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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

Familial Chilblain Lupus - What Can We Learn from Type I Interferonopathies?

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Abstract
Purpose of Review Familial chilblain lupus belongs to the group of type I interferonopathies and is characterized by typical skin manifestations and acral ischaemia. This review aims to give an overview of clinical signs and the pathophysiological mechanisms.
Recent Findings There are several mutations that can lead to this autosomal dominant disease. Most frequent is a mutation of the gene for TREX-1. However, as well cases of families with mutations in the SAMHD1 gene and, recently, with one for the gene that codes for the protein stimulator of interferon genes have been described. These genes are involved in the process of the detection of intracellular DNA, and their mutation results in an increased production of type I interferons and their gene products, resulting in auto-inflammation and auto-immunity. JAK inhibitors have been successfully used to treat this disorder.
Summary Familial chilblain is a rare disorder with very distinct clinical signs. Its pathophysiological mechanism gives insight into the process of interferon-induced inflammation in auto-immune diseases.

Keywords Chilblain lupus · hereditary · STING · Interferon · JAK inhibitors

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Introduction

Type I interferonopathies are clinically heterogeneous diseases. Pathophysiology, however, strongly links them. The term type I interferonopathies was coined by Crow [1] in 2011. It describes the common mechanism of a genetically caused dysfunction of the innate immune system that, in several ways, results in an increased production of type I interferons (IFN-α and -β) [2, 3•]. It is particularly patients with familial chilblain lupus who can be identified in the case of adults, showing very characteristic disease patterns and family histories when seeing a rheumatologist. The clinical characteristics of the most important type I interferonopathies are summarized in Table 1.

Type I interferonopathies are monogenic diseases, i.e. dysfunctions that are very rare in rheumatology compared to cases in pediatric metabolic medicine. When detected and decoded, however, they can grant significant insights into dysfunctions of the immune system leading to auto-immunity or auto-inflammation. This, in return, allows the drawing of conclusions about mechanisms that have an impact on both polygenic and environmental diseases. Studying diseases with monogenic defects resulting in auto-immunity and auto-inflammation, such as type I interferonopathies, can therefore help to understand mechanisms and find new treatments, as also in cases of non-genetic diseases.

Clinical Pattern of Familial Chilblain Lupus

Patients with familial chilblain lupus mainly suffer from acral skin efflorescences that have given the disease its name. They appear due to cold and are partly similar to papules. The disease affects the finger or toe tips as well as the nail fold, and is accompanied by Raynaud's

Table 1 type 1 interferonopathies. The diseases manifest in infancy or childhood. However, there are cases of familial chilblain lupus, in particular, that can only be detected at adult age due to the potentially mild course of the disease

Diagnosis	Genes	Mainly manifesting in
Familial chilblain lupus	TREX1 SAMHD1 TMEM173 (encodes the STING molecule)	Cutaneous erythematous and partly ulcerating, partly mutilating inflammatory acral lesions
Aicardi–Goutières syndrome	TREX1 RNASEH2A RNASEH2B SAMHD1 ADAR1 IFH1	Inflammatory encephalopathy, convulsions, muscular hypotension, severe statomotoric and mental delays in development, fever attacks, inflammatory cutaneous lesions, arthritis
STING-associated vasculopathy (SAVI)	TMEM173 (encodes the STING molecule)	Necrotizing vasculitis, pulmonary interstitial inflammatory changes, fever attacks
Retinal vasculopathy with cerebral leukodystrophy	TREX1	Loss of sight, cerebrovascular disease and dementia
Spondyloenchondrodysplasia	ACP5	Neurological disorders and lupus-like symptoms
Singleton–Merten syndrome	IFIH1	Progressive calcification of the vessels, osteoporosis and osteolysis
CANDLE syndrome	PSMB8	Rash, fever, arthralgia, lipodystrophy, neurological disorders, muscular atrophy and joint contractures

