Research Square

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A Chinese Case Series of Schnitzler Syndrome and Complete Remission in One Tocilizumab-treated Patient

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Research article

Keywords: Autoinflammatory disease, monoclonal gammopathy, Schnitzler syndrome, tocilizumab, urticarial rash

Posted Date: March 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17388/v1

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Version of Record: A version of this preprint was published at Clinical Rheumatology on June 9th, 2020.
See the published version at https://doi.org/10.1007/s10067-020-05204-2.

Abstract

Background: Schnitzler syndrome (SchS) is a rare acquired systemic autoinflammatory disease. The major clinical features of SchS are urticarial rush and monoclonal gammopathy, accompanied by fever, joint pain and lymphadenopathy. There were few reports about SchS in Chinese population. Herein, we describe two patients with SchS in China and conducted a systematic literature review about SchS.

Methods: Two Chinese Han patients were diagnosed as SchS in our department from 2017 to 2019. Their phenotype and genotype were carefully documented and studied. We also conducted a systematic literature review about SchS.

Results: There were one man and one woman with an average disease-onset age of 52. Recurrent fever and urticarial rash occurred in both of them during the febrile attacks and normalized in asymptomatic intervals. Other manifestations included arthritis/arthralgia, lymphadenopathy and hearing loss. Hepatic cirrhosis and epilepsy were seen in one patient. None of them had bone pain or family histories. Serum monoclonal IgM gammopathy was found in both patients. MyD88 gene mutation L258P was identified in one patient. They were treated with tocilizumab and tripterygium wilfordii Hook F (TwHF) respectively and both showed good response.

Conclusions: The rarity and diversity of SchS makes it difficult to be recognized. The patient in our study was the first SchS with concomitant liver and neural damage. Anti-IL-6 agents and TwHF may be alternative therapies when anti-IL-1 therapy is unresponsive or unavailable.

Background

Schnitzler syndrome (SchS) is a rare acquired systemic autoinflammatory disease, which was first described in 1972 by Liliane Schnitzler[1]. It always occurs in patients around 50 years. The main clinical features include urticarial rash and monoclonal gammopathy (usually of the IgM class, rarely IgG), accompanied by fever, bone/ joint pain, and lymphadenopathy. Lymphoproliferative disorders and amyloidosis may happen in some patients with SchS[2, 3]. Since the central pathogenesis of SchS is activation of innate immune system and release of interleukin (IL)-1 β, IL-1 antagonists are effective in about 90% patients with SchS[4].

SchS has been primarily reported in Caucasians[4], but hardly in the Chinese population. To our knowledge, this is the first case series of SchS in the Chinese patients with illustration of phenotype and genotype in English literature.

Methods

From 2017 to 2019, two Chinese patients with SchS were identified based on the Strasbourg criteria[5], and treated by the lead and co-authors in our tertiary medical center. The complete medical records of these patients were established and detailed data were collected and documented. Ethical approval for

this study was approved by the Institutional Review Board of Peking Union Medical College Hospital and performed according to the Declaration of Helsinki. Informed consents were obtained from both participants. Whole exome sequencing by Next Generation Sequencing was performed in the Center for Genetic Testing, Joy Orient Translational Medicine Research Centre Co., Ltd, Beijing, China.

Cases were identified through a PubMed and database search utilizing the search string “Schnitzler syndrome” or “Schnitzler’s syndrome”. Case reports, case series and abstracts with no published articles were excluded. All identified articles were read in full, with relevant information extracted and summarized.

Results

Patient 1

A 66-year-old Chinese Han man presented with recurrent urticarial rash for 11 years and fever for 4 years. He developed urticarial rash on the face, limbs and trunk (Fig. 1A and B) when he was 55 years old. A skin biopsy showed fibrinoid changes of blood vessels, perivascular infiltration of lymphocytes, histiocytes and eosinophils, as well as some nuclear dusts, consistent with urticarial vasculitis (Fig. 1C). He had hearing loss and bilateral sensorineural deafness was diagnosed at the age of 56. He also had intermittent edema of lower limbs since then. He noticed episodes of high fever, headache, fatigue, lymphadenopathy and epilepsy since the age of 62. The episodes occurred every 1–2 weeks, lasted for several hours, and symptoms recovered in between the episodes. The analysis of cerebrospinal fluid was normal. Brain MRI showed chronic ischemic changes and senile atrophy of the brain. Electroencephalogram was unremarkable. Lymph node biopsy showed reactive hyperplasia. There was no report of family history for periodic fever syndrome.

