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Chronic Spontaneous Urticaria with Coexisting Cholinergic Urticaria and Monoclonal Gammopathy: A Diagnostic Challenge in the Differential Diagnosis of Schnitzler Syndrome – A Case Report

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Abstract:

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that can coexist with inducible urticaria subtypes and systemic abnormalities, complicating diagnosis and management. The incidental finding of monoclonal gammopathy in such patients may raise suspicion for rare autoinflammatory disorders, particularly Schnitzler syndrome (SchS), making careful differential diagnosis essential. We report a 58-year-old male with a 4-year history of recurrent urticaria triggered by exertion, heat, and emotional stress. Laboratory evaluation revealed elevated immunoglobulin M (IgM) level with monoclonal gammopathy, positive autologous serum skin test (ASST), and a positive exercise challenge test. Although both major Strasbourg criteria for SchS were present, no minor criteria were fulfilled. A diagnosis of CSU with coexisting cholinergic urticaria was established, and continuous treatment with second-generation antihistamines resulted in clinical improvement. This case highlights the importance of careful differential diagnosis in patients with CSU and monoclonal gammopathy. The presence of MGUS requires multidisciplinary evaluation and long-term hematologic follow-up.

Keywords:

Chronic spontaneous urticaria; Chronic inducible urticaria; Cholinergic urticaria; Monoclonal gammopathy (MGUS); Schnitzler syndrome; case report.

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Background

Chronic spontaneous urticaria (CSU) is characterized by recurrent wheals, angioedema, or both, persisting for more than six weeks without an identifiable trigger **[1]**. Its pathophysiology involves mast cell activation and the release of histamine and other inflammatory mediators **[2]**. The condition affects approximately 1-4% of the

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general population and significantly impairs quality of life **[1]**. CSU frequently coexists with other conditions, particularly chronic inducible urticaria (CIndU), autoimmune diseases, and allergies **[3]**. Moreover, in 10 to 20% of cases, potential triggering factors such as medications, physical stimuli, and stress can be identified, further highlighting the heterogeneity of the disease **[4]**.

Among inducible forms, cholinergic urticaria represents a common subtype of CIndU **[5]** associated with sweating and the development of transient pruritic wheals **[6]**. Given this clinical heterogeneity, management of urticaria requires a standardized therapeutic approach. First-line treatment across all urticaria subtypes consists of second-generation H1 antihistamines **[1]**.

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of monoclonal immunoglobulin in the serum and/or urine without evidence of hematologic malignancy **[7]**. It occurs in approximately 5% of individuals over 50 years of age and carries a yearly progression risk of about 1% **[8]**. The coexistence of CSU and monoclonal gammopathy necessitates consideration of rare autoinflammatory syndromes, particularly Schnitzler syndrome (SchS), which is diagnosed based on Strasbourg criteria **[9]**. SchS is a rare autoinflammatory disorder characterized by chronic urticaria and monoclonal IgM gammopathy **[10]**. A recently published multicenter study highlights the underdiagnosis of SchS and emphasizes that patients with prolonged urticarial wheals accompanied by systemic symptoms, such as fever or arthralgia, should be carefully evaluated for this condition **[11]**. Although SchS remains rare, with a limited number of documented cases, its recognition is clinically important due to potential complications and specific therapeutic implications, including the risk of progression to lymphoproliferative disorders such as Waldenström's macroglobulinemia **[10]**.

In the present case, only the two major Strasbourg criteria were fulfilled, while none of the minor criteria were present. This supports exclusion of SchS and highlights the importance of strict adherence to diagnostic criteria to avoid overdiagnosis and unnecessary treatment **[10]**. Monoclonal gammopathy may occur in patients with chronic urticaria, particularly in older adults, and may represent an incidental finding rather than a manifestation of systemic disease necessitating intensive immunotherapy **[12]**.

The aim of this study is to present a case of CSU coexisting with cholinergic urticaria and MGUS, and to highlight the importance of differential diagnosis.

