Fagan, Conlon, Ridge World Allergy Organization Journal (2023) 16:100815
http://doi.org/10.1016/j.waojou.2023.100815

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Proposal of a new clinical entity: Paraprotein negative IL-1 mediated inflammatory dermatosis (PANID) that may precede Schnitzler syndrome

Nicole Fagan, MB BCh BAO[a,b,c]*, Niall Conlon, PhD[a,b,c] and Katie Ridge, MSc[b,c]

ABSTRACT

Schnitzler syndrome (SchS) is an autoinflammatory disease that is defined by the presence of 2 obligate criteria; an IgM or IgG monoclonal paraprotein and a chronic urticarial rash. Typically, there is an excellent clinical response to IL-1 antagonism. There are reports in the literature of a variant type of SchS that does not fulfil the 2 obligate criteria but responds to IL-1 blockade. Equally, there are reports of an urticarial rash preceding the development of a paraprotein by several years. We describe 3 cases in this manuscript. The first fits the Strasbourg diagnostic criteria of SchS, Simon and Asli (2013); however, with several decades of diagnostic delay. The second case at initial presentation did not fit the major criteria for SchS; however, later developed a monoclonal IgM. Finally we report, a third case that has not yet been confirmed to have a monoclonal IgM/IgG at the time of writing despite 12 years of symptoms and in whom a somatic autoinflammatory disorder remains within the differential. All cases responded strikingly to anakinra, an IL-1 receptor blocker. We propose a new clinical entity, paraprotein negative IL-1 mediated inflammatory dermatosis (PANID), that may act as a precursor or risk factor for the development of SchS or other autoinflammatory conditions.

Keywords: Urticaria, Schnitzler syndrome, Autoinflammatory, Monoclonal gammopathy, Rare disease

Dear Editor,

Schnitzler syndrome (SchS) is a rare, acquired, autoinflammatory disorder that can mimic chronic spontaneous urticaria as well as other somatic autoinflammatory disorders (SAID). The genetic basis of SchS is unknown.[1] Clinical diagnosis is based on the Strasbourg criteria obligating recurrent urticarial rash and a monoclonal IgM or IgG gammopathy.[2] Other minor criteria include recurrent pyrexia, abnormal bone remodelling, a neutrophilic dermal infiltrate on skin biopsy, leukocytosis and raised C-Reactive Protein (CRP). Approximately 300 cases of SchS have been described in the literature; however, the true prevalence is likely unknown due to delayed and, in some cases, missed diagnosis.[3] Our understanding of this disease is complicated by the fact that there are reported cases of SchS

[a]Wellcome-HRB Clinical Research Facility, St. James's Hospital, Dublin, Ireland
*Corresponding author. Clinical Research Facility, St. James's Hospital, Dublin 8, Ireland. E-mail: nifagan@tcd.ie
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2023.100815

Received 31 January 2023; Received in revised from 2 August 2023; Accepted 5 September 2023
Online publication date xxx

who initially did not satisfy the Strasbourg criteria but went on to develop a paraprotein at a staged interval.[4] Furthermore, there are a number of reports in the literature of an "incomplete" SchS without monoclonal gammopathy, who do not satisfy the Strasbourg criteria but respond to IL-1 antagonism.[4–8] Although these patients have been labelled "incomplete" or "variant" SchS, it is important to note that there are other inflammatory skin diseases and SAID that respond to IL-1 targeted therapy. These conditions should remain within the differential and we propose a new clinical entity, paraprotein negative IL-1 mediated inflammatory dermatosis (PANID), for consideration to reflect the current diagnostic difficulty in this field.[9–16]

SAID are a group of rare conditions, most of which display skin manifestations. These include Cryopyrin-Associated Periodic Syndromes (CAPS), SchS, Familial Mediterranean Fever, NLRP12-Associated Periodic Fever Syndrome, and Adult-Onset Still's Disease (AOSD).[17,18] Many of these diseases share similar characteristics, making them hard to distinguish from one another. A unifying feature throughout is significant diagnostic delay due to the need to out rule other conditions and satisfy complex individual criteria.[19] As in other SAID, there is significant morbidity associated with SchS, particularly when untreated, with complications including amyloid A (AA) amyloidosis,[9–11] and lymphoproliferative malignancies.[12–16] Optimising the diagnostic criteria of SchS and other SAID and thereby initiating the correct treatment for patients as promptly as possible is of utmost importance.