Serum tests showed that white blood cell (WBC) count was 19.08×10^9/L (normal range: $3.5–9.5 \times 10^9$/L), erythrocyte sedimentation rate (ESR) 95 mm/h (normal range: 0–15 mm/h), and C-reactive protein (CRP) 111.1 mg/L (normal range: <3 mg/L). IgM κ chain was positive (7.1 g/L). Bone marrow biopsy showed signet ring like cells secreting immunoglobulin. Liver panel showed raised aspartate aminotransferase (AST) (612 U/L, normal range: 15–40 U/L) and alkaline phosphatase (ALP) (298 U/L, normal range: 45–125 U/L). Hepatitis B virus (HBV) markers were as follows: HBsAb, 85.41 IU/ml (normal range: 0–10 IU/ml), HBcAb, 8.64 S/Co (normal range: < 1 S/Co), HBsAg, HBeAg and HBeAb were all negative. Enhanced computed tomography (CT) revealed hepatic cirrhosis and enlarged spleen. FDG PET-CT scans found no evidence of malignancy. Serological markers for systemic autoimmune diseases, including antinuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCA), autoimmune liver disease related antibodies, and autoimmune encephalitis associated antibodies were all negative. Genetic testing was negative, including genes associated with periodic fever syndrome and MyD88 gene.

The patient was treated with antihistamines with no response. He received methylprednisolone 16 mg per day and methotrexate 12.5 mg per week with a complete response. However, his symptoms relapsed after

methylprednisolone tapered to 12 mg per day. Due to unavailability of IL-1 antagonist agents in China, he was treated with tocilizumab 8 mg/kg per month. After 3 months, he was completely symptom-free with only mild fatigue. We assessed serum tests which showed WBC was 9.6×10^9/L, ESR 15 mm/h, and CRP 0.7 mg/L. Liver function showed that AST and ALP were declined to 21 U/L and 72 U/L, respectively. Currently, the patient is treated with tocilizumab 8 mg/kg per month, methylprednisolone 6 mg per day and methotrexate 12.5 mg per week.

Patient 2

A 49-year-old Chinese Han woman presented with recurrent fever, urticarial rash, and arthralgia for one year. She had noted the disease attacked every several weeks, with each flare lasting 2 days to 2 months. The clinical features were characterized by high fever, arthralgia with bilateral elbows and knees involved, myalgia and superficial lymphadenopathy. Recurrent urticarial rash were observed during the disease course. Non-steroidal anti-inflammatory drugs (NSAIDs) were effective to alleviate fever and arthralgia. There was no family history of periodic fever syndrome. Leukocytosis, elevated ESR, and CRP were associated with the attacks, and they normalized in between the disease episodes. Serum IgM κ chain was positive. Serological markers were negative for systemic autoimmune disorders and infection. A skin biopsy showed infiltration of lymphocytes and neutrophils around the blood vessels in the dermis. MyD88 L265P mutation was identified by whole exome sequencing. She received tripterygium wilfordii Hook F (TwHF) 20 mg, three times daily, with a good response.

Systemic literature review

A total of 355 cases of SchS patients were identified through the PubMed search[4, 6, 7, 3]. The clinical manifestation of these patients and our patients were summarized in Table 1. The largest retrospective study including 281 patients with SchS was published in 2014 which contained phenotype of all SchS patients by that time[4]. Patients had disease onset around 50 years old, with a higher ratio of male to female. Among these 357 SchS patients, the common clinical features were urticarial rash (357/357, 100%), monoclonal IgM gammopathy (314/357, 88%), fever (271/357, 76%), join and/or bone pain (203/357, 57%), enlarged lymph nodes (102/357, 29%) (Table 1). In regard to the genotype, it had been confirmed that MyD88 L256P mutation was detected in a third of SchS, and was the most common genetic factor found among SchS patients to date. Meanwhile, no activating NLRP3 mutations were presented in SchS patients except occasional myeloid-lineage-restricted mosaicism[8, 9]. Anti-IL-1 receptor and IL-1β antibodies are preferred treatment of SchS, with highly effective in 90% patients. Anti-IL-6 agent tocilizumab also worked in five patients who had no response to anakinra[4].

