Is the clinical picture of Schnitzler syndrome always Schnitzler syndrome?

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ABSTRACT

Here we present two cases, a female and a male patient with Schnitzler-like syndrome. Both patients had two major (monoclonal gammopathy and chronic urticaria) and almost all minor symptoms (e.g. arthralgia, bone pain, fever, etc.) of Schnitzler syndrome. It is considered that interleukine (IL)-1 has important influence on immunopathogenesis of Schnitzler syndrome. However, when looked at the immune response in our two patients, we found significant differences between them. In the sera of the female patient, IL-1beta was increased. However, the highest increase was found for granulocyte-colony stimulating factor (G-CSF), IL-32 alpha and IL-17E (IL-25). The male patient had a significant increase in the percentage of NK-cells, a decrease in CD4+ helper cells and no increase in cytokine levels. In both patients an increase in CD40L (CD154) was found. Our statement is that, besides clinical symptoms and signs, additional immune parameters should be tested before diagnosis of Schnitzler syndrome is established.

Introduction

Schnitzler syndrome describes the simultaneous occurrence of monoclonal gammopathy and chronic urticaria as major symptoms with at least two additional minor symptoms (arthralgia, bone pain, fever of uncertain origin, hepato- or splenomegaly, lymphadenopathy, increased erythrocyte sedimentation rate, leukocytosis/thrombocytosis or increased bone density). The etiology of disease is unknown (1). Development of a hematological malignancy is the main complication (2). It is considered that interleukine (IL)-1 has important influence on immunopathogenesis of Schnitzler syndrome (1). Some therapy benefit was recorded with anakinra, recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1RA) (3-5), or with pefloxacin (6).

Case report

Here we present two cases, a female and a male patient with Schnitzler-like syndrome, who had two major and almost all minor symptoms (Table I) for several years. The female patient periodically had some benefit from the combination of antihistamine desloratadine and antibiotics: ciprofloxacine and doxycycline, while in the male patient the same therapy was ineffective. Because of the different response to the applied therapy between our patients, we decided to test IL-1 and some other immune parameters in our patients and to check whether our clinical diagnosis is appropriate. Additionally, we would like to search for other immune parameters which may be involved in the immunopathogenesis of Schnitzler syndrome. For that purpose, we tested three sera from both patients using Proteome Profiler Human Cytokine Array Kit, Panel A with 36 different cytokine antibodies (Cat. no. ARY005; R&D Systems Inc, MN, USA). For each tested molecule in the patients, we calculated times increased/decreased in comparison to healthy controls. Two-colour immunofluorescence cytometry was also performed several times with monoclonal antibodies (MoAbs) identifying T cells and T-cell subpopulations, B cells, natural killer (NK) cells and activation markers on T cells and B cells.

Surprisingly, we found significant differences in the immune responses between the two patients (Table I). The male patient had a significant increase in the percentage of NK-cells and a decrease in CD4+ helper cells (Table I). On the contrary, in the female patient, IL-1beta was increased. However, the highest increase was found for granulocyte-colony stimulating factor (G-CSF), IL-32 alpha and IL-17E (IL-25) (Table I). In both patients, soluble (s) CD40L (CD154) was detected, with a higher increase in the male patient.

CD40L (CD154) is a co-stimulatory molecule expressed mainly on activated CD4+ T cells. It contributes to systemic inflammatory and cardiovascular diseases. Soluble CD40L (CD154) has been reported to be increased in several autoimmune diseases, idiopathic urticaria, as well as human immunodeficiency virus type 1-infected patients where it correlates with CD4+ T-cell counts (7-8). IL-32 is a recently

described pro-inflammatory cytokine which, in human peripheral blood mononuclear cells (PBMC), may induce a release of tumor necrosis factor (TNF)-alpha, IL-1-alpha, IL-1beta and IL-6. It is considered that the inhibition of IL-32 may be beneficial in autoimmune and systemic connective tissue diseases (9-10). IL-17E regulates hematopoietic and immune functions and may be one of the pro-inflammatory cytokines favouring Th2 type immune responses. IL-17E may induce the production of various cytokines including IL-6 and G-CSF (10).

It is clear from our results that although both patients had the same clinical pictures and fulfilled all clinical parameters for the diagnosis of Schnitzler syndrome, the male patient most probably does not have Schnitzler syndrome. It is possible, of course, that the male patient may have some different stages of Schnitzler syndrome, but so far there is no support to such an assumption in the available published literature. It could be rather that the male patient has some new unknown syndrome or version of chronic idiopathic urticaria with an increased percentage of NK cells. It is also obvious that some other immune parameters, such as G-CSF, IL-32 alpha and IL-17E (IL-25) could be important in the immunopathogenesis of Schnitzler syndrome and this observation should be further evaluated in other patients with Schnitzler syndrome. However, in both patients, sCD154 was detected, with a higher increase in the male patient. The increase of sCD154 had already been detected in patients with chronic idiopathic urticaria (11).

Our statement is that, besides clinical symptoms and signs, additional immune parameters should be tested before diagnosis of Schnitzler syndrome is established. It would be even more important before the patients are considered as the candidates for the therapy with anakinra.

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Table I. Symptoms, findings and immune parameters in two patients (female and male) with Schnitzler-like syndrome.

Symptoms/findings	Patient 1 – F (aged 50)	Patient 2 – M (aged 48)
	Main symptoms/findings	
Monoclonal gammopathy	Yes	Yes
Chronic urticaria	Yes	Yes
	Minor symptoms/findings	
Arthralgia	Yes	Yes
Bone pain	Mild	Mild
Fever of uncertain origin	Yes	Yes
Hepato- or splenomegaly	Mild	No
Lymphadenopathy	Yes	Yes
Increased erythrocyte sedimentation rate	Yes	Yes
Leukocytosis/thrombocytosis	No	Yes
Increased bone density	n.t.	n.t.
	Immune parameters (extreme values)	
IgM (0.4-2.3)	↑ (7.62)	↑ (19.4)
Total light kappa-chains (1.7-3.7 g/l)	Qualitative changes in IgM heavy and kappa light chains	↑ (4.49 g/l)
Albumins (57-66%)	normal	↓ (43%)
Gamma globulins (14.5-19.5%)	normal	↑ (36.3%)
Total CD3+ (60-85%)	normal	↓ (56.1%)
NK cells CD3-/CD56+ (0-15%)	normal	↑ (38.1%)
CD4+ (500-1500/μl)	normal	↓ (267/μl)
sCD40L (CD154)	↑ (1.9)*	↑ (3.4)*
GM-CSF	↑ (2.2)*	↓ (-2.4)*
MIP-1beta	nsc	↓ (-2.1)*
I-309	↑ (2.1)*	nsc
G-CSF	↑ (2.7)*	nsc
IL-1 beta	↑ (2.0)*	nsc
IL-2	↑ (1.9)*	nsc
IL-17E (IL-25)	↑ (2.5)*	nsc
IL-23	↑ (2.2)*	nsc
IL-32 alpha	↑ (2.7)*	nsc
IP-10	↑ (2.0)*	nsc
TNF-alpha	↑ (1.9)*	nsc
sTREM-1	↑ (2.0)*	nsc

*Times increased/decreased in comparison to healthy controls; nsc: no significant changes to healthy controls; n.t.: not tested.

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