Case Presentation

A 58-year-old male with a four-year history of recurrent urticaria was admitted to the Department of Internal Diseases and Allergology for evaluation of suspected urticarial vasculitis. Skin lesions occurred every 3-4 months, particularly after intense physical activity, exposure to high temperatures, and emotional stress, involving the face, trunk, and extremities. The patient had not received regular treatment for urticaria before admission.

On admission, the patient was in good general condition. Physical examination did not reveal significant abnormalities. Peripheral lymph nodes were not palpable, the tonsils were not enlarged, and no peripheral joint swelling was observed. Laboratory tests revealed elevated immunoglobulin M (IgM) levels (>4.60 initially and 8.29 g/L on repeat testing; reference range: 0.40-2.30 g/L), increased gamma globulin fraction, and monoclonal IgM kappa protein on serum immunofixation. Additionally, free thyroxine (fT4) was decreased (0.811 ng/dL; reference range: 0.93-1.71 ng/dL), while thyroid-stimulating hormone (TSH) remained within the normal range (1.84 µIU/mL; reference range: 0.27-4.20 µIU/mL). Platelet counts were mildly reduced, whereas hemoglobin and leukocyte counts remained within the reference range. C-reactive protein and interleukin-6 were normal. Renal and liver function tests were unremarkable, and urinalysis showed no proteinuria. ANA, anti-dsDNA, ANCA, hepatitis B and C serology, Helicobacter pylori stool antigen, and parasitological stool tests were negative. Abdominal ultrasonography revealed splenomegaly measuring 150 x 64 mm. Chest radiography showed no focal pulmonary consolidations.

A comprehensive allergologic work-up included specific IgE panels for inhalant and food allergens, an autologous serum skin test (ASST), dermographometer provocation, TempTest, and an exercise challenge test on a cycle ergometer. Specific IgE panels were negative. Dermographometer testing and TempTest were negative, whereas ASST and the exercise challenge test were positive. Following exercise provocation,

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generalized transient urticarial wheals developed and resolved within 30 minutes; the photograph documents lesions on the antecubital fossa and forearm (Figure 1). Skin biopsy was not performed because no active spontaneous skin lesions were present during the diagnostic evaluation.

Given the coexistence of urticaria and monoclonal gammopathy, SchS was considered in the differential diagnosis. Assessment using the Strasbourg criteria revealed both major criteria; however, none of the minor criteria were fulfilled, thus excluding a diagnosis of SchS (Table 1). To exclude lymphoproliferative disorders, a hematology consultation was obtained. Hematologic assessment confirmed monoclonal IgM kappa gammopathy with splenomegaly but found no current evidence of proliferative bone marrow disease. A diagnosis of CSU coexisting with cholinergic urticaria and autoreactive CSU was established. Monoclonal IgM kappa gammopathy was considered an important accompanying finding requiring hematologic surveillance.

During discharge planning, the patient was prescribed rupatadine 10 mg once daily. At discharge, the patient was in good general condition. Follow-up recommendations included allergology review and hematology follow-up after four months with repeat IgM measurement and abdominal ultrasonography. No adverse or unanticipated events were recorded during hospitalization. Long-term follow-up outcomes were not available at the time of manuscript preparation.

Discussion

CSU is a heterogeneous condition that may coexist with inducible urticaria subtypes and systemic abnormalities. Current international guidelines recognize that different urticaria phenotypes may occur simultaneously, as observed in this patient **[1]**. To our knowledge, reports describing the coexistence of CSU, cholinergic urticaria, and MGUS without fulfilling SchS criteria remain limited. Despite the lack of follow-up, this case provides important insight into the diagnostic challenges associated with the coexistence of chronic urticaria and monoclonal gammopathy.

From a clinical perspective, it further emphasizes the need for comprehensive diagnostic evaluation, including appropriate specialist consultations and targeted investigations, in patients with CSU presenting with atypical features, such as monoclonal gammopathy or unusual triggers. It also highlights the importance of strict application of diagnostic criteria for rare syndromes such as SchS, as fulfillment of major criteria alone is insufficient without accompanying minor features being present. Furthermore, recognition of overlapping urticaria phenotypes may facilitate earlier diagnosis and allow more individualized therapeutic strategies. Finally, the presence of MGUS necessitates longitudinal hematologic monitoring due to the small but clinically relevant risk of progression to hematologic malignancy, particularly in older individuals **[7, 13]**.