Table 1

Comparison of clinical manifestation of Schnitzler syndrome patients among reported cohorts.

Clinical features	Ref.4	Ref.6	Ref.7	Ref. 3	Our study
Number of cases	281	42	21	11	2
Gender (Male: Female)	ND	31:11	13: 8	8:3	1: 1
Age at onset (mean, years old)	51	56	58	55	52
Delay of diagnosis (years)	ND	2.6	ND	maximally 20	6
Fever (%)	203 (72)	36 (86)	21 (100)	9 (82)	2 (100)
Urticarial rash (%)	281 (100)	42 (100)	21 (100)	11 (100)	2 (100)
Joint/bone pain (%)	155 (55)	16 (38)	21 (100)	10 (91)	1 (50)
Splenomegaly/hepatomegaly (%)	41 (15)	5 (12)	ND	1 (10)	1 (50)
Lymphadenopathy (%)	72 (26)	16 (38)	5 (24)	7 (64)	2 (100)
Elevated ESR/CRP (%)	174 (97)	36 (86)	CRP: 18–257 mg/l*	11 (100)	2 (100)
Monoclonal IgM gammopathy (%)	244 (87)	37 (88)	20 (95)	11 (100)	2 (100)
Gene mutation					
MYD88	ND	ND	ND	ND	1 (50)
NLRP3	ND	ND	0	ND	0

Table 1. Abbreviations: ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ND: no data.

*normal range was not mentioned in this reference.

Discussion

Due to its rarity, SchS is an exclusive diagnosis that must be distinguished from diseases with similar manifestations. The first important differential diagnosis is lymphoproliferative disorders, in which monoclonal gammopathy is one of the significant features. It is known that monoclonal gammopathy is associated with a κ-light chain in more than 90% of SchS patients[4]. But it's worth mentioning that high IgM values may also occur in other diseases, for example, Waldenström macroglobulinemia (WM). WM is an IgM-secreting lymphoproliferative disorder. Moreover, MyD88 is a commonly occurring gene mutation

in patients with WM[10]. Interestingly, 15%-20% of SchS patients develop a clinical overt lymphoproliferative disorders[11], and the MyD88 L256P variant present in 30% of SchS patients[8]. In our report, MyD88 L265P mutation was found in one patient. In contrast to lymphoproliferative disorders, SchS has pronounced urticarial rash yet the lymph nodes are usually reactive hyperplasia. Based on these results, SchS and lymphoproliferative disorders appear connected and likely represent a disease continuum. In our study, both patients had no evidence of lymphoproliferative disorders. Nevertheless, since SchS patients with MyD88 mutation have the high tendency to become lymphoproliferative disorders, they should be carefully followed.

The second important differential diagnosis of SchS is NLRP3-autoinflammatory disease (NLRP3-AID) (formerly named as cryopyrin-associated periodic syndrome, CAPS). The clinical features of SchS closely resemble NLRP3-AID, which is caused by activating mutations in the NLRP3 (nucleotide-binding oligomerization domain-leucine-rich repeats containing pyrin domain 3) gene, including recurrent urticarial rash and over release of IL-1 β. But NLRP3-AID usually occurs during pediatric ages, while SchS onset is around 50 years. Besides, patients with NLRP3-AID have prominent manifestations of central nervous system inflammation, which is absent in SchS. On the other hand, SchS conventionally presents with no germline NLPR3 mutation[8], but with the exception of somatic mosaicism occasionally seen in the myeloid lineage [9]. Additionally, monoclonal IgM in NLRP3-AID is not observed whereas it elevates in SchS. Hence, SchS is distinct from the monogenic autoinflammatory disease NLRP3-AID.

