

Dramatic response to IL1-RA treatment in longstanding multidrug resistant Schnitzler's syndrome: a case report and literature review

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Abstract We report a case of longstanding multidrug resistant Schnitzler's syndrome that finally went into clinical remission upon treatment with anakinra and review the literature concerning IL1-RA treatment for Schnitzler's syndrome. A now 71-year-old patient presenting with recurring episodes of urticaria and fever and secondary weight loss for the past 16 years as well as arthralgia, hearing loss. The patient has anemia, leucocytosis with neutrophilia, thrombocytosis, elevated C-reactive protein and erythrocyte sedimentation rate, lymphadenopathy and a monoclonal IgM kappa band that later became oligoclonal with two IgM kappa bands and one IgM lambda band. The patient was treated with moderate effect with combination of prednisolone, azathioprine, and colchicine. In March 2009, anakinra 100 mg daily sc was added during a disease flare. Within 24 h after the first injection, both the urticaria and the fever disappeared and have not recurred. For the past 6 months, the patient has been in clinical and biochemical remission. Colchicine has been stopped while the azathioprine and prednisolone doses are being reduced. Twenty-four patients with Schnitzler's syndrome, including three patients with a variant of Schnitzler's syndrome and

three patients with a Schnitzler-like syndrome, have been successfully treated with anakinra. Nevertheless, seven out of seven patients, that either interrupted or used anakinra every other day, had relapse of their symptoms within 24–48 h; anakinra was restarted in all patients with the same clinical efficiency. The current case history and the literature review already suggest an important role for IL-1 as a mediator in the pathophysiology of Schnitzler's syndrome.

Keywords Anakinra · Autoinflammatory · Monoclonal gammopathy · Schnitzler syndrome · Urticaria

Introduction

Schnitzler's syndrome is an unfamiliar disease entity with just over 100 patients reported; it crosses the field of several medical specialties as it often presents with chronic urticaria, spiking fever, arthralgia, bone pain, lymphadenopathy, hepato and splenomegaly, persistent acute phase response, leucocytosis, and a monoclonal gammopathy, typically IgM k [1]. As Schnitzler's syndrome has been associated with the development of lymphoproliferative disorders (marginal B-cell lymphoma, IgM myeloma, and Waldenström macroglobulinemia) [1], it is considered a pre-malignant condition. The disease never remits spontaneously and its course is characterized by recurring symptoms that are difficult to treat/prevent [1]. In 2005, sustained clinical remission was reported with the use of anakinra, an IL-1 receptor antagonist [2]. We report a case of longstanding multidrug resistant Schnitzler's syndrome that finally went into clinical remission upon treatment with anakinra and review the literature concerning IL1-RA treatment for Schnitzler syndrome.

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Fig. 1 The skin lesions affecting the chest, back and extremities and disappearing within 24–48 h without sequelae

Case report

A now 71-year-old man has been followed at our department for antihistamine-resistant chronic urticaria since 1993. The skin lesions were non-pruritic maculo-papular with size ranging from 0.5 to 2 cm that were confluent, affecting the chest, back, and extremities and disappearing within 24–48 h without sequelae (Fig. 1). Since 1995, the patient has also been subject to recurrent episodes with acute onset of extensive urticarial rash accompanied by high fever, sweating, and chills at night. During the attacks that lasted 1–3 days, the patient was bedridden, fatigued, and had secondary weight loss with gradual recovery and disappearance of the rash. Intermittent periods with low or no symptoms could last up to 2 weeks. Blood tests revealed a tendency to normocytic anemia, leucocytosis with neutrophilia, thrombocytosis, and acute phase reactants that worsened during attacks (erythrocyte sedimentation rate around 50 mm and C-reactive protein around 40 mg/l). The serum and immuno-electrophoresis did not show a monoclonal band until 1997; it was first identified as a