phenomenon. Spontaneous chilblain lupus mostly manifests with a mild progress, predominantly in cases of middle-aged women, whereas familial chilblain lupus mostly affects patients already in early childhood. The disease can lead to severe mutilations due to acral ischemia. Moreover, manifestations of chilblain lupus can strongly differ in patients, both within the family and depending on their age. The author and cooperation partners were able to characterize a family of Greek origin that repeatedly showed strong chilblain lupus manifestations over 3 generations. The two most severely affected family members had tissue defects of the nose, ears, fingers and toes [4••] (Fig. 1). A detailed description of the cases can be found in [4••]. The family which was affected by chilblain lupus suffers from an autosomal-dominant form of the disease caused by a mutation of the gene for the STING protein (stimulator of interferon genes). Capillaroscopy helped to detect very characteristic alterations in the family members that showed manifestations of ischemia on the fingers and toes: mainly multiple ramifications or clusters of capillaries (Fig. 2), and in one female patient, also ectasia and a reduced flow. There are hardly any results from capillaroscopy on the frequency of such alterations in cases of spontaneous chilblain

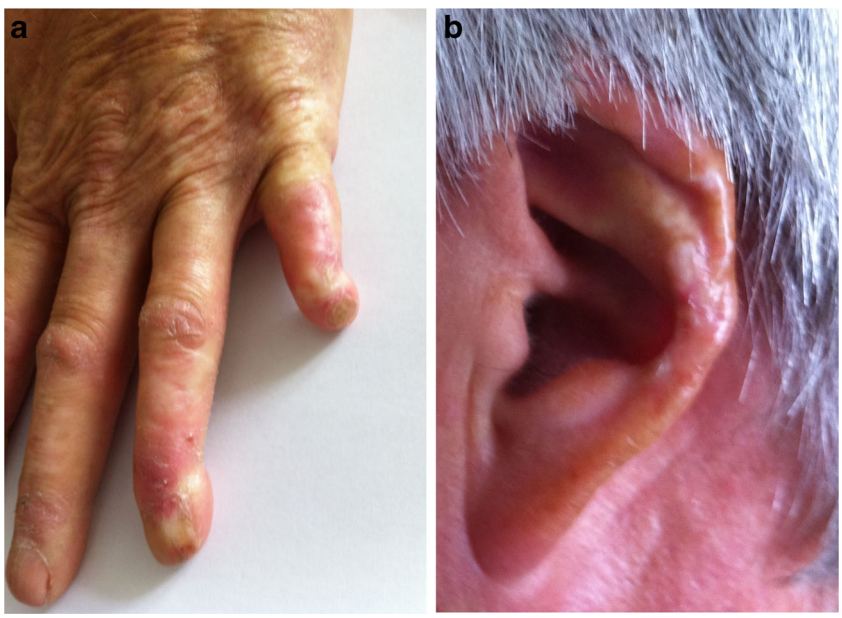

Fig. 1 Manifestations of ischemia in the case of a male patient suffering from familial chilblain lupus. (**a**) Nail loss and mutilations of the fingers. (**b**) Tissue defects of the ear

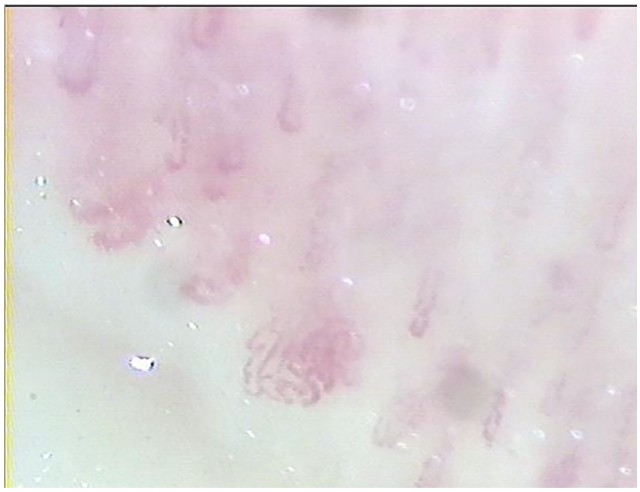

Fig. 2 Capillaroscopy of a female patient with familial chilblain lupus. There are multiple clusters of ramifications

