Case Report on the Rare Diagnosis of Schnitzler’s Syndrome

Varun Srivatsav¹, Ardyth Milne², Karen Holfeld³, Mariam Abbas³

¹Department of Medicine, University of Saskatchewan, Saskatchewan, SK, Canada; ²Division of Rheumatology, Department of Medicine, University of Saskatchewan, Saskatchewan, SK, Canada; ³Department of Medicine, Division of Dermatology, University of Saskatchewan, Saskatchewan, SK, Canada

Corresponding Author: Varun Srivatsav: varun.srivatsav@usask.ca

Submitted: 27 February 2022; Accepted: 30 August 2022; Published: 15 October 2022

DOI: https://doi.org/10.22374/cjgim.v17i4.620

Abstract
A 66-year-old male presented to internal medicine clinic with a 2-year history of an urticarial-like rash with fatigue, decreased appetite, chills, and 45 pounds of weight loss. He had a history of ulcerative colitis diagnosed in 1972, but has not required medication to control his disease for many years. His clinical exam revealed an erythematous blanchable urticarial rash on his trunk and extremities, but was otherwise unremarkable. Investigations revealed leukocytosis of $21.7 \times 10^9/L$ with neutrophilia $19.4 \times 10^9/L$. Microcytic anemia was present with a hemoglobin of $119 \text{ g/L}$, MCV $75.1 \text{ fl}$, TSAT $6\%$, iron $2.6 \text{ umol/L}$, TIBC $44.9 \text{ umol/L}$, and ferritin $1082 \text{ ug/L}$. Thrombocytosis was present with platelets $523 \times 10^9/L$. Serum protein electrophoresis revealed an M-spike of $4.5 \text{ g/L}$ in the gamma globulin region, with immunofixation revealing it to be a monoclonal IgM-type kappa. Given the history of ulcerative colitis and microcytic anemia, the patient underwent a colonoscopy and EGD which were both normal. Skin biopsy performed by dermatology demonstrated urticarial neutrophilic dermatosis. Given the constellation of findings, in consultation with rheumatology and dermatology, the diagnosis of Schnitzler’s syndrome was made as per the Strasbourg criteria. The patient has had improvement of his clinical symptoms on colchicine and is pending provincial approval for use of the IL-1 receptor antagonist Anakinra. Due to the association of the syndrome with lymphoproliferative disorders, the patient underwent a bone marrow biopsy and lymph node biopsy, which demonstrated possible low-grade lymphoma, and the patient is actively followed by hematology for the same.

Résumé
Un homme de 66 ans se rend à la clinique de médecine interne présentant des antécédents d’éruption cutanée urticarienne depuis deux ans ainsi que de la fatigue, une perte d’appétit, des frissons et une perte de poids de 20 kg (45 lb). Il a reçu un diagnostic de colite ulcéreuse en 1972, mais n’a eu besoin d’aucun médicalement pour maîtriser cette affection pendant de nombreuses années. L’examen physique révèle la présence d’une urticaire érythémateuse sur le tronc et les membres qui blanchit au toucher, mais qui est par ailleurs sans particularité. Les examens de laboratoire révèlent une leucocytose de $21.7 \times 10^9/l$ et une neutrophilie de $19.4 \times 10^9/l$. Une anémie microcytaire est présente, appuyée par un taux d’hémoglobine de $119 \text{ g/L}$, un volume...
Case Description

A 66-year-old male was initially referred to the internal medicine clinic for assessment of his anemia and urticarial rash. His medical history is largely unremarkable, excluding ulcerative colitis diagnosed in 1972, which he reports has been in remission for many years on no medications.

The patient described a 1-year history of fatigue, decreased appetite, 45 pounds of weight loss, and intermittent chills. Additionally, he has been struggling with a chronic nonproductive cough. He also described arthralgia of his knee joints bilaterally, as well as myalgia of his lower limbs. He also stated that as of 2 years, he has had a rash consisting primarily of widespread rose-colored macules and slightly raised plaques on his chest and back, which migrates in location and disappears within 24 hours (Figures 1 and 2). Interestingly, he also reported having rashes on his legs and soles. He stated that the rash was occasionally pruritic. Otherwise, his physical examination was normal.

