indivíduos em alguma fase da vida. É classificada como urticária crônica espontânea (UCE) quando as manifestações são diárias ou quase diárias e ultrapassam seis semanas. É de fundamental importância a pesquisa da causa da UCE para o tratamento correto. **Objetivo:** Relatar caso de uma paciente que apresentou remissão total da UCE após tratamento de infecção por *Helicobacter pylori*, com exclusão clínico-laboratorial das diferentes causas de urticária crônica. **Relato do caso:** Mulher de 46 anos apresentava UCE há 15 meses, refratária ao tratamento com anti-histamínicos. Foram excluídas clínica e laboratorialmente diferentes causas da urticária crônica, como neoplasias, doenças autoimunes e infecciosas. Durante o acompanhamento, revelou epigastria, quando foi solicitada endoscopia digestiva, demonstrando gastrite erosiva e presença de *H. pylori*. Recebeu, então, tratamento para infecção por *H. pylori* e apresentou remissão total da urticária. Estudos da literatura sugerem possível associação entre infecção por *H. pylori* e urticária crônica, e que mais estudos são necessários. **Conclusão:** Os autores acreditam ser importante a investigação diagnóstica da infecção por *H. pylori* em pacientes com UCE e manifestações dispépticas, depois de excluir outras causas de urticária crônica, como neoplasias, doenças autoimunes e infecciosas.

**Palavras-chave:** Urticária crônica, *Helicobacter pylori*, Dor abdominal

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Article received: 05/18/2022. Article approved: 08/30/2022. Article published: 11/11/2022.

Responsible Editor: Prof. Dr. Eitan Naaman Berezin (Editor-in-Chief).

## INTRODUCTION

Urticaria is defined by the presence of wheals, angioedema, or both. Wheals consists of a central edema of variable size with reflex erythema, accompanied by pruritus and/or a burning sensation, which lasts less than 24 hours<sup>(1-4)</sup>. It results from the activation of mastocytes, with the release of histamine, cytokines, and other mediators. In addition, there is vasodilation, plasma extravasation, and recruitment of cells to the lesions site<sup>(1,2)</sup>.

It is deemed as acute urticaria when the manifestations last less than six weeks, and chronic urticaria when symptoms occur daily or almost daily, lasting more than six weeks<sup>(1,2,4,5)</sup>. Chronic urticaria is classified as spontaneous when there is no specific triggers, and inducible when urticaria is triggered by external stimuli such as cold, heat, pressure or temperature increase<sup>(1,3-6)</sup>.

Chronic spontaneous urticaria (CSU) affects about 15 to 20% of the general population. It is more frequent in females (60%)<sup>(2)</sup>, and in the ages from 20 to 40 years old<sup>(3,6)</sup>. Around 50% of patients with CSU have episodes one year after the first diagnosis, and 20% of patients with CSU have episodes in the following 20 years<sup>(2,6)</sup>. CSU exceptionally has an allergic etiology. Among the causes of CSU are chronic infections, autoimmune diseases, neoplasms, inborn errors of immunity, and with an undefined cause (idiopathic)<sup>(1)</sup>. It is of fundamental importance to research the causes of CSU to provide the correct treatment to the patient.

*Helicobacter pylori* is a Gram-negative bacterium present in 50 to 80% of the world population<sup>(7,8)</sup>. It colonizes the epithelial cells of the gastric mucosa, resulting in gastrointestinal inflammation, mastocyte activation, neutrophil and lymphocyte recruitment, and release of immune mediators, especially histamine. The literature suggests a possible association between *H. pylori* and extra-gastric diseases, including CSU<sup>(7,9-11)</sup>, and there are still few studies in this regard.

The present study aimed to report the case of a woman with CSU for 15 months who presented complete resolution of urticaria after treatment of *H. pylori* infection. The study was submitted to the Ethics Committee, with approval from the institution (CAAE 47052221.8.0000.5479, approval 4.734.642). The patient signed an informed consent form before the start of this study.

## CASE REPORT

A 46-year-old woman came to the Allergy and Immunodeficiencies Sector of a university hospital, reporting itchy, diffuse urticarial erythematous plaques all over the body for 15 months. She reported that the lesions appeared daily or almost daily and regressed in less than 24 hours, not accompanied by

angioedema. The patient denied fever, pain, malaise, or other complaints. She used antihistamines for several periods, with no change in her condition. There was no association with triggers or physical causes such as heat, exercise, sweating or other factors. She reported that in only one episode the urticaria was severe, diffuse and with facial involvement, when the patient went to the emergency service, where she received antihistamines, and the lesions regressed after five days, with subsequent recurrence.