lupus. None of the 33 patients suffering from chronic chilblain gathered in a pediatric case series, showed anomalies [5]. Pathological capillaroscopy findings could therefore potentially be seen as a differentiator between spontaneous and familial forms of chilblain lupus. It is interesting to see that the same test with spontaneous lupus revealed a rate of only 25% of patients with positive ANA [5]. Our patients also showed very slightly elevated levels of ANA of max. 1:160. We found only one female patient with positive anti-C1q antibodies, but no other specific serological markers such as anti-dsDNA antibodies. Serological changes in laboratory results are therefore of no diagnostic value, whether for spontaneous or familial chilblain lupus.

What stands out is that the manifestations on the fingers and toes are not predominant in all patients. One female patient had strong and extensive efflorescences characterized in biopsy by an inflammatory perivascular infiltration. That same patient had a reddened nose as a single acral manifestation (Fig. 3). She was the only one not to show typical capillaroscopic changes. None of the patients affected in the family with familial lupus that we described had a history of an interstitial lung disease. Lung function tests including CO diffusion tests revealed no findings and no evidence of an interstitial lung disease. Macular efflorescences of the skin, vascular conditions and interstitial lung diseases are, however, signs of the so-called SAVI syndrome (STING-associated vasculopathy with onset in infancy) [6••]. This disease pattern has only recently been studied in the case of children that have an activating mutation of the gene for STING, just like the family we described. So far, only spontaneous cases of this disease have been described [7].

Genetic Causes and Mechanisms of Familial Chilblain Lupus

Familial chilblain lupus is a type I interferonopathy that can be caused by several genetic defects in the process of type I interferon induction. They are induced when intracellular receptors, that detect indications of hazards—such as viral DNA or RNA—are activated. The stages of activating them until setting off the production of interferons follow an intracellular cascade of factors (Fig. 4). Intracellular deoxyribonucleic acids (DNA) are primarily recognized by cyclic GMP-AMP-synthase (cGAS) [8] that catalyzes the formation of cGAMP. The signal is then transmitted by the STING molecule. cGAMP binds to STING, forming a homodimer, and can then lead to type1 interferon induction by means of the factors TBK-1 and interferon response factor 1 (IRF-1). By binding to receptors, the resulting interferons eventually induce interferon-

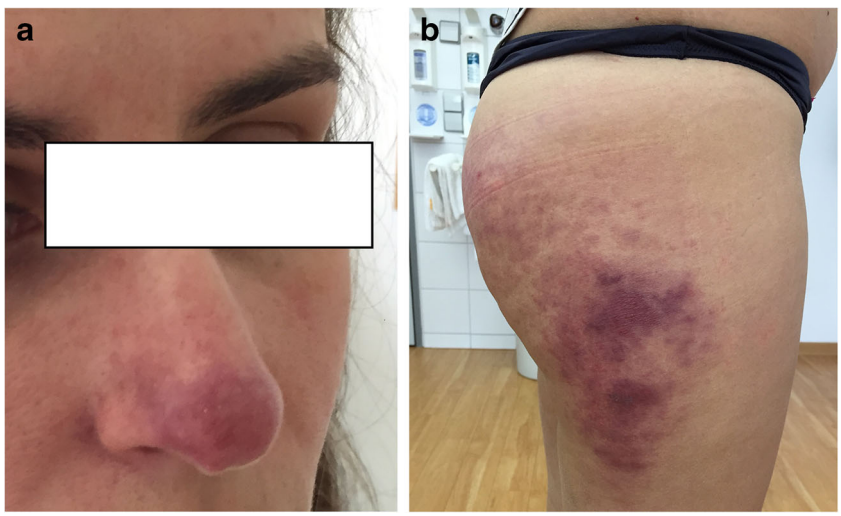

Fig. 3 Efflorescences on the skin of a female patient with mainly cutaneous manifestations. The nasal tip is reddened (**a**) and there are extensive erythematous efflorescences in the gluteal region and on the thigh (**b**)