Investigations revealed a leukocytosis of $21.7 \times 10^9/L$ with neutrophilia $19.4 \times 10^9/L$. The differential was otherwise normal. A microcytic anemia was present with a hemoglobin of 119 g/L, MCV 75.1 fl, TSAT 6%, iron 2.6 umol/L, TIBC 44.9 umol/L, and ferritin 1082 ug/L. Thrombocytosis was present with platelets $523 \times 10^9/L$. Peripheral blood smear revealed hypochromic and microcytic RBCs, but was otherwise normal with TSH 1.76 mIU/L. Investigation also revealed the following results: vitamin B12 278 pmol/L, LDH 153 U/L, Na 136 mmol/L, K 4.2 mmol/L, Cl 100 mmol/L, urea 3.3 mmol/L, creatinine 77 umol/L, and calcium 2.20 mmol/L. Urine analysis was negative for protein and blood. Hepatic function showed a bilirubin count of 7 umol/L, ALP 85 U/L, and ALT 12 U/L. Additional serology showed an RF $< 13$ IU/ml, anti-CCP $< 4.6$ CU, and ANA negative.

Keywords: Schnitzler’s syndrome, leukocytosis, anemia, thrombocytosis, and monoclonal IgM
to hematology for a lymph node and bone marrow biopsy to rule out an associated lymphoproliferative disorder. Lymph node core biopsy and flow cytometry of the left axillary lymph node showed no evidence of non-Hodgkin's lymphoma or metastatic tumor, but rather features were suggestive of dermatopathic lymphadenitis. Bone marrow biopsy and flow cytometry showed a mildly hypercellular marrow age with trilineage hematopoiesis, and no frank evidence of lymphoplasmacytic lymphoma or clonal plasma cell population. However, there was the presence of mildly increased CD20-positive B-cell population (5–10%) with immunoglobulin heavy-chain clonality testing performed recently demonstrating clonal immunoglobulin heavy chain rearrangement. This supports the possible diagnosis of a small population of low-grade B-cell lymphoma involving the bone marrow. The patient is pending reevaluation by hematology for the same.

A trial of dapsone (100 mg po daily) demonstrated no improvement after a few weeks of treatment, along with worsening of symptoms such as myalgias and chills, which led to discontinuation of the therapy. The patient was then placed on colchicine 0.6 mg BID and an application has been placed for provincial drug coverage of Anakinra (IL-1 receptor antagonist). He has received IV iron infusions for his iron deficiency anemia. Follow-up after 2 months, following the use of colchicine, resulted in reported improvement of the patient’s appetite, cough, chills, rash, fatigue, and myalgia. ESR has elevated to 78 mm/h. Repeat lab work shows an improved leukocytosis of 11.4 × 10^9/L with neutrophils of 6.8 × 10^9/L. His thrombocytosis has improved slightly with a platelet count of 499 × 10^9/L. Hemoglobin is 122 g/L with MCV 75.8. He will be closely followed by internal medicine, rheumatology, dermatology, and hematology departments with the hope for a robust response with Anakinra once approval has been obtained.

Discussion

Schnitzler’s syndrome was first discovered by the French dermatologist Liliane Schnitzler in 1974.1 It is similar in presentation to the hereditary autoinflammatory disease cryopyrin-associated periodic syndromes (CAPS).2 It is an extremely rare disorder, with the published literature mostly consisting of case series, with about 300 cases said to be reported worldwide.3,4

This syndrome is characterized by a few cardinal clinical and laboratory features. The median onset of the syndrome is

Figure 2. Urticarial-like rash on the trunk of the patient.

Immunoglobulin levels were IgG 20 g/L (normal 5–17 g/L), IgM 5.85 g/L (normal 0.44–2.47 g/L), and IgA 1.97 g/L (normal 0.87–3.94 g/L). Serum protein electrophoresis revealed an M-spike of 4.5 g/L in the gamma globulin region, with immunofixation revealing it to be a monoclonal IgM, type kappa. Serum-free light chains revealed a Kappa/Lambda ratio of 2.18. Urine protein electrophoresis and fixation did not detect any monoclonal light chains. FIT was negative.