Apart from the main manifestations of SchS, there are also some uncommon symptoms such as hepatosplenomegaly and neuropathy[4]. Hepatomegaly can be found in 9% SchS patients[4]. In 1999, a case of SchS with nodular regenerative hyperplasia of the liver was reported[12]. Hepatic fibrosis is commonly preceded by chronic inflammation[13, 14]. In the recent studies, IL-1β has been proposed as an important mediator of inflammation and tissue damage in chronic liver disease[15]. Meanwhile, IL-1 receptor antagonist modulated liver inflammation and fibrosis in mice[16]. On the other hand, although there has been no reports of neural damage in SchS, inflammatory process in this disorder may originate in the central nervous system or be acquired from systemic circulation through a breakdown in the blood-brain barrier (BBB)[17]. It has been illustrated that IL-1β was also an etiologic trigger for BBB breakdown and played a pivotal role in the activation of astrocytes[17]. In addition, IL-1 blockade managed systemic autoinflammation with intractable epilepsy[18]. In our study, patient 1 was accompanied with hepatic cirrhosis and epilepsy of unknown reason, for which we carefully excluded infections, autoimmune diseases, and alcoholic liver disease. Taking the aforementioned concepts into consideration, and the pivotal role of IL-1β overproduction in SchS, we assumed that hepatic cirrhosis and epilepsy in this patient might be related to SchS. As of now, this was the first case report of SchS associated with concomitant liver and neural damage.

The availability of antagonists of the IL-1 signaling pathway has revolutionized the treatment of SchS. This is especially true for the IL-1 receptor antagonist anakinra[19–21]. A fully humanized IL-1β-specific antibody named canakinumab is also effective to treat SchS[22–24]. Anti-IL-6 treatment such as tocilizumab can be effective[25] and is considered an alternative therapy in patients with SchS when anti-

IL-1 therapy is unresponsive or unavailable[26, 3]. To date, patient 1 in our study was the sixth case of SchS who responded well to tocilizumab in English literature. It has been suggested that both IL-1 pathway (the common pathway) and IL-6 pathway (the alternative pathway) may play a relevant role in SchS[25]. Other potentially therapeutic agents are promising in the treatment of Schs. Due to unavailability and high cost of IL-1 antagonist therapies in China, glucocorticoid and disease modifying anti-rheumatic drugs (DMARDs) were used to control the patients' conditions. Tripterygium wilfordii Hook F (TwHF) is a Chinese traditional herbal which has been widely used for the treatment of autoimmune diseases[27]. Clinical and experimental studies have demonstrated its immunosuppressive and anti-inflammatory effects[28, 29]. It should be noted that TwHF was effective in patients with chronic urticaria[30]. In addition, it could alleviate inflammation in mice models of cardiomyopathy and ulcerative colitis through inhibiting expression of NLRP3 inflammasome[31–33]. In our study, the second patient had a good response to TwHF treatment. Taken these data together, we suggest that TwHF is useful in SchS patients. However, due to the sample limitation of our study, more clinical trials are required.

Conclusions

In summary, this is the first case series of SchS in the Chinese patients with illustration of phenotype and genotype in English literature. The rarity and diversity of SchS makes it difficult to be recognized. The patient in our study was the first SchS with concomitant liver and neural damage. Our report highlighted that anti-IL-6 agent and TwHF might be alternative therapies when anti-IL-1 therapy was unresponsive or unavailable. Further studies are needed to explore the genotypes and treatment of SchS.

Abbreviations

ALP
alkaline phosphatase
ANA
antinuclear antibodies
ANCA
anti-neutrophil cytoplasmic antibodies
AST
aspartate aminotransferase
BBB
blood- brain barrier
CRP
C-reactive protein
CT
computed tomography
DMARDs
disease modifying anti-rheumatic drugs

ESR
erythrocyte sedimentation rate
IL
interleukin
HBV
hepatitis B virus
NSAIDs
non-steroidal anti-inflammatory drugs
SchS
Schnitzler syndrome
TwHF
tripterygium wilfordii Hook F
WBC
white blood cell
WM
Waldenström macroglobulinemia

Declarations

Ethics approval and consent to participate: ethical approval for this study was approved by the Institutional Review Board of Peking Union Medical College Hospital and performed according to the Declaration of Helsinki. Informed consents were obtained from both participants.

