Atrophoderma Vermiculatum: A Cutaneous Feature of Loeys-Dietz Syndrome

Atrophoderma vermiculatum (AV) is a rare skin disorder, typically presenting in childhood with a reticular pattern of skin atrophy on the cheeks, preauricular area, and forehead that seems to result from inflammation around follicular plugs. The causative mechanism leading to AV is unclear. It can present as an isolated skin manifestation, or AV can be part of other conditions including genetic disorders.

Atrophoderma vermiculatum can be related to Loeys-Dietz syndrome (LDS). Herein we report the association of AV with TGFBR2-related Loeys-Dietz syndrome (LDS).

Report of Cases

**Patient 1.** A 12-year-old boy with cardiac (widened aortic root and pulmonary artery, patent ductus arteriosus) and skeletal abnormalities (sagittal craniosynostosis, thoracic scoliosis, lordosis, pectus excavatum, long extremities, vertical talus, varus deformity, hyperlaxity) was diagnosed with LDS. Furthermore, dysmorphic facial features, amelogenesis imperfecta, and a high arched palate with lobulated uvula were also noted. A de novo pathogenic mutation in TGFBR2 (c.1639G>C p.Asp547His) was identified. At age 4 years, the patient had developed atrophic skin lesions on both cheeks, which stabilized after a few months of progression. At age 10 years, both cheeks showed reticulate atrophic lesions with a few follicular papules, which was diagnosed as AV (Figure, A).

A, Before treatment, swelling and violaceous discoloration are apparent on the proximal fingernail folds along with oozing of blood, hemorrhagic crusting of the fingernails, and pus discharging from the lateral nail folds. B, After treatment, the hemorrhagic crusting and paronychia have completely resolved, with resultant atrophy of the fingernails.
Patient 2. A 12-year-old boy (Figure, B) had been born with a cleft palate, associated Pierre Robin sequence, and talipes equinovarus. At age 6 years, he was noted to have mild reticulate scarring fitting the diagnosis of AV on both cheeks as well as milia in the infra-orbital region and the auricles. He also had cardiac (enlarged aortic annulus and aortic sinuses, aortic root dilatation, and bilateral carotid artery tortuosity) and skeletal abnormalities (postural scoliosis, mild pectus excavatum, metatarsus varus, joint hypermobility, bilateral fifth finger clinodactyly, and clinodactyly of left proximal interphalangeal joints II and III) and was diagnosed with LDS. In addition, a left inguinal hernia and a bifid uvula were documented. A de novo heterozygous mutation in \textit{TGFBR2} (c.1546_1557del12bp; p.Val516_Asp519del) was identified.

Discussion | Both of the described patients had AV and LDS due to heterozygous \textit{TGFBR2} mutations; LDS is characterized by aggressive arterial aneurysms and widespread systemic involvement. To our knowledge, only 2 patients with AV and an aortic aneurysm syndrome have been reported in the literature. The first, a 14-year-old boy, was evaluated for Marfan syndrome, but genetic analysis of the \textit{FBN1} gene was not completed at the time of publication.\(^2\) The second, 24-year-old patient, was included in a study of 25 patients with LDS.\(^3\) She had multiple facial milia around the eyes and malar AV. A mutation in \textit{TGFBR2} was identified. Of additional interest, 3 other patients in that same study also had facial milia and a \textit{TGFBR2} mutation.\(^3\) Therefore, milia may be a feature of \textit{TGFBR2}-related LDS.

Both AV and LDS are quite rare, so the association of these 2 conditions in several cases does not seem simple coincidence. It is difficult to explain the occurrence of AV in patients with LDS. The pathogenesis of LDS is aberrant TGF-\(\beta\) signaling due to mutations in \textit{TGFBR1/2}, but many questions still remain. Similarly, the pathogenesis of AV is largely unknown. It has been hypothesized that the keratinocytes in patients with AV mediate release of inflammatory cytokines in response...
to the plug formation. This inflammation then leads to fibrosis and atrophy. It may be that TGF-β signaling may also be involved because it is known that TGF-β signaling plays an important role in wound healing and scar formation. In LDS, atrophic scars and delayed wound healing have been reported.5 Interestingly, TGFBR1 null mutations cause multiple self-healing squamous epithelioma (MSSE)6 with subsequent atrophic scarring, which is also typical for AV. However, patients with MSSE do not have features of LDS, which is usually caused by missense mutations in the TGFBR1- or TGFBR2-kinase domain.5 Further investigations are needed to clarify the relationship between AV and LDS.

In conclusion, it appears that AV should be added as a cutaneous feature of LDS, possibly more specifically TGFBR2-related LDS. In view of the crucial importance of early detection and management of aortopathy in LDS, we suggest a careful evaluation for clinical features of LDS, including cardiac ultrasonography and possibly TGFBR1/2 DNA analysis in every patient presenting with AV.

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Acute Onset of Acrokeratosis Paraneoplastica (Bazex Syndrome)

Acrokeratosis paraneoplastica, or Bazex syndrome, is a well-characterized but rare dermatosis first described by Bazex et al1 in 1965 in association with a malignant neoplasm of the upper aerodigestive tract. It is typically seen in men older than 40 years.2-5

Report of a Case | A 57-year-old man sought medical attention for dysphagia, chest pain, and a 40-lb weight loss over 6 months. Imaging demonstrated a distal esophageal ulcerating mass covering 50% to 75% of the esophageal circumference. Biopsy showed a poorly differentiated epithelioid malignant neoplasm; immunohistochemical staining was negative for pan-cytokeratins, melanoma, and mesenchymal markers.

On physical examination, the patient had desquamative, edematous digits of the hands and feet with hyperpigmented, lichenified plaques. He had numerous grouped and clustered tense vesicles (1-3 mm) and a few hemorrhagic bullae (Figure 1). He also had an ill-defined hyperkeratotic, violaceous patch on his nose and small vesicles on the ears. His knees exhibited hyperpigmented hyperkeratotic plaques. The patient reported that his cutaneous manifestations developed in less than a week.

Biopsy specimens from the wrist showed an acanthotic and mildly spongiosis epidermis with minimal interface, vacuolar damage, and overlying parakeratosis (Figure 2). In the dermis, there was an increased number of eosinophils and pigment incontinence. Direct immunofluorescence demonstrated broad-based band staining of fibrin at the basement membrane zone and granular deposits of C3.

Skin-directed therapies included a brief course of oral prednisone, clobetasol ointment, and aluminum acetate soaks, with mild improvement in discomfort and appearance of the skin lesions. Systemic chemotherapy was initiated to treat the metastatic, poorly differentiated epithelioid malignant condition. The patient also received palliative radiation therapy to the esophagus and salvage systemic therapy, but he died after 4 months.

Discussion | Acrokeratosis paraneoplastica is a rare paraneoplastic phenomenon with characteristic findings, though its