Given the history of ulcerative colitis and microcytic anemia, the patient underwent a colonoscopy and EGD which were both normal. A capsule endoscopy study is pending to rule out small bowel bleeding as a cause of the patient’s iron deficiency anemia. CT scan of the chest, abdomen, and pelvis was performed to exclude malignancy and demonstrated a normal spleen and liver. Various mildly prominent lymph nodes were identified within the bilateral axilla, mesentery, and inguinal regions. Within the mesentery, the largest measured 8.5 mm in the upper abdomen. The largest inguinal lymph nodes measured 8.9 and 9.3 mm. The largest node along the left external iliac chain measured 11 mm.

The patient was subsequently referred to dermatology department for skin biopsy of the rash. This demonstrated mild to moderate chronic inflammatory cell infiltrate, consisting of eosinophils and neutrophils around the blood vessels. There was interstitial and epidermal presence of neutrophils. There was no evidence of vasculitis. These findings were morphologically in keeping with neutrophilic urticarial dermatosis. Rheumatology was consulted and a diagnosis of Schnitzler’s syndrome was made given the constellation of findings. The patient was also referred to dermatology for a lymph node and bone marrow biopsy to rule out an associated lymphoproliferative disorder. Lymph node core biopsy and flow cytometry of the left axillary lymph node showed no evidence of non-Hodgkin’s lymphoma or metastatic tumor, but rather features were suggestive of dermatopathic lymphadenitis. Bone marrow biopsy and flow cytometry showed a mildly hypercellular marrow age with trilineage hematopoiesis, and no frank evidence of lymphoplasmacytic lymphoma or clonal plasma cell population. However, there was the presence of mildly increased CD20-positive B-cell population (5–10%) with immunoglobulin heavy-chain clonality testing performed recently demonstrating clonal immunoglobulin heavy chain rearrangement. This supports the possible diagnosis of a small population of low-grade B-cell lymphoma involving the bone marrow. The patient is pending reevaluation by hematology for the same.

A trial of dapsone (100 mg po daily) demonstrated no improvement after a few weeks of treatment, along with worsening of symptoms such as myalgias and chills, which led to discontinuation of the therapy. The patient was then placed on colchicine 0.6 mg BID and an application has been placed for provincial drug coverage of Anakinra (IL-1 receptor antagonist). He has received IV iron infusions for his iron deficiency anemia. Follow-up after 2 months, following the use of colchicine, resulted in reported improvement of the patient’s appetite, cough, chills, rash, fatigue, and myalgia. ESR has elevated to 78 mm/h. Repeat lab work shows an improved leukocytosis of 11.4 × 10^9/L with neutrophils of 6.8 × 10^9/L. His thrombocytosis has improved slightly with a platelet count of 499 × 10^9/L. Hemoglobin is 122 g/L with MCV 75.8. He will be closely followed by internal medicine, rheumatology, dermatology, and hematology departments with the hope for a robust response with Anakinra once approval has been obtained.
at 55 years. Clinically, it is characterized by recurrent fevers, rash, fatigue, joint pain, and enlarged lymph nodes. The rash, which is a required criteria of the syndrome, is classically the first sign and often appears urticarial in nature, with rose-colored macules and slightly raised plaques. It occurs periodically and usually lasts less than 24 hours, often being slightly pruritic. It is mostly noticed on the trunks and limbs. The histopathological findings consist of a neutrophilic dermal infiltrate, such as neutrophilic urticarial dermatosis demonstrated in our patient. Organomegaly, consisting of hepatosplenomegaly, can be present in one-third of patients, and palpable lymph nodes have been found in 45% of patients.

In terms of laboratory features, patients are frequently seen to have an inflammatory or anemia of chronic disease as well as leukocytosis and neutrophilia. It is not uncommon for a thrombocytosis to be present. However, a monoclonal IgM component is the cardinal feature of the syndrome, often associated with a kappa light chain. The M-spike is usually low (less than 10 g/L). Schnitzler’s syndrome is often difficult to diagnose, given its wide range of findings and obscurity. The Strasbourg criteria was published in 2013 and was validated in 2016. In efforts to standardize the diagnosis of this rare disease (Table 1) and was validated in 2016.