Consent for publication: not applicable.

Availability of data and materials: all data generated or analysed during this study are included in this published article.

Competing interests: we declare that we have no conflicts of interest to this work.

Funding: this work was supported by the Natural Science Foundation of Beijing [grant number 7192170]; the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) [grant number 2017-I2M-3-001]; and the National Key Research and Development Program of China [grant number 2016YFC0901500; 2016YFC0901501].

Authors' contributions: Min Shen designed the study. Ruyu Yan drafted the manuscript. Min Shen revised the manuscript. Ruyu Yan, Wei Cao, Xinchao Liu and Feng Li were treating physicians for the patients and had contributed suggestions for the diagnosis and management of the patients. All authors read and approved the final manuscript.

Acknowledgements: we appreciate all supports from the patients and their families.

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Figures

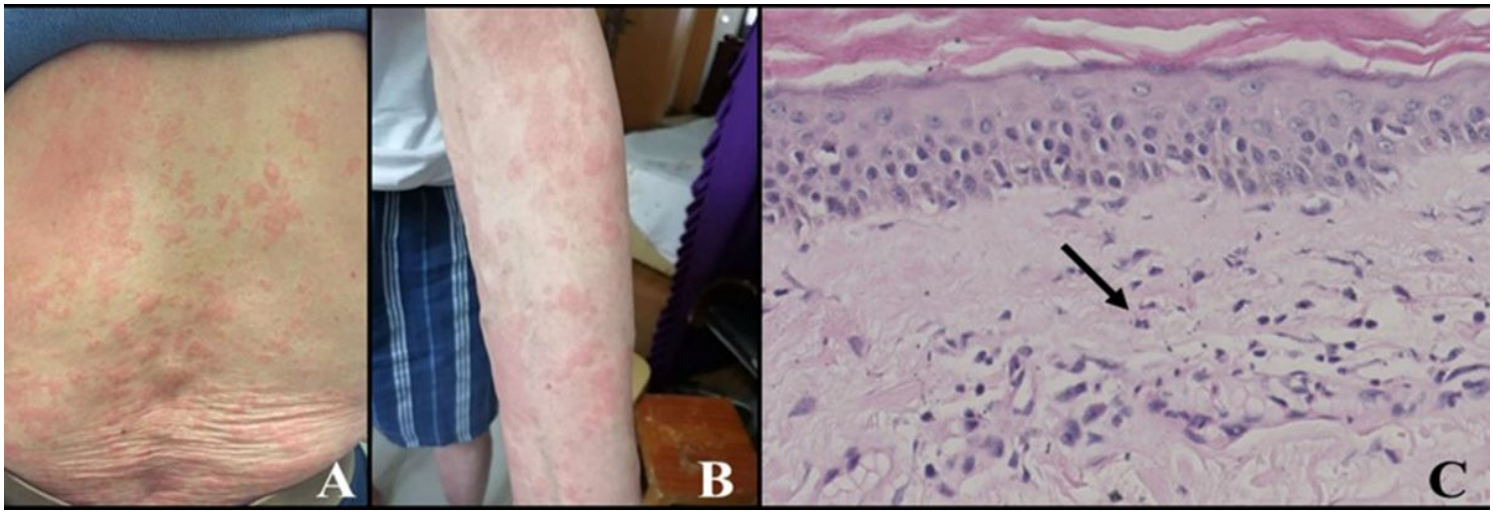


Figure 1

Clinical manifestation of Chinese patients with SchS. (A) Urticarial rash on the trunk of patient 1. (B) urticarial rash on the left arm of patient 1. (C) Skin biopsy from the right leg of patient 1. Fibrinoid changes of blood vessels, perivascular infiltration of lymphocytes, histiocytes and eosinophils, as well as some nuclear dusts, consistent with urticarial vasculitis. Black arrow: eosinophils infiltration.