monoclonal IgM kappa in 1999 and later as oligoclonal with two IgM kappa bands and one IgM lambda band. IgM serum level increased from 2.68 in 1995 to 11.8 in 2009 (Table 1). On the other hand, IgG and IgA levels have gradually decreased. Bence Jones proteinuria has always been negative. The patient was negative for HIV, hepatitis B and C as well for *Borrelia*, syphilis, cytomegalovirus, Epstein-Barr virus, and human herpes virus. The Latex test was positive and the Waaler test was negative. Antinuclear, anticardiolipin, anti-desmosom, anti-basal membrane antibodies as well as anti-neutrophil cytoplasmic antibodies, cryoglobulinemia were negative. C4, C3, and C1-esterase inhibitor were normal. In 2003, the patient complained of arthralgia over fingers distally, without clinical evidence of synovitis. Computed tomography scan of the thorax and the abdomen revealed axillary and inguinal lymphadenopathies without hepato-splenomegaly. The biopsy in 1995 and cytopunction in 2004 of an axillary lymph node showed no signs of malignancy. Repeated bone marrow biopsies in 1995, 1997, and 2004 were not suggestive for a lymphoproliferative disease. During the disease course, the patient underwent quadruple coronary bypass for an unstable angina in 2006 and was diagnosed with a left-sided vestibular schwannoma in 2008 with progressive left-sided hearing loss and tinnitus.

The initial working diagnose of normocomplementemic urticarial vasculitis was later revised to Schnitzler's syndrome. The patient was treated with some effect with prednisolone although the symptoms worsened with a prednisolone dose fewer than 15 mg daily. Azathioprine up to 150 mg daily and colchicine up to 1.5 mg daily were added later for immunosuppressive and corticosteroid sparing properties but with moderate effect only. The addition of cyclosporine in 1998 and the initiation of interferon-2 α in 2004 were unsuccessful. In March 2009, anakinra 100 mg daily sc was added to azathioprine 150 mg, colchicine 0.5 mg, and prednisolone 12.5 mg daily during a disease flare. Within 24 h after the first injection, both the urticaria and the fever disappeared and

Table 1 Results of patient's laboratory tests and serum electrophoresis over time

Date	1995	1996	1998	2000	4/2009	8/2009
Hemoglobin g/l	13.3	13.5	12.4	13.4	12.6	12.5
Leucocytes	12.8	14.9	22.1	18.9	7.7	7.9
ESR mm/t	52	45	49	34	50	28
CRP mg/L	80	72	104	20	24	<5
IgM g/l	2.68	3.8	7.31	7.9	11.5	11.8
IgG g/l	20.4	12.6	10.1	8.2	5.6	5.1
IgA g/l	2.03	1.9	1.57	0.8	0.36	0.36
Immuno-Electrophoresis	Neg	Neg	Weak IgMk	Oligoclonal : IgMk	2 bands IgMk 1 band IgM λ	Unchanged

Table 2 Summary of reported data in 24 patients with Schnitzler's syndrome treated with anakinra