At the physical examination, the patient showed erythematous and edematous plaques disseminated throughout the body, without angioedema, presence of red dermatographism, without adenomegaly, splenomegaly or hepatomegaly. Rhinoscopy revealed normal colored mucosa, with hypertrophy of right turbinate. There were no other findings at the physical examination. The laboratory tests were normal: hemogram, stool parasitology, urinalysis, erythrocyte sedimentation rate, C-reactive protein, blood glucose, thyroid-stimulating hormone (TSH), free T3 and T4, antithyroid antibodies, and other autoantibodies. Total complement was 335 U/mL, C3 121 mg/dL, and C4 23 mg/dL, also within normal range.

In view of the situation, the diagnosis of CSU was established and daily therapy with second-generation antihistamine was initiated, alternating drugs (loratadine, cetirizine, ebastine, fexofenadine), but without clinical improvement. A first-generation antihistamine was tried for two months, also without improvement.

During outpatient follow-up, the patient complained of epigastric pain for two years, with early satiety after eating. The pain had started nine months before the urticaria. Upper digestive endoscopy with biopsy was then performed, revealing erosive pangastritis, and the presence of *H. pylori*. The patient received treatment for *H. pylori* infection (Amoxicillin 2 g/day, Clarithromycin 1g/day, and Omeprazole 40 mg/day for fourteen days). After treatment, the patient showed improvement in urticaria, with total remission for two years, without recurrence. The patient reported a significant improvement in quality of life after the resolution of the urticaria.

## DISCUSSION

In view of the almost daily urticaria, lasting for more than six weeks and absence of triggering factors, the diagnosis of chronic urticaria was established. It is always necessary to search for CSU causes, as was done in the present case: physical examination without changes, outpatient follow-up without interurrences, in addition to laboratorial tests excluding systemic infectious diseases, autoimmune

diseases and neoplasms. Inducible chronic urticaria was also excluded by the absence of triggering factors. Thus, after excluding different causes of chronic urticaria, the diagnosis of CSU was established.

The continuous outpatient follow-up allowed the patient to remember to mention epigastric pain that had begun nine months before the urticaria, which led to upper digestive endoscopy with biopsy, showing the importance of following up patients with CSU.

After diagnosis of erosive pangastritis with *H. pylori* infection, the patient received treatment for *H. pylori* infection. There was improvement of urticaria after such therapy, with total remission of CSU after 40 days, without reoccurrence in the following two years. In the present case, this suggests a causal relationship between CSU and *H. pylori* infection. The patient also reported an important improvement in quality of life, similar to that described in patients with CSU, in relation to sleep, daily activities, emotional disorders, and social isolation<sup>(1,6,12,13)</sup>.

A literature review using GRADE (Grading of Recommendations, Assessment, Development and Evaluations)<sup>(14)</sup> analyzed 19 studies on chronic urticaria and *H. pylori*: 17 observational, and two double-blind randomized controlled clinical trials. Ten of these studies reported remission of urticaria after the eradication of *H. pylori* infection. The other studies did not conclude this association existed; however, among these studies it can be observed that they used small samples, short follow-up times or imprecise follow-up, specially due to high dropout rates<sup>(14)</sup>.

A recent study with 522 patients infected by *H. pylori* showed improvement in CSU after two weeks of antibiotic therapy for *H. pylori*<sup>(8)</sup>. Brazilian researchers also observed that 70% of patients with UCE and *H. pylori* showed a significant CSU improvement in urticaria after eradication of the bacteria<sup>(9)</sup>. Another Brazilian study reported a case of a 13-year-old adolescent with CSU, epigastric pain, and active gastritis associated with the presence of *H. pylori*; the treatment of the bacteria infection culminated in the remission of the urticaria<sup>(14)</sup>. The same study describes that after five years the patient presented urticaria once again, associated with epigastralgia, when endoscopy was repeated, confirming *H. pylori* infection. After repeating antibiotic therapy, urticaria disappeared again, suggesting a causal relation between *H. pylori* infection and CSU<sup>(14)</sup>. According to the literature, the rate of reinfection by *H. pylori* after treatment varies from 1.5% to 12%, usually appearing due to the reactivation of the infection<sup>(9)</sup>.