**Table 1. Strasbourg diagnostic criteria of Schnitzler’s syndrome**

<table>
<thead>
<tr>
<th>Obligate criteria</th>
<th>Minor criteria</th>
<th>Definite diagnosis if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic urticarial rash</td>
<td>Recurrent fever</td>
<td>Two obligate criteria AND at least two minor criteria if IgM, and three minor criteria if IgG.</td>
</tr>
<tr>
<td>Monoclonal IgM or IgG</td>
<td>Objective findings of abnormal bone remodeling with or without bone pain</td>
<td></td>
</tr>
<tr>
<td>A neutrophilic dermal infiltrate on skin biopsy</td>
<td>Leukocytosis and/or elevated CRP</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis and/or elevated CRP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The pathophysiology of Schnitzler’s syndrome is still unknown, but recent strides are being made continually to expand our understanding. It is known that inflammation and proinflammatory cytokines may be responsible for the pathogenesis of the disease, particularly IL-1. This supports the observation that Anakinra, an IL-1 antagonist, is able to improve symptoms in over 80% of patients. The syndrome therefore appears to behave as an autoinflammatory disease, which is caused by acquired or hereditary dysfunction of the innate immune system. Given its similarities to CAPS, which is caused by activating mutations in the NLRP3 gene, Rowczenio et al. searched for mutations of the same gene in 21 patients with Schnitzler’s syndrome. Only one patient presented with this mutation, but otherwise there were no other documented genetic abnormalities that may predispose patients to the disease. However, they did find increased IL-1 and IL-18, indicating inflammatory activation. Therefore, there is currently no data supporting the genetic basis, and the mechanism of this disease is still unknown.

Our patient fits the Strasbourg diagnostic criteria for Schnitzler’s syndrome with two obligate criteria: a chronic urticarial rash and monoclonal IgM. Additionally, he has two minor criteria: a neutrophilic dermal infiltrate on skin biopsy and persistent leukocytosis. It should be acknowledged that our patient also has a unique presentation of the disease, in terms of the location of the rash. Our patient had the rash develop on the soles of his feet, which is uncommon as the rash of Schnitzler’s syndrome often presents on the trunk.

Additionally, it is imperative to note that patients with Schnitzler’s syndrome have a high likelihood of developing a lymphoproliferative disorder, with some studies suggesting that this occurs in 19% of patients. As described in our patient, although the lymph node biopsy was negative, the presence of mildly increased CD20-positive B-cell population (5–10%) in the bone marrow biopsy, with clonality testing demonstrating clonal immunoglobulin heavy chain rearrangement, is suspicious for low-grade lymphoma.

Treatment of Schnitzler’s syndrome, as per the Strasbourg criteria, can consist of hydroxychloroquine, colchicine, or Anakinra. Anakinra appears to be the most effective in majority of the patients, and is recommended when there is severe impairment to quality of life or persistent elevation of inflammatory markers. The patient’s response to Anakinra is to be determined, and it will be interesting to see if his or her biological markers, including anemia, also improves with symptom control of the disorder.
**Key Points**

1. Schnitzler’s syndrome is an underdiagnosed rare disorder that should be considered in patients with a recurrent urticarial rash, constitutional symptoms, and laboratory abnormalities consisting of leukocytosis, anemia, thrombocytosis, and monoclonal IgM.

2. Diagnosis of the condition will often involve multiple specialists including internal medicine, rheumatology, allergy and immunology, and dermatology.

3. Given the ambiguity of clinical signs and the current obscurity of the disorder, patients often go years without a diagnosis. The goal of this case report is to increase awareness and a greater understanding of the disorder among clinicians.

4. Anakinra appears to be the most effective drug in controlling symptoms and inflammation in majority of the patients.

**Conflict of Interest**

No conflicts of interest exist for either author.

**Funding**

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

**References**


