We report a 2-year-old girl with developmental delay who, from the age of 1 year, developed pernio-like lesions of the hands and feet initially diagnosed as chilblain lupus. Histological examination showed features of epidermal necrosis with intraepidermal bulla formation, interface dermatitis, lymphocytic vasculitis with fibrinoid necrosis and thrombi formation, both superficial and deep dermal lymphocytic infiltrate, lymphocytic eccrine hidradenitis and absence of marked dermal edema. Subsequent investigations suggested a clinical diagnosis of Aicardi–Goutières syndrome (AGS), a rare genetic leukoencephalopathy. Recently, both AGS and familial chilblain lupus, an autosomal dominant form of systemic lupus erythematosus (SLE), have been shown to be allelic thus suggesting a common pathogenic basis. In addition, a phenotypic overlap is apparent between SLE and AGS. To our knowledge, this is the first comprehensive dermatopathological report of the cutaneous lesions seen in AGS, and our paper highlights the importance of considering AGS in the differential diagnosis of pernio and chilblain lupus.


Aicardi–Goutières syndrome (AGS) is a genetic leukoencephalopathy typically associated with basal ganglia calcification as well as increased levels of interferon-alpha (IFN-α) and white cells in the cerebrospinal fluid (CSF). Chilblain-like lesions are seen in approximately 40% of cases and represent the most important extra-neurological manifestation of the disease. Here, we describe a child with skin lesions, which were initially diagnosed as chilblain lupus but in whom subsequent investigations suggested a diagnosis of AGS. Our case is important in illustrating the skin manifestations of AGS and highlighting the clinical and pathogenic overlap between cutaneous forms of systemic lupus erythematosus (SLE) and AGS.

Case report
A 9-month-old female infant, born to first cousins of Moroccan origin, was seen at the pediatric neurology department because of psychomotor delay. The girl was delivered at 39 weeks gestation after an uneventful pregnancy. Her neonatal history was unremarkable. Clinical examination showed truncal hypotonia, pyramidal tract signs and convergent strabismus. A brain magnetic resonance imaging (MRI) showed the presence of diffuse and mostly periventricular white matter changes. Serology for TORCH infections (Toxoplasmosis, Rubella, CMV, Herpes simplex) was negative. CSF analysis, performed at the age of 15 months, was normal with no
pleocytosis detected. Metabolic work-up including blood and CSF lactate, blood and urine amino-acids and urine organic acids was unremarkable. Immunological investigations were normal except for a weakly positive antinuclear antibody (ANA) titer (1/80). No structural chromosomal abnormalities were observed on karyotype examination.

The infant was seen at the pediatric dermatology department at the age of 2 years because of recurrent acral eruptions on the hands and feet, which had been present for 1 year. The skin lesions were exacerbated by exposure to cold, and the parents also reported intermittent episodes of fever since the age of 13 months. Clinical examination of the hands showed periungual erythema and erythematous plaques on the dorsal side of the interphalangeal joints (Fig. 1). Areas of necrosis with crust formation were also seen on these plaques. Infiltrated painful papules on the erythematous and swollen soles were additionally observed (Fig. 2). We noticed infiltrated plaques with necrotic bulla formation at the center and on the dorsal side of the feet (Fig. 3).

Biopsy was performed at the edge of a necrotic bulla. At low magnification intraepidermal bulla formation was seen in association with both superficial and deep dermal infiltrates. At higher magnification the intraepidermal bulla were showed to result from loss of cohesion between apoptotic keratinocytes (Fig. 4). Interface dermatitis and basal vacuolar degeneration were also present (Fig. 5). In the superficial dermis, a dense lymphocytic infiltrate was seen. Fibrinoid necrosis was present within small vessel walls. Thrombi were also apparent within the lumen of the affected vessels (Fig. 6). In the deep dermis, a lymphocytic infiltrate was present that was located around eccrine coils (Fig. 7). No marked edema was seen within the papillary dermis. Alcian blue stain did not show any increase of mucin.

