



CASE REPORT

REVISED 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



This article is included in the **Royal College of Pathologists** gateway.

Open Peer Review

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- Sinisa Savic** , University of Leeds, Leeds, UK
- Patrick Yong**, Royal Surrey County Hospital, Guildford, UK
- 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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REVISED Amendments from Version 2

We have made some minor changes. The maximum UAS7 score is now stated as 42. We have also cited the latest EAACI Urticaria Guidelines.

See referee reports

Introduction

Urticaria is a dermatological disorder that manifests as raised erythematous lesions that range in size. They are pruritic and typically resolve with no changes to the appearance of the skin. Urticarial lesions may be associated with episodes of swellings known as ‘angioedema’. The role of infection as a potential trigger for urticaria and angioedema is well described but the precise mechanism by which infection induces release of histamine from mast cells is unknown. Infections, including dental infections, have been associated with urticaria; however, current chronic urticaria guidelines do not recommend routine screening for underlying infection^{1,2}. Instead, they advise targeted investigations, based on the clinical history and examination findings. We report a case of severe chronic spontaneous urticaria that rapidly resolved following root canal treatment.

Case report

A 19-year-old male patient was referred to the Immunology clinic by his General Practitioner (GP). He presented with a two-month history of urticaria with intermittent episodes of angioedema. His initial symptoms included facial pruritis, periorbital erythema and angioedema involving the upper and lower lips. Within 30 minutes of his first episode of angioedema, he developed widespread urticaria which responded to treatment with antihistamines. The following day, he experienced a recurrence of the symptoms and continued to have almost daily symptoms of urticaria with intermittent episodes of angioedema. He was commenced on an alternative anti-histamine by his GP but continued to develop urticaria and experience swellings of the hands and feet. His treatment was escalated at his initial visit to Immunology Clinic to fexofenadine 180mg twice a day with an additional 10–20mg of cetirizine. In addition, montelukast, a leukotriene receptor antagonist, was commenced.

The number of hives and degree of pruritis were graded using an objective scoring system known as the Urticaria Activity Score 7 (UAS7) that provides a weekly average score out of a maximum score of 42. The patient recorded weekly UAS7 scores of 30, despite treatment with maximum doses of antihistamines and montelukast. Therefore, Anti-IgE therapy with the monoclonal antibody ‘Omalizumab’ was offered. In the interim, he presented to his dentist with a broken tooth and was found to have carious molars requiring root canal treatment. One week after this intervention, his UAS7 score fell to 4 and then to 0, and he has remained in remission (UAS 7 score 0) for 9 months. As he was rather needle-phobic, he was delighted that this obviated the need for Omalizumab injections. Initial investigations including full blood count, renal function, liver function and thyroid function tests were all within the normal ranges.

Discussion

Chronic spontaneous urticaria (CSU) is defined as daily or almost daily urticaria for at least 6 weeks¹. In up to 50% of patients, urticaria may be associated with episodes of angioedema³. 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 antagonists¹. 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 implicated⁴. 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 infection⁵.

A number of studies have demonstrated an increased prevalence of oropharyngeal infections including dental infections, sinusitis and tonsillitis in patients with chronic urticaria^{3,6,7}. An early study from 1964 demonstrated radiological evidence of focal dental infection in 29% of their cohort of patients with chronic urticaria³. In addition, cases have been reported of resolution of urticaria after treatment of dental infections^{8,9}. In one case bacterial cultures from dental lesions grew the gram-negative bacteria *Veillonella parvula*¹⁰. It is thought that Lipopolysaccharide from gram negative bacteria induces an inflammatory response characterised by histamine release from mast cells and resulting urticaria¹¹.

Other infections reported to be associated with CSU include *Helicobacter pylori* which is known to have immunomodulatory effects¹². However, *H. pylori* eradication in CSU patients has had mixed results^{13–15}. Infection with viral hepatitis has also been associated with CSU^{16,17} and guidelines suggest performing a hepatitis screen if transaminases are abnormal¹. 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 population¹⁸.

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 elevated¹⁹. 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 urticaria²⁰.

Our patient had failed first and second line treatments for chronic urticaria with persistent and troublesome symptoms.

With a UAS 7 >28, demonstrating poorly controlled chronic urticaria, he was eligible to commence anti-IgE therapy²¹. 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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Riccardo Asero 

Ambulatorio di Allergologia, Clinica San Carlo, Milan, Italy

The authors have responded to my comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Allergology.

I have read this submission. I 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, 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.

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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 have read this submission. I 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

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

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

Version 1

Reviewer Report 01 April 2019

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Sinisa Savic 

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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 outcomes¹. 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 recommended².

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.

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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 have read this submission. I 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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