

### Articular angioedema in patients with chronic spontaneous urticaria is frequently misdiagnosed as arthritis

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#### Clinical Implications

- This report shows that angioedema of the hands and feet, in patients with chronic spontaneous urticaria, can mimic arthritis/arthralgia. This can lead to unnecessary and ineffective treatment and to a delay of effective treatment. The clinical implications of these findings include that patients with chronic spontaneous urticaria who report episodes of joint pain should be assessed for recurrent angioedema and treated appropriately.

Chronic spontaneous urticaria (CSU) is characterized by the occurrence of itchy wheals, recurrent angioedema, or both, for longer than 6 weeks. About 50% of patients with CSU develop wheals but no angioedema. Thirty-five percent have both wheals and angioedema, and 15% exclusively develop angioedema, the severity of which is independent on Urticaria Activity Score (UAS7).<sup>1-3</sup> Comorbidities such as fatigue, depression, shortness of breath, and autoimmunity are well recognized in patients with CSU. Occasionally, patients complain about episodes of joint pain and articular swelling, which evolve mainly when whealing and/or angioedema attacks are frequent and are localized at hands and feet. Some of these cases are misdiagnosed as arthritis (especially when angioedema is exclusive).<sup>4</sup> How often this happens and what consequence this has is currently unknown. We therefore assessed the frequency of joint pain in patients with CSU, we investigated the diagnostic workup and treatment of patients with CSU with joint pain, and we characterized patients with CSU with joint pain with respect to their disease characteristics including the occurrence of wheals and angioedema as well as their response to treatment.

This study included 420 patients with CSU who visited our 3 outpatient clinics in the north of Israel, between 2018 and 2019, covering a population of more than 1 million people. All patients were prospectively assessed for the occurrence of extracutaneous signs and symptoms of their urticaria with the help of a questionnaire, which was filled and updated at each visit (see [Figure E1](#) in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The study was approved by our Local Ethical Committee of the Bnai-Zion Medical Center, Israel. Patients who indicated that they had experienced episodes of joint pain/arthralgia during the course of their urticaria were classified as having mild, moderate, or severe articular involvement. Episodes of arthralgia/arthritis (see [Figure 1](#)) were assessed in relation to disease duration and response to treatment. CSU activity was assessed using the UAS7, a validated patient-report outcome assessing daily pruritus and number of wheals during 1 week (range, 0-42).<sup>5</sup>

Of 420 patients with CSU, 60 patients (14%) experienced recurrent episodes of joint pain, which we divided into 3 groups: mild, moderate, and severe (see [Table I](#)). In 37 (61%) of these 60 patients, joint pain appeared when CSU disease activity was high (UAS7 > 30), and wheals were the main symptom (frequently involving hands and feet) with minimal angioedema. In these patients, joint pain occurred (1-2 times/wk), was located primarily at the hands and feet, and was usually of 8- to 10-hour duration. High-dose antihistamines, a short course of oral glucocorticoid treatment, or omalizumab achieved remission of whealing as well as joint pain. Episodes of joint pain did not reoccur when patients remained on high-dose antihistamines or on omalizumab. In the other 23 (38%) of 60 patients with recurrent episodes of joint pain, angioedema, mainly articular angioedema (occasionally involving lips and eyes), was the main underlying cause, but the patients were referred to a rheumatologist. In 10 of these patients, with moderate angioedema lasting 10 to 14 hours, rheumatologists recognized that periarticular angioedema rather than arthritis was the cause of joint pain. A good response to high-dose antihistamines and few days of oral steroids established the diagnosis of CSU rather than arthritis. The remaining 13 patients had episodes of severe angioedema lasting the whole day, and were treated for arthritis with nonsteroidal anti-inflammatory drugs, sulfasalazine, short courses of oral glucocorticoids, and/or methotrexate, before periarticular angioedema was diagnosed at an urticaria specialist center. All relevant serological analyses were normal (anti nuclear antibody, rheumatoid Factor, and anti-citrullinated proteins). In all these cases, joint pain ceased to occur when therapy for CSU (high-dose antihistamines or omalizumab) was initiated.