Considering the clinical presentation of acral chilblain-like necrotic lesions worsened by exposure to cold, the histological findings documented above and the weakly positive ANA titer, we suspected a diagnosis of chilblain (pernicious) lupus. However, repeat ANA titers were normal despite subsequent serum dilutions. Antiphospholipid antibodies were negative. Complement levels, coagulation indices, white blood count and sedimentation were also normal. Cryoglobulinemia was excluded. Direct immunofluorescence of the skin lesions was negative and capillaroscopy was normal. There were no clinical or biological indications of internal organ involvement. Diagnosis of lupus could therefore no longer be sustained. In addition, lack of increased mucin in Alcian blue stain was another argument against this diagnosis.
AGS was considered because of the combination of small vessel vasculitis, developmental delay, recurrent fevers, the MRI findings and chilblain-like lesions. A subsequent cerebral computed tomography scan was performed that demonstrated the presence of basal ganglia and periventricular calcifications, a feature seen frequently in AGS.1,2 A second CSF analysis showed an equivocal IFN-α concentration of 2 IU/l (normal <2 UI/ml). Again, no CSF pleocytosis was observed. Subsequent mutation analysis of the AGS1-4 genes was normal.

**Discussion**

AGS is an early onset encephalopathy typically associated with intracranial calcifications, a leukodystrophy and raised numbers of white cells and increased titers of IFN-α in the CSF. Chilblain-like lesions are seen in approximately 40% of cases. Exclusion criteria require the absence of any evidence of prenatal/perinatal TORCH infection and of any other metabolic or neurodegenerative disorder.1,3-6

The developmental delay observed in our case, together with the recorded parental consanguinity, imaging features of intracranial calcification and white matter involvement, recurrent fevers and skin lesions are highly indicative of AGS. It is of note that our case showed neither a CSF pleocytosis nor a significant increase in CSF IFN-α. However, it is well recognized that levels of white cells and IFN-α tend to return to normal in the first few months/years after disease onset, and consistently normal CSF white cells numbers have been recorded in several cases.1,7 Moreover, although we were unable to detect a mutation in AGS1-4, evidence exists for further genetic heterogeneity with approximately 20% of bona-fide clinical cases being mutation negative using current gene screening strategies (personal communication).

Chilblain-like skin lesions represent the most striking of the extra-neurological features of AGS.

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**Fig. 4.** Intraepidermal bulla resulting from loss of cohesion between apoptotic keratinocytes.

**Fig. 5.** Interface dermatitis with basal vacuolar degeneration.

**Fig. 6.** Thrombi within lumen of affected vessels.

**Fig. 7.** Lymphocytic eccrine hidradenitis.
These lesions typically present as intermittent puffy swelling and necrotic areas on the hands, feet and pressure points (ears and elbows). Acrocyanosis with cold hands and feet are also seen. Erythematous periungual skin, which may be complicated by periungual infection, is a typical finding of this syndrome. Lesions are cold sensitive being much worse in the winter months. The cutaneous features seen in perniosis was absent in our case. Microvascular injury with thrombi formation, both superficial and deep dermal lymphocytic infiltrate and lymphocytic eccrine hidradenitis initially resulted in a diagnosis of chilblain lupus. However, as already mentioned, no increased mucin was observed in the Alcian blue stain. Keratinocyte apoptosis was considered to be secondary to the ischemia provoked by the necrotizing vasculitis. The presence of perivascular and periadnexal lymphoid infiltrates with extension around eccrine coils, as well as apoptotic keratinocytes is seen in both perniosis and chilblain lupus. However, we favored a diagnosis of perniotic lupus because basal vacuolar change is more characteristic of chilblain lupus. In this disorder, it is more widespread than the focal interface change seen in idiopathic perniosis.