Thyroid abnormalities observed in this patient may be consistent with previously reported associations between chronic urticaria and thyroid dysfunction **[14]**.

Limitations of this case include the absence of histopathological examination and follow-up data at the time of manuscript preparation.

Conclusion

This case underscores the importance of thorough diagnostic evaluation in patients with chronic urticaria, particularly when atypical features such as inducible triggers or monoclonal gammopathy are present. Strict application of diagnostic criteria is essential to avoid misdiagnosis of rare conditions such as SchS. Multidisciplinary management, including monitoring for potential disease progression, remains crucial, especially in patients with MGUS.

Take-Home Messages

Patients with chronic urticaria and monoclonal gammopathy require careful differential diagnosis to distinguish CSU with incidental MGUS from rare systemic disorders such as Schnitzler syndrome.

Fulfilment of the major Strasbourg criteria alone is insufficient for diagnosing Schnitzler syndrome; minor criteria should be systematically assessed before establishing this diagnosis.

Coexisting inducible urticaria, such as cholinergic urticaria, should be actively considered when symptoms are triggered by heat, exertion, or emotional stress.

Multidisciplinary follow-up is important in patients with MGUS because of the potential risk of progression to hematologic disease.

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Declarations

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Figure and Table Legends

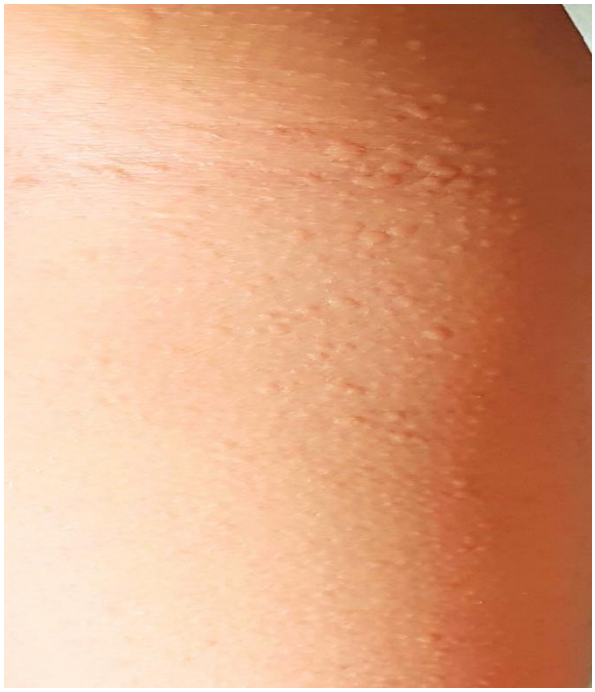

Figure 1. Urticarial wheals on the antecubital fossa and forearm after exercise provocation testing. The exercise challenge induced generalized transient urticaria, while the photograph shows the documented area only. The lesions resolved spontaneously within 30 minutes.

Strasbourg Diagnostic Criteria	**Patient's results**
Obligate criteria:	**Obligate criteria:**
Chronic urticarial rash	criterion met
Monoclonal IgM or IgG	criterion met (monoclonal IgM)
Minor criteria:	**Minor criteria:**
Recurrent fever	criterion not met
Objective findings of abnormal bone remodeling with or without bone pain	criterion not met
A neutrophilic dermal infiltrate on skin biopsy	criterion not met
Leukocytosis and/or elevated CRP	criterion not met
Definite diagnosis: if two obligate criteria and at least two minor criteria if IgM, and three minor criteria if IgG	
Probable diagnosis: if two obligate criteria and at least one minor criterion if IgM, and two minor criteria if IgG	

Table 1. Strasbourg diagnostic criteria for Schnitzler syndrome and their assessment in the presented patient. *Abbreviations: CRP, C-reactive protein; IgG, immunoglobulin G; IgM, immunoglobulin M.*