Our report shows that episodes of joint pain, in patients with CSU, can be linked to periarticular angioedema, but are occasionally suspected to be due to arthritis. Episodes of mild joint pains and swelling are distinguished relatively fast from true arthralgia. However, when angioedema of hands and feet is moderate to severe and urticarial hives are few, arthritis is frequently misdiagnosed. Longer bouts of joint pain are occasionally suspected to be due to arthritis and treated as such,



**FIGURE 1.** Episode of hand angioedema involving Metacarpophalangeal (MCP) and Proximal Interphalangeal (PIP) joints, lasting less than 24 hours.

**TABLE I.** Patients with CSU with joint pains (60 of 420 [14%])

Joint involvement	CSU\Angioedema symptoms	Occurrence of joint pains	Duration of joint pains (h)	Treatment response
Mild (n = 37 [61%])	Hives, involve hands and feet. Minimal angioedema	1-2 episodes weekly	8-10	Joint pains resolved after high-dose antihistamines
Moderate (n = 10 [17%])	Occasionally hives and mainly angioedema involving hands and feet	Daily	10-14	Joint pains resolved or decreased significantly after 2-3 d of oral steroids and omalizumab
Severe (n = 13 [22%])	Angioedema mainly with minimal/no hives involving hands and feet	Daily	24	Unresponsive to salazopyrine or nonsteroidal anti-inflammatory drugs. Partially responded to high-dose antihistamines, but resolved after treatment with omalizumab

thereby delaying effective treatment of the underlying angioedema. The beneficial response to high-dose antihistamines and omalizumab and the lack of serological markers of rheumatic diseases makes arthritis in these cases unlikely. Acknowledging angioedema as the cause of joint pain can prevent unnecessary treatments and focus on relevant therapies for CSU.

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Conflicts of interest: E. Toubi has received honoraria (as a speaker) from Novartis and Sanofi. A. M. Giemenz-Arnau is medical advisor for Uriach Pharma, Genentech, Novartis, FAES, GlaxoSmithKline (GSK), Sanofi, AMGEN, and ASTRAZENECA; has received research grants supported by Uriach Pharma and Novartis; has received grants from Instituto Carlos III-FEDER; and has conducted educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO-PHARMA, GSK, MSD, Almirall, and Sanofi. M. Maurer has received honoraria (advisory board, speaker) and/or institutional grant/research support from Allakos, Amgen, AstraZeneca, Bayer, Dr Pflieger, FAES, Genentech, GSK, Innate Pharma, Kyowa Kirin, Lilly, Merckle Recordati, Moxie, Novartis, Regeneron, Roche, Sanofi, MSD, UCB, and Uriach. Z. Vadasz has received honoraria (as a speaker) from Novartis, Kamada, Rafa, and Sanofi.

Received for publication February 10, 2020; revised April 21, 2020; accepted for publication May 22, 2020.

Available online June 7, 2020.

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**ONLINE REPOSITORY**

Date: .....

Initials: .....

Age/Gender

CSU since (M/Y): .....

CSU severity (UAS7): .....

Angioedema (location): .....

Joint Pain: Mild  Moderate  Severe

Location: Hands  Feet  Others  .....

Occurrence: 1-2\week  Daily

Duration: 8-10H  10-14H  Whole day

Treatment:

1. High dose H1-antihistamine (dose/duration): .....

Response: poor response  moderate response  complete response

2. Oral Steroids (dose/duration):.....

Response: poor response  moderate response  complete response

3. Omalizumab (dose/duration): .....

Response: poor response  moderate response  complete response

**FIGURE E1.** A questionnaire for the presence of articular symptoms filled by patients with CSU at each visit.