In addition, the marked edema in the papillary dermis seen in perniosis was absent in our case. Microvascular injury with thrombi formation, which is a well-known finding in perniosis and chilblain lupus, is also established to be present in AGS.

AGS is inherited in an autosomal recessive manner and the syndrome shows genetic heterogeneity. AGS1 at 3p21 is caused by mutations in the gene encoding the DNA exonuclease TREQ1, while AGS2, AGS3 and AGS4 result from mutations in genes encoding the three non-allelic subunits (respectively B, C and A) of the RNASEH2 endonuclease complex. In addition, further genetic heterogeneity exists so that other disease-causing genes are yet to be identified. Considering their presumed roles in nucleic acid metabolism, it has been proposed that a failure of three primer repair exonuclease 1 (TREX1) and RNASEH2 nuclease activity results in the survival and accumulation of intracellular DNA/RNA repair and replication intermediates. These fragments might then trigger an inappropriate immune response with subsequent overproduction of IFN-α. We speculate that an IFN-α induced vasculitis is the cause of leukodystrophy and skin lesions seen in AGS. Both AGS and placentally acquired viral infections are characterized by the production of high levels of IFN-α. AGS is therefore considered a Mendelian mimic of the sequelae of congenital viral infection.

Overlap between infantile SLE and AGS is apparent at both the phenotypic and pathological level, suggesting a common immune dysfunction. Hypocomplementemia, positive ANA and perniotic lesions on the extremities can be seen in both AGS and SLE. De Laet has reported two sisters with AGS, one of whom also developed SLE. AGS with antiphospholipid antibodies has been described in two sisters. Additionally, intracranial calcification with a predilection for the basal ganglia has been reported in up to 30% of patients with cerebral SLE and the basal ganglia calcification and white matter attenuation seen with central nervous system involvement in neonatal lupus are remarkably similar to the radiological features observed in AGS. Tubuloreticular inclusions, ultrastructural features related to the presence of circulating IFN-α, are found in SLE as well as in AGS.

Finally, the vasculitic skin lesions seen in AGS, with immunoglobulin deposition at the dermal/epidermal junction, are highly suggestive of underlying immune pathology. The role of IFN-α in SLE is well established and it is known that therapy with this molecule can induce SLE. Cutaneous lesions of both AGS and chilblain lupus result from microvascular injury and IFN-α-induced vasculitis may have a key role in their pathogenesis. Despite these similarities between AGS and lupus, distinct diagnostic criteria have been proposed for each disorder. The association of an early onset leukodystrophy with diffuse demyelination on MRI and increased levels of interferon in the CSF has not been described in SLE but is highly characteristic of AGS. In addition, positive ANA are found in only a minority of patients with AGS.

Lee Kirsch et al. recently reported that a gene for familial chilblain lupus (FCL) mapped to chromosome 3p21, and subsequently, Rice et al. have shown that AGS and FCL are allelic disorders by showing heterozygous TREX1 mutations in an FCL family. Our report serves to further highlight the association between cutaneous chilblain lesions and AGS.

We believe that the histological similarities between AGS and chilblain lupus should also be seen within this overlap. These similarities include interface dermatitis with basal vacuolar degeneration, lymphocytic vasculitis with fibrinoid necrosis and thrombi formation, superficial and deep dermal lymphocytic infiltrate associated with lymphocytic eccrine hidradenitis, without marked dermal papillary edema.
Conclusion
As far as we are aware, this is the first dermatopathological report on AGS. By presenting this case, we would wish to conclude to the following statements: (a) Diagnosis of AGS should be included in the histological differential of perniosis and mostly of chilblain lupus, especially in presence of ongoing unexplained leukodystrophy. (b) IFN-induced microvascular injury can be seen as a common immune dysfunction within pathogenesis of both AGS and chilblain lupus and could explain their clinical and histopathological similarities. (c) Chilblains are a clinical manifestation of the phenotypic overlap between AGS, FCL and chilblain lupus within SLE.

References