Sex	Age y	Sympt. Debut y	Clinical symptoms	Monoclonal Gammopathy	Previous treatment, immunosuppressives	Combination w anakinra	Discontinuation anakinra	Remission mo	Ref.nr
F	42	1	U-F-B	IgM k	Cos, Aza, RTX, CyA, INT α , INF + MTX	Yes + MTX	NR	10	2
F	55	16	U-F-A-B-L-S-hearing loss	IgG k	Cos, Dap, CyA, Col, Tha	No	NR	18	3
M	58	15	U-F-A-hearing loss	IgG k	None	No	NR	6	3
M	60	3	U-F-A-B	IgM k	Cos	No	NR	12	3
M	59	4	U-F-B	IgM k	Cos, MTX, Pent, Dap, HCQ, Col	Yes + Cos + coxib	NR	6	4
F	58	13	U-F-A-B-H-S	No, elevated IgA-IgG	Cos, MTX	No	NR	3,5	5
M	44	2	U-B-night sweats	IgM k	Cos, Aza, Col, Dap, CyA, ETA, INF, INT α , MMF, MTX, Plasm, Tha	Yes + Cos	NR	14	6
M	54	6	U-A-B-sweating attacks	IgM k	Cos, Aza, CyA, RTX	Yes + Cos	NR	10	7,12
F	53	1	U-F-A-B	IgM k	None	No	NR	1	8
F	45	8	U-F-A-B-L-H-S	N R	Col, Dap, Aza, Cys, ADA, ETA	Yes + MTX + COS	NR	8	9
M	42	1	U-F-B	IgM k	Cos, Aza, RTX, CyA, INT α , INF + MTX	Yes + MTX	NR	36	10
M	72	1	U-F-B	IgM k	Cos, MTX	No	Relapse if anakinra eod	12	11
M	58	4	U-F-A	IgM k	CyA, MTX, ADA, LEF, Cos	No	Relapse 48 h after	9	12
F	52	1,5	U-F-A	IgM k	Cos, Dap	No	NR	5	12
F	50	8	U-F-A	No, elevated IgM	Cos	No	NR	12	13
M	42	10	U-F-A	No, previous k-light chains	None	No	Relapse if anakinra eod	6	14
M	43	NR	U-F-A-L	IgM k	Cos, MTX, INF, , Aza, MMF	No	Relapse if discontinued	21	15
M	50	10	U-F-A-L-H-oedema legs	IgM k	Cos, Dap, Chl, Col, Tha, Aza, MTX, CyA, Cyc, RTX, Flu	Yes + Cos	Relapse if discontinued	7	16
F	63	4	U-F-A	IgM k	Cos, CyA, MTX, Col	No	Relapse if anakinra eod	26	17
M	72	2	U-F-B-L-dry cough-breast tenderness	IgM k	Cos	No	Relapse if discontinued	NR	18
M	62	1	U-F-A	IgM k	Cos, CyA	No	NR	3	19
NR	55	NR	U-F-A	IgM λ	Col, HCQ, Cos	No	NR	12	20
NR	69	1	U-F-A	IgM k	Cos, Col	No	NR	2	20
M	71	16	U-F-A-L-hearing loss	2 bands IgMk and 1 band IgM λ	Cos, Col, Aza, CyA, INT α	Yes + Aza + Cos	NR	4	Actual case

M male, F female, U urticaria, F fever, A arthralgia, B bone pain, L lymphadenopathy, H hepatomegaly, S splenomegaly, ADA adalimumab, Aza azathioprine, Chl chlorambucil, Col colchicine, Cos corticosteroids, Cyc cyclophosphamide, CyA cyclosporine A, Dap dapsone, ETA etanercept, Flu fludarabine, HCQ hydroxychloroquine, INF infliximab, INT α interferon-2 α , IVIg intravenous immunoglobulins, LEF leflunomide, MMF mycophenolate mofetil, MTX methotrexate, Plasm plasmapheresis, RTX rituximab, Tha thalidomide, Y year, mo month, eod every other day

have not recurred For the past 6 months, the patient has been in clinical and biochemical remission (Table 1). Colchicine has been stopped while the azathioprine and prednisolone doses are being reduced.

Discussion

A MEDLINE literature search on using the key word Schnitzler's syndrome and anakinra together with cross-references in the English, Spanish, and Swedish literature revealed 23 additional reports on anakinra treatment in patients with Schnitzler's syndrome [2–20]. All 23 patients do not fulfill the diagnostic criteria defined by Lipsker et al. [21] as shown in Table 2; it includes three patients with a variant of Schnitzler's syndrome [3, 20] and three patients with a Schnitzler-like syndrome [5, 13, 14] as defined previously by de Koning et al. [1].).

