CASE REPORT

**Case Report: Resolution of chronic urticaria following treatment of odontogenic infection [version 3; peer review: 3 approved]**

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**Abstract**

**Background:** Chronic spontaneous urticaria (CSU) is a condition characterised by the presence of hives with/without angioedema, that affects individuals on more days than not for 6 weeks or more. The role of infection as a potential trigger for CSU is well described, but the current clinical guidelines do not recommend routine screening for underlying infections.

**Main observations:** We report a case of severe prolonged chronic spontaneous urticaria in a 19-year-old, that went into rapid remission following the treatment of dental infection.

**Conclusions:** Clinicians should recognise the potential role that infection can have in causing chronic urticaria. There should be a low threshold to treat infection in such circumstances.

**Keywords**

Chronic Spontaneous Urticaria, Dental Infection

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**Open Peer Review**

**Approval Status**

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**version 2**

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14 May 2019

**version 1**

02 Nov 2018

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1. **Sinisa Savic**, University of Leeds, Leeds, UK

2. **Patrick Yong**, Royal Surrey County Hospital, Guildford, UK

3. **Riccardo Asero**, Clinica San Carlo, Paderno Dugnano (Milan), Italy

Any reports and responses or comments on the article can be found at the end of the article.
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Author roles: Tadros S: Writing – Original Draft Preparation; Bahal S: Writing – Review & Editing; Nagendran V: Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

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Discussion

Chronic spontaneous urticaria (CSU) is defined as daily or almost daily urticaria for at least 6 weeks. In up to 50% of patients, urticaria may be associated with episodes of angioedema. These features are the result of degranulation of mast cells with the release of granule contents, predominantly histamine. Patients often present to their GP and are referred for further assessment and management by Immunologists, Allergists or Dermatologists when first line treatment with antihistamines fail to control the symptoms. The mainstay of treatment is high dose antihistamines and leukotriene receptor antagonists. In recent years, the anti-IgE monoclonal antibody therapy, Omalizumab, has been used as an effective treatment for patients who fail to respond to first and second line therapy.

In cases of CSU, triggers such as food-based allergens or airborne allergens are rarely implicated. In acute urticaria (defined as having a duration of less than 6 weeks), causes are more likely to be identified. In one study of 79 cases of acute urticaria, 36.7% were secondary to infection. A number of studies have demonstrated an increased prevalence of oropharyngeal infections including dental infections, sinusitis and tonsillitis in patients with chronic urticaria. An early study from 1964 demonstrated radiological evidence of focal dental infection in 29% of their cohort of patients with chronic urticaria. In addition, cases have been reported of resolution of urticaria after treatment of dental infections. In one case bacterial cultures from dental lesions grew the gram-negative bacteria Veillonella parvula. It is thought that lipopolysaccharide from gram negative bacteria induces an inflammatory response characterised by histamine release from mast cells and resulting urticaria.

Other infections reported to be associated with CSU include Helicobacter pylori which is known to have immunomodulatory effects. However, H. pylori eradication in CSU patients has had mixed results. Infection with viral hepatitis has also been associated with CSU and guidelines suggest performing a hepatitis screen if transaminases are abnormal. However, a systematic review on the subject revealed that the prevalence of hepatitis B and hepatitis C was no greater in CSU patients than compared with the general population.

The presented case history demonstrates the close temporal relationship between treatment of dental infection and the improvement of urticaria and reduction in medication requirements. Inflammatory markers were not monitored in this case but may have been elevated. Measurement of markers of the acute inflammatory response, including CRP, can easily be included in assessment of patients with chronic urticaria. Together with a careful history, an elevation in acute inflammatory markers, may highlight the presence of infection/inflammation. Where infection has been excluded, the elevated inflammatory markers may identify patients with more severe chronic urticaria.

Our patient had failed first and second line treatments for chronic urticaria with persistent and troublesome symptoms.
With a UAS >28, demonstrating poorly controlled chronic urticaria, he was eligible to commence anti-IgE therapy\(^1\). Monoclonal antibody anti-IgE treatment with Omalizumab is now provided by some immunology and dermatology units in the UK. Patients are given Omalizumab by sub-cutaneous injection once a month for 6 months, and their response is monitored throughout. Although relatively safe, any new treatment is not without the risk of side effects. In addition, the treatment is costly, and should be reserved for patients who have severe CSU that fail to respond to treatment with the maximum dose of anti-histamine treatment and leukotriene receptor antagonists.

