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Genetic predisposition (*NLRP3* V198M mutation) for IL-1–mediated inflammation in a patient with Schnitzler syndrome

To the Editor:

Schnitzler syndrome is a rare, enigmatic disorder characterized by chronic urticarial rashes and a monoclonal IgM gammopathy, variably combined with intermittent fever, arthralgia or arthritis, lymphadenopathy, hepatomegaly and/or splenomegaly, leukocytosis, and an elevated erythrocyte sedimentation rate.[1] Patients have an excess risk for Waldenström macroglobulinemia and amyloidosis.[2] Both increased secretion of the proinflammatory cytokine IL-1 from PBMCs and efficacy of anakinra (soluble IL-1 receptor antagonist) treatment suggest an important role of IL-1 in the disease process. However, the cause of increased IL-1 secretion has remained obscure.[2,3] Here, we report on a gain-of-function mutation (V198M) of a gene (nucleotide-binding domain protein and leucine-rich repeat containing gene family, pyrin domain containing 3 *[NLRP3]*, also known as *CIAS1*) predisposing for excessive IL-1β secretion in a patient with Schnitzler syndrome. To our knowledge, this is the first report on a *NLRP3* gene mutation found in this disease.

We diagnosed Schnitzler syndrome in a 52-year-old woman who was admitted to our department because of an 18-month history of chronic urticaria with annular erythematous and maculopapular lesions, periodic fever, polyarthralgia, night sweats, and 10-kg weight loss starting days after a clinically diagnosed respiratory infection that had not been further investigated. Skin eruptions initially occurred at mechanically stressed regions but generalized within 2 months, sparing the neck and face. At presentation, leukocytosis (12.100/μL), and elevated erythrocyte sedimentation rate (54 mm/h) and C-reactive protein (23 mg/L) were present. Mild anemia (hemoglobin 10.5 g/dL) was noted. The thrombocyte count was within the normal range. Serum IgM levels were markedly increased (7.8 g/L; normal range, 0.4-2.3) with a monoclonal IgMκ component. The rheumatoid factor was elevated (46 U/L; threshold ≥20 U/L). Other autoantibodies (antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophil cytoplasmic autoantibodies) and cryoglobulins were not detected. Complement, IgG, IgA, IgD, IgE, C1 esterase inhibitor, and tryptase levels were normal. A skin biopsy disclosed neutrophilic urticaria vasculitis. Chronic infections (*Helicobacter pylori*, HIV, hepatitis B and C), occult cancer, leukemia, multiple myeloma, Waldenström macroglobulinemia, and lymphoma were excluded by laboratory tests, sonographic examination, chest radiograph, magnetic resonance imaging of the abdomen, endoscopy of the upper and lower gastrointestinal tract, and bone marrow analysis. Splenomegaly and lytic bone lesions were not present. The patient responded to high-dose prednisolone treatment, but attempts to taper the dose below 40 mg/d were followed by reoccurrence of urticaria, fever, polyarthralgia, and an increase of the erythrocyte sedimentation rate. However, addition of the soluble IL-1 receptor antagonist anakinra (100 mg/d subcutaneously) resulted in complete clinical remission within 1 day. Remission has been sustained and prednisolone discontinued with daily anakinra injections on follow-up for >2 years. An attempt by the patient to taper down anakinra to injections every other day was followed by a recurrence of the skin lesions, which rapidly disappeared after reintroduction of daily application.

Considering the hypothesis of autoinflammation and the pivotal role of IL-1 in Schnitzler syndrome,[2] sequencing of the *NLRP3* gene from PBMCs of our patient was performed. The V198M mutation was disclosed (Fig 1), which has been known as one of the gain-of-function mutations causing the so-called cryopyrin-associated periodic syndromes (cryopyrinopathies) in infants.[4,5]

NLRP3 encodes neuronal apoptosis inhibitory protein, MHC class II transcription activator, HET-E and telomerase-associated protein [NACHT], leucine-rich repeat [LRR] and pyrin containing-domain protein 3 (NALP3), also called cryopyrin, an intracellular pattern-recognition receptor mediating monocyte and macrophage IL-1β secretion in response to a heterogeneous group of exogenous and host danger signals including microbial and host DNA, amyloid-β, adenosine triphosphate, and monosodium urate and calcium pyrophosphate dehydrate crystals.[6-8] On sensing danger signals, NALP3 is activated by postulated unfolding from an autorepressed form, then forming oligomers, and recruiting caspase-1 via adaptor molecules (apoptosis-associated speck-like protein containing a CARD [ASC], CARD inhibitor of NFkB-activating ligands [CARDINAL]). The activated caspase-1 in this oligomer-complex coined NALP3 inflammasome cleaves pro–IL-1β to convert it into active IL-1β.[6]