The mean age of 55 years and the male-female ratio is 1.75 in the reviewed anakinra treated group are comparable to other Schnitzler's cohort studies [1, 21]. The symptoms and signs are comparable to other Schnitzler's cohort studies although arthralgia is more frequent (Table 3) in the anakinra-treated group. The average disease duration is 5.8 years and the number of prior immunosuppressive drugs is 4.2 per patient (Table 3).

None of the reviewed patients reported spontaneous remission and only partial and inconsistent remission with corticosteroids, colchicine, Interferon α -2b, thalidomide, and pefloxacin [1]. Anakinra was effective in treating Schnitzler's syndrome, variant of Schnitzler's syndrome and Schnitzler-like syndrome patients. Therefore, being classified as a variant or as Schnitzler-like syndrome should not be a determinant for anakinra treatment in such patients. It also seems that Schnitzler-like syndrome is not necessarily an early form for Schnitzler syndrome as patients with Schnitzler-like syndrome have had a longstanding disease—between 8 and 13 years [5, 13, 14] before being treated with anakinra.

All patients treated with anakinra went rapidly into clinical remission; the longest remission reported is 36 months [10]. There has not yet been reported any treatment failure with anakinra. Nevertheless, seven out of seven patients, that either interrupted or used anakinra every other day, had relapse of their symptoms within 24–48 h; anakinra was restarted in all patients with the same clinical efficiency [11, 12, 14–18]. In view of these results, as Gilson et al. advocate, anakinra could be used as a diagnostic tool [11]. Anakinra was combined to methotrexate in three patients [2, 9, 10] and azathioprine in the presented case. Considering the efficacy of anakinra in monotherapy, there is no clear indication for such combinations [22].

No decrease in IgM or IgG gammopathy quantification has been reported under anakinra treatment [6, 8, 11, 13,

19, 20]. Anakinra has never been used in patient with Schnitzler's syndrome associated with a lymphoproliferative disorder, as the treatment of the lymphoproliferative disease prevailed. Rituximab proved to be an effective therapy for the Schnitzler's symptoms in these patients [23, 24]. The efficacy of anakinra in preventing lymphoproliferative disease (that affects 15% of the patients over a 10-year period) [1] or AA-amyloidosis is also unknown.

Schnitzler's syndrome has many similarities with auto-inflammatory diseases such as cryopyrin-associated periodic syndrome, mevalonate kinase deficiency and adult onset Still's disease [1] because of its remitting and recurrent pattern and the efficacy of anakinra. It has been therefore hypothesized that disturbances of the innate immune system are responsible for the Schnitzler's syndrome [1, 25]. IL-1 is considered a “master” cytokine that regulates the induction of a network of pro-inflammatory cytokines, chemokines and adhesion molecules in the microenvironment. The IL-1 family consists of two agonistic proteins (IL-1 α and IL-1 β) together with one natural inhibitor, the IL-1 receptor antagonist (IL-1Ra) that silences the IL-1 receptor by binding but not sending an activation signal. Whereas IL-1 α is mainly active in membrane bound form, IL-1 β is only active in secreted form and produced mainly (but not exclusively) by macrophages. While the current case history and the literature review already suggest an important role for IL-1 as a mediator in the pathophysiology of Schnitzler's syndrome, recent ex vivo data have also established the presence of an exaggerated IL-1 response to lipopolysaccharides (LPS) stimulation in a patient with Schnitzler's syndrome [13] and thus provide a rationale for the success of IL1-RA therapy in this incapacitating condition.

Table 3 Summary of reported data in 24 patients with Schnitzler's syndrome treated with anakinra

	N=24
Mean age (years)	55
Female (%)	36.3%
Disease duration (years)	5.8
No. prior immunosuppressive drugs used	4.2
Urticaria	100%
Fever (and equivalent)	92 (100)%
Arthralgia	75%
Bone pain	50%
Lymphadenopathy	25%
Hepatomegaly	12.5%
Splenomegaly	12.5%
Hearing loss	12.5%
IgM monoclonal	75%
IgG monoclonal	12.5%
No monoclonal	12.5%

Disclosures None

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