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CASE REPORT

Complete remission of severe idiopathic cold urticaria on interleukin-1 receptor antagonist (anakinra)

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ABSTRACT

A 62-year-old patient had suffered from severe cold intolerance with an urticarial rash and oropharyngeal angio-oedema upon cold exposure since early childhood. This could be provoked by the ice cube test and by exposure in a cold room. Her family history was negative, and she did not carry any mutations in the *NRLP3* gene. Treatment with IL-1 receptor antagonist anakinra resulted in complete resolution of these symptoms, with a radical beneficial change in her quality of life. In recent years this patient had developed progressive neurological symptoms leading to a diagnosis of amyotrophic lateral sclerosis (ALS), which seems unrelated to the idiopathic cold urticaria. The neurological symptoms did not respond to anakinra treatment and were eventually fatal.

Conclusion: We describe the first case of IL-1RA treatment in idiopathic cold urticaria with good response. Anakinra had no effect on the progression of her symptoms of ALS.

KEYWORDS

Amyotrophic lateral sclerosis, interleukin-1, interleukin 1 receptor antagonist protein, urticaria

INTRODUCTION

Cold urticaria/urticaria-like syndromes are rare disorders, characterised by intolerance to cold. Upon cold exposure, patients develop an urticarial rash, which is described as itchy or burning, often accompanied by fever and chills, recurrent arthralgia, and conjunctivitis.[1] Acquired cold urticaria can be idiopathic or secondary to e.g. cryoglobulinaemia or infectious diseases.

A hereditary form, familial cold autoinflammatory syndrome (FCAS, previously known as familial cold urticaria), is caused by mutations in the gene for cryopyrin (syn., NLRP3, NALP3, PYPAF1).[2] Cryopyrin forms part of an inflammasome, a protein complex crucial in the activation of interleukin-1β (IL-1β).[3] Inhibition of IL-1β signalling by recombinant interleukin-1 receptor antagonist (rIL-1RA, anakinra) is an effective treatment of FCAS.[4]

There are no data available on response to anakinra in acquired or idiopathic cold urticaria. Most patients respond to oral antihistamine treatment but this is often a partial response and avoidance of cold exposure can be greatly disabling.[5]

Recently, we saw a patient with severe sporadic cold urticaria, in whom we evaluated the effect of anakinra treatment. This patient also developed neurological symptoms.

CASE REPORT

A 62-year-old Caucasian woman suffered from severe cold intolerance with an urticarial rash and oropharyngeal angio-oedema upon cold exposure since early childhood. She had never been able to go out in the snow, go ice skating or drink cold drinks in the summer. Even at ambient temperatures slightly lower than 20°C she was at risk of developing symptoms. Family history was negative. Physical examination at that time showed an increased breathing frequency of 18/min and an urticarial rash on her arms

that lasted for 30 minutes. The ice cube test (application of ice cube to patient's forearm for five minutes) resulted in a localised urticarial rash after three minutes, still visible 24 hours later (*figure 1*). Exposure to generalised cold in a cold room (4°C, with only regular indoor clothing) was only tolerated for five minutes; this caused general malaise with difficulties in swallowing and dyspnoea. Symptoms were not accompanied by an acute phase response.

In the past she had been investigated by several physicians, and no evidence for an underlying disease (e.g., infection, cryoglobulinaemia) was found. Hence and because of the life-long history, the diagnosis of idiopathic cold urticaria had been made. We sequenced the *CIAS1* gene, the causative gene in FCAS which encodes for cryopyrin, but no mutations were found. Previous treatment by oral antihistamines and steroids had been ineffective.

In the year before presentation, she had gradually developed neurological symptoms, which consisted chiefly of difficulties with speech and swallowing. On examination there was pseudobulbar dysarthria, slight right-sided anterior tibial weakness, elevated arm reflexes and knee jerks, subclonic Achilles tendon jerks and plantar responses in extensor. Extensive ancillary investigations yielded a tentative diagnosis of primary lateral sclerosis.