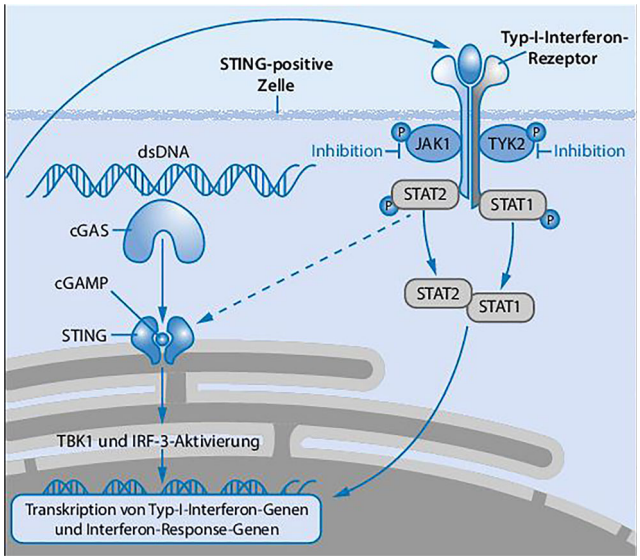

Fig. 4 Overview of the interferon activation process through the detection of intracellular DNA (according to Liu et al. [4••]) (with permission from Springer, Berlin 2017)

stimulated genes (ISG) that are part of a complex network of mechanisms inhibiting the reproduction of viral particles. The stages inactivating ISG are controlled by the intracellular messenger molecules, JAK1 and STAT2, as well as TYK1 and STAT1 (Fig. 4).

The cytosol receptors for intracellular nucleic acids are complemented by toll-like receptors. They recognize extracellular and endocytosed bacterial components of the cell walls or nucleic acids, and also activate the type 1 interferon system [3•].

Mutations in several molecules, all being involved in the type 1 interferon activation process mentioned above, are described as genetic causes of familial chilblain lupus. Most frequent are mutations in the TREX1 molecule gene (Three-prime Repair Exonuclease1) for which evidence has so far been found in the case of 3 families [9–12]. This mutation is also known from Aicardi–Goutières syndrome, a genetic disease manifesting in early childhood and predominantly with a severe neurologic disorder (Table 1). The children, however, also show lupus-like, autoimmune phenomena such as arthritis, hepatopathy, cytopenia, and evidence of ANA as well as acral chilblain lesions due to cold [13–15]. One family with familial chilblain lupus proved to have a mutation in the gene of the SAMHD1 molecule (SAM domain and HD domain-containing protein 1) [16]. Both mutations are autosomal dominant conditions with their respective symptoms already manifesting in early childhood. The TREX1 gene is responsible for the intracellular decomposition of DNA and, with it, inhibits auto-inflammatory lupus-like diseases [17–19]. SAMHD 1 regulates the intracellular decomposition of dNTP and RNA [20]. Defects in both molecules therefore lead to an intracellular accumulation of nucleic acids and, consequently, activate the system of intracellular DNA recognition resulting in type1 interferon production. The case of the family described above proved to be the first one in which familial chilblain lupus was caused by an autosomal dominant mutation of the STING molecule following at a lower stage of the signal cascade of type1 interferon induction [4••] (Fig. 4). This mutation affects a component of the dimer interface for STING that has been highly conserved throughout evolution. A missense mutation (Gly166Glu) is detected at position 166 in which glycine is replaced by glutamate. This mutation co-segregates with the phenotype of the familial chilblain lupus found in the affected family. This proved that changes in configuration through the mutation lead to new and previously nonexistent polar interactions of the STING molecules stabilizing the dimer. This results in an upregulation of interferon-stimulating genes in the affected patients. Cells transfected with the mutant in vitro showed a constitutive expression of IRF and interferon-β, i.e. an expression of these molecules without cGAMP, necessary in the case of its wild-type. Hence, the activating STING mutation leads to a permanent activation of the type I interferon system with the clinical phenotype of familial chilblain lupus.