We report a case series of 3 patients with varying presentations of recalcitrant urticaria and systemic inflammation for whom an initial diagnosis was unclear and the establishment of effective treatment was delayed. Two of these cases were eventually confirmed as cases of SchS and 1 remains in diagnostic uncertainty. All 3 cases had an exquisite clinical and marked improvement in inflammatory indices within 24 hours of IL-1 blockade. These cases vary in their presence and absence of obligate Strasbourg Criteria for SchS and we propose that they highlight important challenges in managing patients with refractory urticaria and objective inflammation even in the absence of a monoclonal band.

The first case is a classical SchS which has been previously described by our service and is therefore only briefly summarised here.[20] Refractory urticaria was present and an IgM kappa paraprotein was detected within months of symptom onset. The patient in question had untreated symptoms spanning 31 years at the time of presentation to Immunology services. Dysregulated systemic inflammation, characterised by persistently elevated CRP, over decades likely contributed to the development of bladder AA amyloid and coronary disease under the age of 50. The patient was also diagnosed with Waldenström's macroglobulinaemia, a known complication of SchS.[14] Despite decades of chronic inflammation, the patient described a dramatic improvement in his symptoms 24 hours after IL-1 blockade. Subsequent next generation sequencing (NGS) of an autoinflammatory panel (Invitae) did not identify causative variants.[21] However, a decade after the initial case report, long-standing sequelae including chronic pain and functional limitation due to inflammatory osteoarthritis, intermittent urinary symptoms and congestive cardiac failure continue to impact on the patient.

Case 2 is notable for the delayed development of an IgM paraprotein. A 47-year-old female presented with a four-year history of recurrent urticaria and non-specific joint pain. Clinical examination demonstrated a florid erythematous urticarial rash. A skin biopsy revealed a mild vasculopathic reaction in the superficial dermis with a mixed inflammatory cell infiltrate, mild dermal oedema and a moderate increase in CD117 positive mast cells. This was not felt to represent evidence of mastocytosis. No fibrinoid necrosis of the vessel walls was noted, a pathogenic requirement for a diagnosis of vasculitis. Laboratory investigations demonstrated thrombocytosis, reduced C4 at 0.06 g/l (0.14–0.54 g/l) and persistently raised CRP >90 mg/l (0–5 mg/l), ESR > 100 mm/hr (0–20 mm/hr) and IL-6 > 20 pg/ml (0–7 pg/ml) on repeat testing. Screening for connective tissue diseases, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies and cryoglobulin proteins was negative. An NGS autoinflammatory panel was negative. Serum free light chain κ/λ ratio was normal. A persistently raised IgM was apparent (3.07 g/l) on initial assessment and confirmed on

first visit to our clinic 4 years after symptom onset. No paraprotein was identified on serum electrophoresis despite repeat testing.

As part of a working diagnosis of hypocomplementaemic urticarial vasculitis, the patient was trialled on high dose antihistamines, azathioprine and oral corticosteroids at different time points with little to no improvement in symptoms. Marginal improvement was reported after the initiation of omalizumab with an Urticaria Control Test (UCT) score shift from 0 to 5, indicating slight improvement but significant ongoing symptom burden.[22] Inflammatory markers remained persistently elevated. Repeat laboratory investigations drawn immediately prior to pre-planned administration of first dose IL-1 blockade showed a minor increase in IgM to 3.97 g/l and for the first time identified a 3.1 g/l paraprotein on immunofixation. This was confirmed on repeat testing. The patient was diagnosed with SchS, 5 years after initial symptom onset with the delayed development of a monoclonal band. Dramatic clinical and biochemical improvement occurred within 24 hours of IL-1 blockade.