Several studies have revealed that dyspeptic symptoms are present in patients with CSU<sup>(9,14-17)</sup>. A meta-analysis with 16 studies observed that *H. pylori* infection is more present in patients with CSU, suggesting that the infection may represent a risk factor for the development of the infection<sup>(11)</sup>. Another study observed that 85.7% of CSU patients treated for *H. pylori* infection had urticaria remission, also suggesting that *H. pylori* infection is related to the development and persistency of CSU<sup>(7)</sup>. Other case reports showed that 70% of patients with CSU responded to therapy for *H. pylori* infection, indicating a causal relationship<sup>(18-20)</sup>.

The immunomodulatory role of *H. pylori* infection in CSU is subject of intense discussion<sup>(9)</sup>. Studies have shown that proteins of *H. pylori*, such as vacuolating cytotoxin A (VacA) and neutrophil-activating protein (HP-NAP), can activate mastocytes<sup>(21)</sup>. Furthermore, it is described that a component of the mixed protein extracted from *H. pylori* stimulates the production of histamine and other mediators, such as TNF- $\alpha$ , IL-1, IL-3, INF- $\gamma$ , LTC-4, LTB-4, and PAF, as well as greater secretion of Th2 cytokines, with greater synthesis of IgE and mastocyte activation<sup>(8,10,11)</sup>. Therefore, several inflammatory mediators released during *H. pylori* infection could play a role in the pathogenesis of urticaria, resulting in increased vascular permeability of the skin<sup>(8)</sup>. Studies have also observed eosinophilic infiltration in the gastric mucosa of patients with *H. pylori* infection and CSU, which could contribute to the aggravation of the skin lesions<sup>(9,11)</sup>.

In the present report, we observed that the specific treatment of *H. pylori* infection resulted in the complete remission of CSU, which persisted for almost a year and half, after excluding other causes of CSU, such as autoimmune, infectious and neoplastic diseases.

## CONCLUSION

We concluded that the treatment for *H. pylori* infection in a patient with dyspeptic symptoms, *H. pylori* infection and CSU for 15 months led to complete remission of urticaria, without reoccurrence in the following two years, suggesting an association between *H. pylori* infection and chronic urticaria. We believe it is important to investigate *H. pylori* infection in patients with CSU and dyspeptic symptoms. In addition, it is necessary to exclude other causes of CSU, such as autoimmune, infectious and neoplastic diseases. The investigation of *H. pylori* in patients with CSU and epigastric pain can change the evolution of urticaria, promoting an improvement in the patients' quality of life, as reported in the present case.

