Blue (or purple) toes: Chilblains or chilblain lupus-like lesions are a manifestation of Aicardi–Goutières syndrome and familial chilblain lupus

To the Editor: In their comprehensive review of blue (or purple) toe syndrome, Hirschmann and Raugi do not refer to Aicardi–Goutières syndrome (AGS; OMIM #225750), or familial chilblain lupus (OMIM #610448), in which chilblain-like lesions on the fingers and toes are an important diagnostic sign. First described in 1984, AGS is a genetically-determined encephalopathy characterized by basal ganglia calcification, white matter abnormalities, chronic lymphocytosis in the cerebrospinal fluid (CSF), and raised levels of interferon alfa (IFN-α) in the CSF of affected infants. It may present at birth or develop several months later after an initial period of apparently normal development. The majority of children have microcephaly and severe neurologic and intellectual impairment, although a small number of mildly affected patients have been identified. The clinical features and radiographic evidence of basal ganglia calcification in the newborn period may lead to a mistaken diagnosis of congenital viral infection.

Chilblain-like lesions on the fingers and toes are a characteristic finding seen in approximately 40% of AGS cases (Fig 1). They typically develop after the first year of life and may result in cutaneous or digital ischemia. The clinical morphology may be indistinguishable from that of chilblain lupus erythematosus (LE). Histopathologic examination is rarely reported, but in one case showed an interface dermatitis with changes similar to those seen in chilblain LE. Granular deposition of immunoglobulin M along the basement membrane has also been reported. A small number of children have had more extensive cutaneous or systemic disease with positive serology, suggesting a diagnosis of systemic LE (SLE).

Two severely neurologically impaired children, previously thought to have cerebral palsy and an unclassified connective tissue disease/vasculitis, were diagnosed with AGS at British Columbia’s Children’s Hospital. A 3-year-old white girl presented with transient leukocytoclastic vasculitis on the lower extremities, persistent chilblain lupus-like lesions on the hands and feet, and a violaceous discoloration on the eyelids, face, and chest characterized histopathologically by dermal mucin deposition; she died at 9 years of age as a result of intracranial hemorrhage from a carotid aneurysm associated with an intracranial angiopathy. A 10-year-old East Indian boy had purple fingers and toes resulting in severe ischemic necrosis, with similar but milder changes on the nose and helical rims of the ears; he died suddenly of unknown causes at 22 years of age. Both children had positive autoimmune serology (antinuclear, anti–double stranded DNA, antihistone, anticardiolipin, and antineutrophil cytoplasmic antibodies were...
variably detected in one or both patients) without a consistent diagnostic pattern.

AGS is genetically heterogeneous. Autosomal recessive inheritance of mutations in the gene encoding the DNA exonuclease TREDX1 (AGS1) and any of the three RNASEH2B/C/A genes (AGS2, AGS3, and AGS4, respectively) coding for the RNASEH2 endonuclease complex can cause AGS and associated chilblains. Heterozygous TREDX1 mutations have also been identified in pedigrees segregating familial chilblain LE.\(^7\) In addition, heterozygous TREDX1 mutations are reported in SLE,\(^8\) making TREDX1 mutations the most common monogenic cause of LE yet identified. It is postulated that defective nuclease function results in inadequate removal of endogenous nucleic acids, which then trigger IFN-\(\alpha\)-mediated activation of the innate immune response and may also “spill over” into an adaptive immune response with the production of antibodies against native DNA and RNA.\(^9\)

Dermatologists should consider these genetic syndromes when blue (or purple) toes suggestive of chilblain LE or severe digital ischemia are observed, both in patients with congenital or early onset neurologic impairment and in otherwise healthy individuals.

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Funding sources: None.