Our case history illustrates the importance of searching for infections, including odontogenic infections, prior to commencing immunosuppression or anti-IgE therapy in patients who are resistant to first line treatment of CSU.

**Consent**

Written informed consent was obtained from the patient for the publication of their clinical details.

**Data availability**

No data is associated with this article.

**Grant information**

The author(s) declared that no grants were involved in supporting this work.

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**References**


Open Peer Review

Current Peer Review Status: ✓ ✓ ✓

Version 3

Reviewer Report 10 June 2019

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✓ Riccardo Asero
Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (Milan), Italy

The authors have responded to my comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Allergology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 31 May 2019

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? Riccardo Asero
Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (Milan), Italy

Tadros and co-workers report a case of severe chronic urticaria unresponsive to second generation antihistamines given at higher than licensed doses that resolved following the treatment of dental infection.
General comments
The clinical case is nicely described and easy to follow.

Specific points
The authors completely overlook the last version of the EAACI/GA²LEN/EDF/WAO guidelines¹ that address most of the points discussed in the present article.

The role of infection of CSU has long been debated (as also shown by the fact that many of the cited references are dated) but an unquestionable proof is missing. Those who, like this reviewer, have been dealing with urticaria patients for decades can easily remember that many years ago patients underwent systematically dental X-rays followed by root canal treatment (when necessary), in most cases without any benefit on the skin disease. The same holds true for eradication of H. pylori infection. The EAACI guidelines include the research for infectious disease within the “extended diagnostic program”, based on clinical history.

CRP is included on the routine diagnostic tests to be performed in all CSU patients. The last part of the discussion addresses Omalizumab, but this is out of scope of the present case report as this drug was eventually not given.

Minor points
The maximum theoretical score of UAS 7 is 42 (6 x 7) and not 40.

References

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Allergology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have
significant reservations, as outlined above.

Reviewer Report 31 May 2019

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Patrick Yong
Department of Allergy and Clinical Immunology, Royal Surrey County Hospital, Guildford, UK

This report presents a case of CSU which improved following treatment of dental infection. This is a recognised association with CSU, and serves as a useful reminder to clinicians treating patients with CSU.

The case report and summary of the literature is concise and to the point. The only suggestion I would make is that it may be worth citing other urticaria guidelines (e.g. EAACI 2018 which is more recent), and making it clearer in the introduction that infection (along with various other causes) is listed as a cause of CSU in guidelines. Extended testing for the various causes is guided by the history. Also, some of the initial tests in the EAACI guidelines i.e. FBC/CRP can give a hint that there may be infection.

One small correction in the case report is that the UAS7 score has a maximum of 42, not 40.

Is the background of the case's history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Yes

Is the case presented with sufficient detail to be useful for other practitioners? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Sinisa Savic

Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, University of Leeds, Leeds, UK

The authors have adequately addressed all my comments.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
This case report describes a patient who developed CSU refractory to 1st and 2nd line therapies. His CSU resolved promptly after treatment of the concurrent dental infection.

This case illustrates importance of searching for underlying causes of CSU as part of routine clinical assessment. The authors state that routine infection screen is not recommended by the current guidelines, however the guidelines state: ‘The diagnosis is based primarily on the clinical history. Investigations are determined by the clinical history and presentation, but may not be necessary’. Although infection screen is not specifically mentioned, taking a thorough clinical history as suggested by the guidelines should include enquiry about possible infections and subsequent investigations might include an infection screen.

One of the reasons why infections might be overlooked when assessing CSU, is that the past recommendations for routine screening for H. Pylori and its eradication failed to produce desired outcomes. There are other examples in the literature where chronic infection has been linked with CSU, and one such example is HepC and HepB. However, a comprehensive review of the literature failed to find an obvious associations, and routine screening is not recommended.

In summary, this is well written article with a useful message, but discussion regarding the role of infection triggers in CSU should be more comprehensive and include the points mentioned above.

References

Is the background of the case’s history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: Clinician scientist (clinical immunology and allergy), areas of interest: auto-inflammatory disorder, chronic urticaria, primary immunodeficiency, drug allergies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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