**Funding:** None.

**Conflicts of interest:** None.

**Authors' contribution:** All authors are responsible for the stages of the present study.

## REFERENCES

- Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018; 73(7):1393-414. <https://doi.org/10.1111/all.13397>
- Forte WCN. Reações IgE-mediadas. In: Forte WCN. *Rimunologia do básico ao aplicado*. 3ª ed. São Paulo: Atheneu; 2015. p. 131-80.
- Cherrez Ojeda I, Vanegas E, Felix M, Mata V, Cherrez S, Simancas-Racines D, et al. Etiology of chronic urticaria: the Ecuadorian experience. *World Allergy Organ J*. 2018; 11(1):1. <https://doi.org/10.1186%2Fs40413-017-0181-0>
- Dionigi PCL, Menezes MCS, Forte WCN. A prospective ten-year follow-up of patients with chronic urticaria. *Allergol Immunopathol*. 2016; 44(4):286-91. <https://doi.org/10.1016/j.aller.2015.10.004>
- Ensina L, Valle S, Campos R, Agondi R, Criado P, Bedrikow R, et al. Guia prático da Associação Brasileira de Alergia e Imunologia para o diagnóstico e tratamento das urticárias baseado em diretrizes internacionais. *Arq Asma Alerg Imunol*. 2019; 3(4):382-92. <https://doi.org/10.5935/2526-5393.20190052>
- Valle SOR, Motta AA, Amaral CSF, Ensina LFC, Mallozi MC, Spengler MGMT, et al. O que há de novo na urticária crônica espontânea? *Braz J Allergy Immunol*. 2016; 4(1):9-25. <https://doi.org/10.5935/2318-5015.20160002>
- Elhendawy M, Hagraas MM, Soliman SS, Shaker ESE. Positive effect of *Helicobacter pylori* treatment on outcome of patients with chronic spontaneous urticaria. *Am J Clin Pathol*. 2021; 155(3):405-11. <https://doi.org/10.1093/ajcp/aqaa134>
- Guo Y, Li H-M, Zhu W-Q, Li Z. Role of *Helicobacter pylori* eradication in chronic spontaneous urticaria: a propensity score matching analysis. *Clin Cosmet Investig Dermatol*. 2021; 14:129-36. <https://doi.org/10.2147/ccid.s293737>
- Mamede LQ, Gomes LA, Pereira GF, Araújo AMFS, Souza AB, Perez IL, et al. A influência do tratamento do *Helicobacter pylori* no paciente com urticária crônica espontânea. *Arq Asma Alerg Imunol*. 2019; 3(4):459-64. <https://doi.org/10.5935/2526-5393.20190061>
- Rasooly MM, Moye NA, Kirshenbaum AS. *Helicobacter pylori*: A significant and treatable cause of chronic urticaria and angioedema. *Nurse Pract*. 2015; 40(10):1-6. <https://doi.org/10.1097/01.npr.0000471366.32982.f2>
- Gu H, Li L, Gu M, Zhang G. Association between *Helicobacter pylori* Infection and chronic urticaria: a meta-analysis. *Gastroenterol Res Pract*. 2015; 2015:486974. <https://doi.org/10.1155/2015/486974>
- Sugrañes-Montalván A, Barreto-Suárez E, Nicolau-Pestana E, Quesada-Leyva L. Relación entre infección por *Helicobacter pylori* y urticaria crónica. *Rev Alerg Mex*. 2017; 64(4):396-402. <https://doi.org/10.29262/ram.v64i4.283>
- Vezir S, Kaya F, Vezir E, Karaosmanoğlu N, Adiloğlu AK. Evaluation of intestinal parasites in patients with chronic spontaneous urticaria in a territory hospital in Turkey. *J Infect Dev Ctries*. 2019; 13(10):927-32. <https://doi.org/10.3855/jidc.11552>
- Shakouri A, Compalati E, Lang DM, Khan DA. Effectiveness of *Helicobacter pylori* eradication in chronic urticaria: evidence-based analysis using the grading of recommendations assessment, development, and evaluation system. *Curr Opin Allergy Clin Immunol*. 2010; 10(4):362-9. <https://doi.org/10.1097/aci.0b013e32833c79d7>
- Bruscky DMV, da Rocha LAR, Costa AJF. Recurrence of chronic urticaria caused by reinfection by *Helicobacter pylori*. *Rev Paul Pediatr*. 2013; 31(2):272-5. <https://doi.org/10.1590/S0103-05822013000200021>
- Niv Y, Hazazi R. *Helicobacter pylori* recurrence in developed and developing countries: meta-analysis of 13C-urea breath test follow-up after eradication. *Helicobacter*. 2008; 13(1):56-61. <https://doi.org/10.1111/j.1523-5378.2008.00571.x>
- Kim HJ, Kim Y-J, Lee HJ, Hong JY, Park AY, Chung EH, et al. Systematic review and meta-analysis: Effect of *Helicobacter pylori* eradication on chronic spontaneous urticaria. *Helicobacter*. 2019; 24(6):e12661. <https://doi.org/10.1111/hel.12661>
- Yadav MK, Rishi JP, Nijawan S. Chronic urticaria and *Helicobacter pylori*. *Indian J Med Sci*. 2008; 62(4):157-62.
- Muñoz-López F. *Helicobacter pylori* and allergic disease. *Allergol Immunopathol*. 2003; 31(5):253-8. [https://doi.org/10.1016/s0301-0546\(03\)79191-5](https://doi.org/10.1016/s0301-0546(03)79191-5)
- Ferrer M, Luquin E, Sanchez-Ibarrola A, Moreno C, Sanz ML, Kaplan AP. Secretion of cytokines, histamine and leukotrienes in chronic urticaria. *Int Arch Allergy Immunol*. 2002; 129(3):254-60. <https://doi.org/10.1159/000066772>
- Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, et al. The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology*. 2016; 151(1):51-69. <https://doi.org/10.1053/j.gastro.2016.04.006>

