

Giornale Italiano di Dermatologia e Venereologia

=====

Title: Urticarial eruption in a patient with intermittent fever and monoclonal IgM gammopathy  
Paper code: G Ital Dermatol Venereol-6039  
Submission Date: 2018-04-11 10:42:28  
Article Type: Letter to the Editor

Files:

- 1): Manuscript  
Version: 2  
Description: manoscritto originale  
File format: application/msword
- 2): Figures 1  
Version: 1  
Description: Figura 1  
File format: image/tiff
- 3): Figures 2  
Version: 1  
Description: Figura 2  
File format: image/tiff

PEER REVIEW COPY  
Giornale Italiano di Dermatologia e Venereologia

## Urticarial eruption in a patient with intermittent fever and monoclonal IgM gammopathy

Genovese G<sup>1</sup>, Marzano AV<sup>1</sup>, Ferrucci SM<sup>1</sup>

<sup>1</sup> Unità Operativa di Dermatologia, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

**Corresponding author:** *Giovanni Genovese*, M.D. ; E-mail: [giov.genov@gmail.com](mailto:giov.genov@gmail.com); Phone number: +393338756183; Fax number: +390255033562

Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Unità Operativa di Dermatologia, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milano, Italy  
Via Pace, 9 – 20122 Milano

**Manuscript word count:** 599 words; **Figures:** 2; **Tables:** 0

**Running head:** urticarial rash, fever and IgM gammopathy

**Keywords:** Schnitzler's syndrome; paraproteinemia; immunoglobulin M; urticarial rash; autoinflammation

**Funding/support:** none; **Conflicts of interest:** none; **Acknowledgements:** none.

**Author contributions:** Dr. Genovese and Dr. Ferrucci had full access to all of the data in the study and take responsibility for the integrity of the data. **Analysis and interpretation of data:** Dr. Genovese, Dr. Ferrucci, Prof. Marzano. **Drafting of the manuscript:** Dr. Genovese. **Critical revision of the manuscript:** Prof. Marzano, Dr. Ferrucci

Dear Editor,

Schnitzler's syndrome (SchS), first described by Liliane Schnitzler in 1972,<sup>1</sup> is an acquired autoinflammatory disease of unknown origin whose main clinicopathological features are recurrent episodes of urticarial rash with neutrophilic dermal infiltrate, intermittent fever and monoclonal IgM – or more rarely IgG – gammopathy.<sup>2</sup> Due to the rarity of this entity, the diagnosis is usually achieved with an average delay of five or more years from disease onset.<sup>3</sup>

A 55-year-old woman presented with a 4-year history of chronic urticaria-like rash unresponsive to first- and second-generation oral antihistamines and systemic corticosteroids. In the last year, the skin eruption was accompanied by intermittent fever, fatigue, and diffuse arthralgias. Lymphadenopathy was absent. Physical examination revealed red, slightly raised, and partially coalescing plaques involving the entire skin surface except for the head and hands (Fig. 1). She also complained of mild pruritus. Laboratory exams dating back to the onset of cutaneous manifestations had revealed neutrophilic leukocytosis, increased levels of C-reactive protein (CRP) (110 mg/dl) and a monoclonal immunoglobulin (Ig) M $\kappa$  component (8.3 g/l). Cryoglobulins were absent. Ferritin levels were normal. Haemoglobin, liver function and renal function tests were within the normal range. Histopathological analysis of a recent urticarial plaque located on the right arm showed mild acanthosis and a perivascular and interstitial dermal infiltrate of neutrophils associated with leukocytoclasia, in absence of vasculitis, fibrinoid necrosis or significant dermal edema (Fig. 2). Direct and indirect immunofluorescence tests were negative. According to Strasbourg criteria, a diagnosis of SchS was made.<sup>4</sup> Bone marrow biopsy showed ruled out Waldenström macroglobulinemia revealing no lymphoplasmacytic infiltration, and the anti-IL-1 receptor antagonist anakinra was initiated.

Although it has been demonstrated that pro-inflammatory cytokines, in particular IL-1 $\beta$ , trigger inflammasome activation playing a crucial role in the pathogenic pathway related to SchS

interleukin-1 blocking agents represent the mainstay of therapy, the pathophysiology of the disease remains not completely understood and the role of IgM paraprotein is still unclear, as it may precede or follow first clinical manifestations of the disease.<sup>4</sup>

The diagnosis is made according to Strasbourg criteria,<sup>4</sup> which enclose two major criteria (chronic urticarial eruption and monoclonal IgM or IgG) and four minor criteria (recurrent fever; bone remodeling assessed by scintigraphy, magnetic resonance imaging or increased bone alkaline phosphatase; neutrophilic dermal infiltrate on cutaneous biopsy; leucocytosis and/or elevated CRP). Both major criteria and at least two minor criteria are necessary for a definite diagnosis of SchS. In our case, the patient satisfied both major criteria and three minor criteria (fever, laboratory and histopathological findings). Furthermore, in presence of high levels of the monoclonal component, bone marrow biopsy need to be performed in order to rule out Waldenström macroglobulinemia.<sup>2</sup>

The typical histopathological pattern of SchS skin lesions, observed also in our patient, is a dermal neutrophilic infiltrate, usually with a perivascular distribution. The neutrophils may also be dispersed among the collagen bundles. More rarely, a focal neutrophilic infiltrate may be seen around eccrine glands. These findings correspond to the histopathological entity described as “neutrophilic urticarial dermatosis”.<sup>2</sup> Eosinophilic or mild mononuclear cell infiltrate with a perivascular pattern generally represent a minor histopathological component. Leukocytoclasia may be seen. However, unlike urticarial vasculitis, vasculitis should be lacking, as well as fibrinoid necrosis within blood vessels. Lastly, the absence of dermal oedema allows excluding Sweet’s syndrome.<sup>2</sup>

In conclusion, this case emphasizes the need for high index of suspicion, careful clinicopathologic evaluation, and close collaboration between dermatologists, hematologists and pathologists in order to avoid diagnostic delay in patients affected by SchS. Correlation of clinical, serologic, and histopathologic data may help to rule out other diseases in the differential diagnosis and start a prompt treatment with IL-1 antagonists.

## References

- 1) Schnitzler L. Chronic permanent urticarial lesions (erythema petaloide?). *J Dermatol Angers* 1972; **46**.
- 2) Gusdorf L, Lipsker D. Schnitzler Syndrome: a Review. *Curr Rheumatol Rep* 2017; **19**: 46.
- 3) de Koning HD. Schnitzler's syndrome: lessons from 281 cases. *Clin Transl Allergy* 2014; **4**:41.
- 4) Simon A, Asli B, Braun-Falco M, et al. Schnitzler's syndrome: diagnosis, treatment and follow-up. *Allergy* 2013; **68**:562-8.

PEER REVIEW COPY  
Giornale Italiano di Dermatologia e  
Venereologia

**Figures legend**

**FIGURE 1** | Erythematous urticarial plaques on the back (a), left arm (b), and abdomen (c)

**FIGURE 2** | Histology showing a predominantly neutrophilic dermal infiltrate without vasculitis or significant dermal oedema.

PEER REVIEW COPY  
Giornale Italiano di Dermatologia e  
Venereologia