We studied cytokine production by peripheral blood mononuclear cells (PBMCs). Cells isolated from the patient and two healthy volunteers were stimulated for 24 hours at 37°C with lipopolysaccharide (LPS); supernatant concentrations of IL-1β, TNFα and IL-10 were measured by ELISA. This revealed no increased cytokine production by patient cells; rather, a trend towards less IL-1β production (*figure 2*). Incubation of the cells at a lower temperature (20°C) blocked cytokine production almost completely in both volunteers and patient. There was also no difference in cytokine production by patient cells isolated while symptomatic or symptom-free (data not shown). Serum IL-1α and IL-1β concentrations were not increased.

Figure 1. *Patient's right forearm, 24 hours after five-minute ice cube application, still showing a localised urticarial rash*

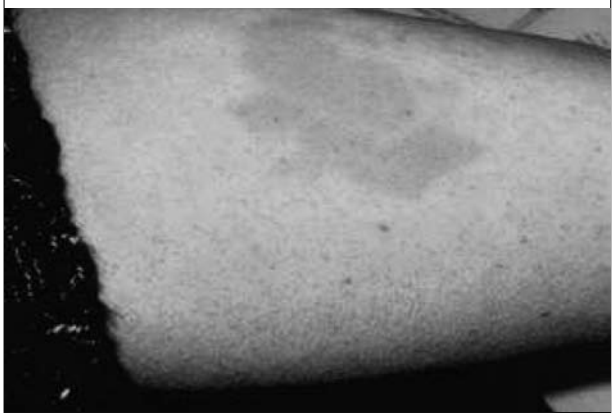
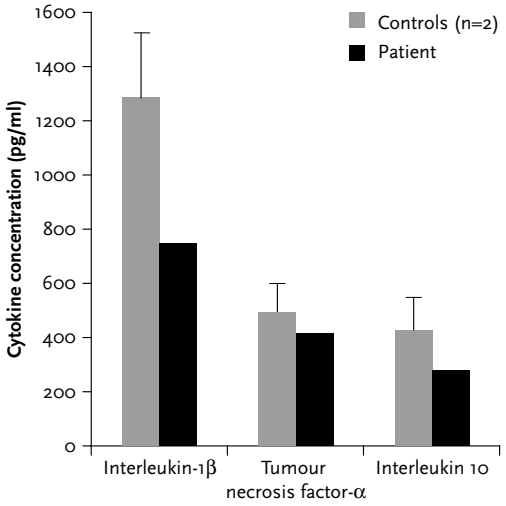


Figure 2. *Cytokine production by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells of two controls and the patient during the asymptomatic phase*



We decided to treat the patient with anakinra because of the severe, debilitating, cold urticaria, which clinically resembled FCAS. Anakinra treatment 100 mg subcutaneously a day had an immediate effect on the cold tolerance. After two doses, she was able to tolerate cold exposure in the cold room for at least 15 minutes (as long as the investigator, EB), without symptoms. The ice cube test did not lead to an urticarial rash (*table 1*). She was able to drink cold drinks without any symptoms. There was an impressive improvement in general well-being and activity. During follow-up of more than two years on daily anakinra, there was no recurrence of the cold urticaria and cold intolerance.

However, the response of the neurological symptoms was only subjective and temporary. After three weeks of anakinra treatment the patient reported greatly improved swallowing and greater speech facility, but speech analysis did not reveal a clear improvement. Over the ensuing months the neurological signs progressed and electromyographic examination showed signs of spontaneous muscle fibre activity and reinnervation in the thoracic and lumbosacral regions consistent with a diagnosis of ALS. The last examination in June 2008 showed nearly complete loss of the motor ability that enables speech, dropped head, inability to cough voluntarily, generalised weakness of the legs and she admitted to suffering from forced yawning. We decided to try a series of intravenous anakinra 300 mg infusions, but this did not result in any neurological improvement after ten injections. The side effects of anakinra were limited to transient skin lesions at the injection site during the first month; the high dose of intravenous anakinra was well tolerated. The patient recently died from complications of her neurological disease.