The type I interferon gene signature is also of importance in systemic lupus erythematosus (SLE). Increased type I interferon expressions can be detected in the blood and skin and in synovial biopsies of patients with SLE compared with healthy subjects [21, 22]. Clinical studies with monoclonal antibodies against interferon-α brought evidence of significant therapeutic results, and research continues in this respect [23]. It is interesting to see that there is an increased potential for SLE patients to have heterozygous forms of TREX1 which contribute to the clinical pattern of SLE with multiple factors and can, for instance, be associated with an affection of the skin and photosensitivity [24, 25]. This also applies to other enzymes that contribute to degrading intracellular DNA. Another interesting finding is that antimalarial drugs, playing a very important role in SLE treatment, can interfere in the process of intracellular DNA recognition. An et al. [26] were able to show that chloroquine and hydroxychloroquine can inhibit cGAS, i.e. the molecule that recognizes intracellular DNA and then activates the STING molecule by forming cGAMP.

As described before, the pathogenesis of familial chilblain lupus proves to be related to SLE and hence helps better understand the processes of this multifactorial and polygenetic disease.

It is remarkable that a STING-activating mutation in spontaneous cases of the SAVI syndrome leads to another clinical phenotype. The pediatric SAVI patients

described suffer especially from a heavier systemic inflammation with frequent fever and interstitial lung diseases, and with a clinical pattern that can feign granulomatosis with polyangiitis [6••, 7, 27, 28]. In the case of the family described by the author and his cooperation partners, the constitutive expressions of IRF and interferon-β within cells were compared, considering whether they had been transfected with the SAVI mutant N154S or the chilblain mutant G166E. This showed that the SAVI mutant induced an even stronger constitutive expression than the chilblain mutant [4••]. The varying clinical patterns of the two diseases caused by STING mutations therefore seem due to the quantitative difference between the two mutations in activating the interferon system.

Treatment Approach with JAK Inhibition

As described before, the induction of interferon-induced genes is also regulated by the JAK1 and STAT2 systems (Fig. 4). JAK inhibition is therefore an approach in treatment that can be derived pathophysiologically. The work of Liu et al. also showed in vitro the effects of the JAK inhibitor tofacitinib on cell level [6••]. I treated the two patients with the most severe expressions of familial chilblain lupus of the family described in [4••] with the JAK inhibitor tofacitinib with 5 mg p.o. twice a day. Due to restrictions in medication availability, treatment could only be continued for 14 days. Nevertheless, both patients proved to be completely freed from the painful acral ischemia symptoms after only a few days. Before starting treatment, both patients showed a notably increased IFN gene signature that had returned to normal after 12 days [4••]. In the meantime, attempts to treat several other type I interferonopathies with JAK inhibitors have been published; that is the case for 2 patients with Aicardi–Goutières syndrome [29•] and 3 patients suffering from SAVI syndrome [30], all showing clinical response. The treatment proved to lower the IFN gene signature that was upregulated due to the mutation; in sequential tests under longer treatment, however, this proved not always to be permanent and partly only incomplete [31•]. Both IFN gene signature upregulations by intercurrent infections and counter-regulatory IFN production mechanisms, that eventually help avoid infections, have been discussed [29•, 31•].

Finally, JAK inhibitors are also tested with several non-monogenic autoimmune diseases. The database www.clinicaltrials.gov contains two phase II studies on SLE with the JAK inhibitor tofacitinib and one with baricitinib. Some individual cases of both non-genetic chilblain lupus [32] and refractory dermatomyositis [33] have been described as being successfully treated with JAK inhibitor ruxolitimib. Additionally, JAK inhibitors can be effective against alopecia areata [34]. Tofacitinib has been tested both systemically and as a local therapy in clinical trials of this indication (www.clinicaltrial.gov).

Conclusion

In summary, familial chilblain lupus belongs to the new group of type I interferonopathies with which rheumatologists also have to deal for adult patients. Its clinical pattern is characteristic and shows severe acral manifestations of the chilblains as well as ischemia-related tissue defects. Understanding the pathophysiological mechanisms resulting from the respective mutations, that eventually all lead to an increased production of type I interferons, can help draw conclusions on how auto-inflammation and auto-immunity are caused.

Compliance with Ethical Standards

Conflict of Interest Dr. Fiehn declares he has no conflicts to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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