To study IL-1β secretion in our patient, PBMCs were isolated from blood obtained at the end of a voluntary 60-hour interval between anakinra doses. At that time, a relapse of urticaria had occurred, which rapidly resolved within hours after resuming anakinra treatment. Fractionation of PBMCs by CD14 positivity (a marker of monocytes) was performed by using CD14 microbeads (Miltenyi Biotec, Bergisch-Gladbach, Germany) as described by the manufacturer. The spontaneous IL-1α and IL-1β secretion from both CD14-positive and CD14-negative PBMCs of the patient was below the limit of determination of the ELISA (<1 pg/mL,

METHODS

Subjects

For a case-control study of AD, 376 independent patients with AD (age 16-64 years; mean, 29.7 years) were recruited. AD was diagnosed in subjects according to the criteria of Hanifin and Rajka.[E1] All patients had pruritus, a typical appearance of AD, and a tendency toward chronic or chronically relapsing dermatitis. Control subjects for the case-control study were 923 healthy adults (age 19-78 years; mean, 46.2 years) with no history of any allergic disease. The subjects were the same in our previous study.[E2] A full verbal and written explanation of the study was given to patients and controls, and subjects who gave informed consent participated in this study. This study was approved by the Committee of Ethics of the University of Tsukuba.

Genotyping of *FLG* null mutations

Genomic DNA was extracted from whole-blood samples by using a DNA-isolation kit (QuickGene-810R; Fuji, Tokyo, Japan). The 3321delA genotype was determined by sizing a fluorescently labeled PCR fragment on an Applied Biosystems 3100 DNA Sequencer (Applied Biosystems, Foster City, Calif) as described previously.[E3] S2554X, S2889X, and S3296X were genotyped on a TaqMan Assay-by-Design system for single nucleotide polymorphism genotyping (Applied Biosystems). The accuracy of genotyping was confirmed by using direct sequences/restriction fragment length polymorphism analysis[E4] of samples obtained from all carriers and selected noncarriers of the *FLG* null mutations.

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TABLE E1. AD case-control study

Polymorphism	Population*	Genotyped (%)	Genotype count (frequency, %) AA	Aa	aa	Genotypic *P* value*	Allelic *P* value†	Odds ratio (95% CI)‡
3321delA	AD	97.3	356 (97.3)	10 (2.7)	0 (0)	.077	.079	2.1 (0.9-4.9)
	Controls	99	902 (98.7)	12 (1.3)	0 (0)			
			AA	Aa	aa			
S2554X*	AD	99.7	365 (97.3)	10 (2.7)	0 (0)	.0012	.0012	5.0 (1.7-14.8)
	Controls	100	918 (99.5)	5 (0.5)	0 (0)			
			AA	Aa	aa			
S2889X	AD	97.6	346 (94.3)	21 (5.7)	0 (0)	.0058	.0063	2.27 (1.25-4.14)
	Controls	100	899 (97.0)	24 (3.0)	0 (0)			
			AA	Aa	aa			
S3296X	AD	98.7	369 (99.5)	2 (0.5)	0 (0)	.82	.82	0.83 (0.17-4.12)
	Controls	100	917 (99.3)	6 (0.7)	0 (0)			
Combined			AA	Aa	aa			
(4 null mutations)	AD	93.4	308 (87.7)	43 (12.3)	0 (0)	.000011	.000016	2.57 (1.67-3.97)
	Controls	99	867 (94.9)	47 (5.1)	0 (0)			

AA, Wild-type for the mutation; *Aa*, heterozygote for the mutation; *aa*, homozygote for the mutation or a compound heterozygote for mutations.
*Genotypic *P* value was calculated with χ^2 test in comparison with wild-type homozygote versus minor allele heterozygote plus minor allele homozygote.
†Alleleic *P* values were calculated with χ^2 test in comparison with genotype and allele counts in controls, respectively.
‡Odds ratio for the wild-type homozygote versus minor allele heterozygote and minor allele homozygote.

倫理面への配慮

本研究の過程で取り扱った個人情報については、漏洩することのないように研究代表者が責任を持って保護致します。