Table 1. *Patient characteristics with and without anakinra treatment*

Condition	Untreated	Anakinra 100 mg/day
CRP (mg/l)	<5	<5
Ice cube test	Localised urticarial rash	Asymptomatic
Cold room 4°C	Urticarial rash, dyspnoea	Asymptomatic
Outside temperature <20°C	Urticarial rash, dyspnoea	Asymptomatic
Cold drinks	Angio-oedema	Asymptomatic

DISCUSSION

We describe a patient with idiopathic lifelong cold intolerance with urticaria, who had a remarkable response to the interleukin-1 antagonist anakinra, which enabled her to restore her social life. Treatment of sporadic or idiopathic cold urticaria with anakinra has not been reported before, perhaps because many patients can be managed with antihistaminic drugs and occasional steroids.[5,6] However, in a severe case like this, anakinra seems to be a beneficial treatment with relatively few side effects. It was recently pointed out that the quality of life is severely hampered in patients with FCAS;[7] the severe cold intolerance in our patient had a similar impact.

From the effect of selective IL-1 inhibition, as is established by anakinra, it can be inferred that the symptoms in our patient were mediated by interleukin-1. This is, however, not mirrored by the cytokine studies, which did not demonstrate any increased serum concentrations of IL-1β and IL-1α, and no significant differences in production of cytokines (IL-1β, TNFα and IL-10) between patient and controls (*figure 2*). Interestingly, the IL-1β production by the cells of the patient tended to be lower than that of the controls, where one might have expected higher production. It is not an unusual observation, however, that mononuclear cells from blood do not show relevant cytokine changes, even in clinical situations that are assumed to be cytokine driven (e.g., rheumatoid arthritis, familial Mediterranean fever, and infections such as typhoid fever.)[8-10]

The combination of cold urticaria and neurological symptoms is found in the two other clinical syndromes that form part of the spectrum of cryopyrin-associated periodic syndromes (CAPS): in Muckle-Wells syndrome, sensorineuronal hearing loss can develop, and in CINCA/NOMID (abbreviations for chronic infantile neurological cutaneous and articular syndrome or neonatal-onset multisystem inflammatory disease, two names for the same disease), there is often severe neurological involvement which can include chronic meningitis (headache, seizures and spasticity of the lower extremities), cerebral atrophy, and sensorineuronal hearing loss.[11,12] These neurological complications also respond, at least partially, to anakinra treatment.[13] Our patient had neither a positive family history nor a CIAS1 gene mutation, but in about a third of patients who receive a clinical diagnosis of CINCA/NOMID no gene mutation can be found, and they still respond to anakinra.[10] However, the neurological phenotype of our patient did not closely resemble that of CINCA/NOMID, and there was no objective improvement or reversal of the gradual deterioration on anakinra treatment, even in a higher intravenous dose.

In the end, a definite, concomitant diagnosis of ALS was reached. We are not aware of any connection between urticaria and ALS. There have been a number of studies, mostly in mouse models of ALS, pointing to a role for IL-1β and caspase-1, the converting enzyme necessary for activation of pro-IL-1β in the pathogenesis of ALS.[14-18] Inhibition of caspase-1, either by pharmacological means[16] or by crossing the ALS mouse with a mouse with a dominant negative form of caspase-1 expressed in neuronal tissue,[18] had a positive effect on morbidity and mortality. We saw no improvement in our patient despite a high intravenous dose of anakinra. It can be argued that the drug is rapidly cleared from the body and may not reach adequate concentrations at the level of the central nervous system.

Anakinra has been found to be effective in a number of autoinflammatory syndromes in recent years, including familial Mediterranean fever (FMF),[19] Schnitzler syndrome,[20] hyper-IgD syndrome (HIDS),[21,22] and TNF-receptor associated periodic syndrome.[23]

In conclusion, this patient with severe idiopathic cold intolerance and urticaria unequivocally responded to IL-1RA, and daily injections gave her a normalised social life. The patient showed progressive neurological deterioration which turned out to be ALS, which did not respond to anakinra treatment.

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