Case 3 highlights an individual with symptoms suggestive of a SchS who did not fit Strasbourg criteria and yet demonstrated complete response to IL-1 blockade. The patient is a 61-year-old female initially referred to Dermatology services in 2015 with a four-year history of urticarial rash. She received a clinical diagnosis of urticarial vasculitis however histopathological report of a skin biopsy demonstrated perivascular infiltrate of lymphocytes and neutrophils without evidence of vasculitis. The patient was commenced on high dose antihistamines and disengaged from hospital services for 3 years. At this point, the patient returned with refractory urticarial rash. Laboratory investigations revealed a CRP raised persistently above 20 mg/l (0–5 mg/l), ESR $>$ 40 mm/hr (0–20 mm/hr) and IL-6 (0.50 pg/ml) (0–7.2 pg/ml). Despite treatment with multiple immunomodulatory drugs including omalizumab, ciclosporin, dapsone, oral corticosteroids, azathioprine and colchicine over a three-year period, symptoms failed to improve, and quality of life was greatly impacted. A repeat skin biopsy demonstrated leukocytoclasis and perivascular neutrophils with no frank fibrinoid vasculitis. Serum electrophoresis showed an isolated raised IgA (3.9 g/l) with no monoclonal band. Serum free light chain κ/λ ratio was normal. An NSG genetic screening panel for SAID did not reveal a variant of significance. High clinical suspicion based upon long standing recalcitrant urticaria and persistently raised inflammatory markers led to a trial of IL-1 blockade as a diagnostic challenge (1). Within 24 hours of treatment, the patient had complete resolution of urticarial rash. Within 48 hours, C-reactive protein (CRP) fell from 59.3 mg/l to 16.8 mg/l. While a unifying diagnosis in this case under current criteria remains unclear, the patient remains asymptomatic on IL-1 blockade and inflammatory markers have normalised.

In such as a case as that described above where there is diagnostic uncertainty, out ruling differentials such as AOSD and periodic fever syndromes using clinical, laboratory and genetic parameters as in these cases is vital.[3] Importantly, none of these three cases at presentation met the Yamaguchi, Cush, or Fautrel diagnostic requirements for AOSD.[23–25] They did not satisfy criteria for other periodic fever syndromes and each case had an extensive NSG panel (Invitae) carried out.[21] These were non-contributory. A thorough work up allowed us to exclude other key IL-1 responsive dermatoses.

The 3 cases described here demonstrate the significant diagnostic challenge and delay to diagnosis that many patients with rare conditions face. Two of the cases (Case 2 and Case 3) would not have fit the Strasbourg Criteria for SchS at time of presentation given the absence of a monoclonal IgG or IgM. Despite this, Case 3 who had a symptom burden of 12 years at time of initiation of IL-1 blockade, demonstrated rapid response. As evidenced by Case 1, 31 years of unregulated inflammation led to widely acknowledged complications of SchS and in addition, may have contributed to significant cardiovascular disease, in the absence of other risk factors.[20] The importance of early detection of SchS and other SAID emphasises why every healthcare interaction with these patients must be used as an opportunity to refine diagnosis (Table 1).

The concept that Schnitzler's like disease can occur in the absence of monoclonal gammopathy

Demographics	Patient 1	Patient 2	Patient 3
Age at onset	30	43	50
Duration of symptoms before diagnosis (years)	31	5	12
Strasbourg Major Criteria			
Chronic recurrent urticaria	x	x	x
IgM/IgG gammopathy	IgMκ	IgMκ [a]	
Strasbourg Minor Criteria			
Recurrent, unexplained pyrexia >38	x		
Abnormal bone remodelling ± bone pain	x	x	x
Neutrophilic dermal infiltrate on biopsy	x	x	x
Leukocytosis and/or raised CRP	x	x	x
Complications			
Amyloidosis	x		
Waldenströms macroglobulinaemia	x		
Previous failed treatments			
High dose antihistamines		x	x
Ciclosporin			x
Dapsone			x
Corticosteroids	x	x	x
Colchicine	x		x
Azathioprine	x	x	x
Omalizumab		x[b]	x
Response to IL-1 blockade			
Anakinra	Yes	Yes	Yes

Table 1. Clinical characteristics, complications, and treatments of the three cases. Patient demographics and the Strasbourg major and minor criteria fulfilled by the three cases. Despite previous failed treatments, all patients demonstrated response to anakinra, an IL-1 receptor blocker. *x8Ea Delayed IgMκ development after 5 years. x8Eb = equates to partial response*

or that monoclonal gammopathy can appear many years after initial presentation is not new, but requires more emphasis (See Table 2).[5] In addition, the delayed development of a monoclonal gammopathy over time is noted as a key consideration.[4] Importantly, the existing literature on SchS is influenced by the existing diagnostic criteria and a recent review of 281 cases of SchS, excluded reports of patients that did not have a paraprotein at time of presentation.[3] We propose that the true prevalence of SchS is likely higher given the potential for a monoclonal gammopathy to emerge at a staged interval.

The European Academy of Allergology and Clinical Immunology (EAACI) guidelines advise consideration of SAID as a differential diagnosis in urticaria where there is evidence of systemic inflammation or the absence of angioedema.[26] We propose that greater recognition is required

Cases reported in this case series				
Age	Sex	Hypergammaglobulinemia	Treatment with IL-1 blockade	Response
47	F	Delayed IgM κ after 5 years	Anakinra	+
62	F	Polyclonal IgA	Anakinra	+
Previously reported cases (table updated and modified, see reference 5 for full citation links)[5]				
58	F	Polyclonal IgA and IgG	Anakinra	+
54	F	Polyclonal IgA	Anakinra	+
36	M	Polyclonal IgG	NA[a]	NA
64	M	Polyclonal IgA	Anakinra	+
21	F	Polyclonal IgM	Anakinra	+
57	M	Polyclonal IgM and IgE	NA	NA
63	M	Biclonal IgM κ, λ	NA	NA
71	M	Delayed IgM κ after	Anakinra	+
58	M	Delayed IgM after 20 months	Canakinumab	=[b]
51	M	Delayed IgM after 4 years	Anakinra	+
44	F	None	Anakinra & Canakinumab	+
62	M	None	Anakinra	+
52	F	None	Anakinra	+
69	M	None	Anakinra	+
43	F	None	Canakinumab	+[8]
75	M	None	Anakinra	+[7]

Table 2. Cases of Schnitzler-like syndrome with delayed or absent monoclonal gammopathy. Summary of published cases of a Schnitzler-like syndrome including the two cases reported in this case series that displayed delayed or absent monoclonal gammopathy. *x8Ea NA refers to not available. x8Eb = equates to partial response*

amongst a range of specialties including Rheumatology, Dermatology, Allergy and Immunology that chronic treatment resistant urticaria with signs of systemic inflammation in the absence of a paraprotein, may warrant a treatment trial of an IL-1 antagonist. In addition, we highlight the important consideration of monitoring serum protein electrophoresis in patients with recalcitrant urticaria and signs of systemic inflammation where there is no monoclonal gammopathy. We emphasise the importance of remaining vigilant of SAID throughout the entirety of a patient's treatment journey given the possibility for the delayed emergence of obligate criteria.

The current diagnostic criteria for SchS do not incorporate the possibility of a spectrum of disease or indeed, whether SchS without a monoclonal gammopathy is a distinct clinical entity. Despite this, the reporting of SchS like cases without monoclonal gammopathy challenges our understanding and management of these patients. We propose for consideration, a new clinical entity; paraprotein negative IL-1 mediated inflammatory dermatosis (PANID). For patients who develop a monoclonal gammopathy at a delayed interval, PANID can be seen as a precursor or risk factor for the development of SchS. However, since SchS is not the only disease that responds to IL-1-targeted therapy, it is important to note that cases within

PANID may later exhibit characteristics of other autoinflammatory syndromes apart from SchS. We propose that recognition of this clinical entity could improve patient outcomes by enabling more prompt consideration of IL-1 blockade.

Abbreviations

AA, Amyloid A; C-reactive protein, CRP; EAACI, The European Academy of Allergology and Clinical Immunology; IgA, Immunoglobulin A; IgM, Immunoglobulin M; IgG, Immunoglobulin G; Il-1, Interleukin 1; IL-6, Interleukin 6; κ, Kappa; λ, Lamda; NGS, Next generation sequencing; PANID, paraprotein negative IL-1 mediated inflammatory dermatosis; SchS, Schnitzler's syndrome; SAID, somatic autoinflammatory disorders; UCT, Urticaria Control Test

Funding

The work of Dr. Katie Ridge was funded by the Irish Clinical Academic Training (ICAT) Programme, supported by the Wellcome Trust and the Health Research Board (Grant Number 203930/B/16/Z) and the Health Service Executive, National Doctors Training and Planning and the Health and Social Care, Research and Development Division, Northern Ireland.

Ethics approval

Ethical approval was not required but full informed consent was obtained from all patients.

Author contributions

NF- Conceptualization, Writing- original draft of the manuscript, Writing- Review and Editing, Final approval of manuscript. **NC**- Conceptualization, Writing- Review and Editing, Visualization, Final approval of manuscript. **KR**- Conceptualization, Writing- Review and Editing, Supervision, Final approval of manuscript.

Availability of data and materials

No new data were generated or analysed in support of this research.

Authors' consent for publication

This manuscript has received consent from all authors for publication.

Declaration of competing interest

The authors report no competing interests.

Acknowledgements

We would like to thank the patients for their permission to publish the clinical cases. We would also like to acknowledge the assistance and support of the Wellcome - HRB Clinical Research Facility at St. James's Hospital in providing a dedicated environment for the conduct of high-quality clinical research activities.

Author details

[a]Wellcome-HRB Clinical Research Facility, St. James's Hospital, Dublin, Ireland. [b]UCARE Centre, Clinical and Diagnostic Immunology, St. James's Hospital, Dublin, Ireland. [c]School of Medicine, Trinity College Dublin, Dublin, Ireland.

REFERENCES

1. Simon A, Asli B, Braun-Falco M, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. *Allergy*. 2013;68(5):562–568. https://doi.org/10.1111/all.12129.
2. Al-Hakim A, Mistry A, Savic S. Improving diagnosis and clinical management of acquired systemic autoinflammatory diseases. *J Inflamm Res*. 2022;15:5739–5755. https://doi.org/10.2147/JIR.S343261.
3. de Koning HD. Schnitzler's syndrome: lessons from 281 cases. *Clin Transl Allergy*. 2014;4(1):41. https://doi.org/10.1186/2045-7022-4-41.
4. S Gladue H. Schnitzler's syndrome in the absence of a monoclonal gammopathy: a report of two cases. *J Clin Cell Immunol*. 2014;5(5). https://doi.org/10.4172/2155-9899.1000265.
5. Chu CQ. Schnitzler syndrome and Schnitzler-like syndromes. *Chin Med J (Engl)*. 2022;135(10):1190–1202. https://doi.org/10.1097/CM9.0000000000002015.
6. Henning MAS, Jemec GBE, Ibler KS. Incomplete Schnitzler syndrome. *Acta Dermatovenerol Croat*. 2020;28(1):38–40.
7. Wesselmann AS, Künstner A, Fähnrich A, et al. Case report: Schnitzler-like syndrome without monoclonal gammopathy. *Front Immunol*. 2023;14, 1166620. https://doi.org/10.3389/FIMMU.2023.1166620.
8. Fujita Y, Asano T, Sakai A, et al. A case of Schnitzler's syndrome without monoclonal gammopathy successfully treated with canakinumab. *BMC Muscoskel Disord*. 2021;22(1):1–6. https://doi.org/10.1186/S12891-021-04120-Z/FIGURES/3.
9. Claes K, Bammens B, Delforge M, Evenepoel P, Kuypers D, Vanrenterghem Y. Another devastating complication of the Schnitzler syndrome: AA amyloidosis. *Br J Dermatol*. 2008;158(1):182–184. https://doi.org/10.1111/J.1365-2133.2007.08251.X.
10. Mittal N, Renaut P, Sharma R, Robbie M. Gastrointestinal amyloidosis associated with Schnitzler's syndrome. *Pathology*. 2013;45(4):424–426. https://doi.org/10.1097/PAT.0b013e328360e00c.
11. Terré A, Colombat M, Cez A, et al. AA amyloidosis complicating monoclonal gammopathies, an unusual feature validating the concept of "monoclonal gammopathy of inflammatory significance". *Int J Clin Pract*. 2021;75(11), e14817. https://doi.org/10.1111/IJCP.14817.
12. Lim W, Shumak KH, Reis M, et al. Malignant evolution of Schnitzler's syndrome–chronic urticaria and IgM monoclonal gammopathy: report of a new case and review of the literature 2009;. 2009;43(1):181–186. https://doi.org/10.1080/10428190210181.
13. Dalle S, Balme B, Sebban C, Pariset C, Berger F, Thomas L. Schnitzler syndrome associated with systemic marginal zone B-cell lymphoma. *Br J Dermatol*. 2006;155(4):827–829. https://doi.org/10.1111/J.1365-2133.2006.07417.X.

14. Transformation of IgM-MGUS into Waldenström's macr... | proLékaře.cz. https://www.prolekare.cz/en/journals/internal-medicine/2021-e-3/transformation-of-igm-mgus-into-waldenstroem-s-macroglobulinemia-in-two-of-six-patients-treated-for-schnitzler-s-syndrome-127342. Accessed June 26, 2023.
15. Vanderschueren S, van der Veen A. The Schnitzler syndrome: chronic urticaria in disguise: a single-centre report of 11 cases and a critical reappraisal of the literature. *Clin Exp Rheumatol*. 2017;35(1):69–73. https://www.clinexprheumatol.org/abstract.asp?a=10598. Accessed June 26, 2023.
16. de Koning HD, Bodar EJ, van der Meer JWM, Simon A. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum*. 2007;37(3):137–148. https://doi.org/10.1016/J.SEMARTHRIT.2007.04.001.
17. Krainer J, Siebenhandl S, Weinhäusel A. *Systemic Autoinflammatory Diseases*. 2020. https://doi.org/10.1016/j.jaut.2020.102421. Published online.
18. Savic S, Caseley EA, McDermott MF. Moving towards a systems-based classification of innate immune-mediated diseases, 2020 16:4 *Nat Rev Rheumatol*. 2020;16(4):222–237. https://doi.org/10.1038/s41584-020-0377-5.
19. Autoinflammatory Alliance. *Comparison Chart of Systemic Autoinflammatory Diseases Involving Periodic Fevers. Webpage*; 2023. https://www.autoinflammatory.org/downloads/comparative_chart_front.pdf.
20. Conlon NP, Hayden P, Barnes L, Doran M, O'Shea F, Feighery C. Schnitzler's syndrome; a case highlighting the complications of long-standing acquired autoinflammation. *Eur J Dermatol*. 2014;24(3):405–406. https://doi.org/10.1684/ejd.2014.2345.
21. Invitae Genetic Testing. https://www.invitae.com/en.
22. Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol*. 2014;133(5). https://doi.org/10.1016/j.jaci.2013.12.1076.
23. Cush JJ, Medsger TA, Christy WC, Herbert DC, Cooperstein LA. Adult-onset still's disease. *Arthritis Rheum*. 1987;30(2):186–194. https://doi.org/10.1002/ART.1780300209.
24. Fautrel B, Zing E, Golmard JL, et al. Proposal for a new set of classification criteria for adult-onset still disease. *Medicine*. 2002;81(3):194–200. https://doi.org/10.1097/00005792-200205000-00003.
25. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult still's disease. *J Rheumatol*. 1992;19:424–454.
26. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393–1414. https://doi.org/10.1111/all.13397.