A recessive case of Thévenard’s disease, aka. ulcero-mutilating acropathology syndrome with hypodontia

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Abstract
Thévenard’s disease, aka. ulcero-mutilating acropathology syndrome, is a rare hereditary disorder. In this report, we describe the case of a 6-year old patient with deep, non-healing ulcers on her lower extremities that progressed to spontaneous mutilation of her toes and distal phalanges. In this case, seldom-reported features were encountered such as hands’ involvement, absence of family history and congenital absence of teeth eruption. Diagnosing this case can be challenging due to the rarity of the disease. Early detection and appropriate approach help to better-control complications and further-delay disability, especially that no cure has been identified for this case yet. Therefore, it is vital to keep this syndrome as part of a deferential diagnosis when approaching patients with similar symptoms. It is also important to emphasize that regular examinations and rapid response to new lesions are crucial and should be combined with education and support to patients and their families.

INTRODUCTION
Thévenard’s disease, aka. ulcero-mutilating acropathology syndrome, is a rare hereditary disorder with very few reported cases in the medical literature. It was first described in 1852 in a patient with non-healing ulcers on his feet [1]. In the 1990s, 29 cases were followed up and the disease was classified as a Type 1 hereditary sensory neuropathy with dysautonomia and atrophy in the posterior spinal ganglia—confirmed by autopsies of deceased patients [2, 3]. The mode of inheritance of ulcero-mutilating acropathology is autosomal dominant. However, recessive forms were less frequently encountered [4].

Clinically, the disease often starts with slowly evolving ulcerative lesions on the distal parts of the lower extremities [2]. These ulcers, which are attributed to hypoesthesia, progress to involve bones and may get infected. As the disease progresses, osseous lesions, osteo-articular destruction and mutilations occur. The disease is diagnosed based on clinical manifestations and progression [2, 5].

The diagnosis of this case can be challenging due to the rarity of the disease and the wide differential diagnosis to consider while approaching it. Here, we report an advanced, misdiagnosed, recessive form of Thévenard’s disease with hands involvement in a female child from Syria.

CASE REPORT
A 6-year-old female was admitted to the orthopedics department, and a dermatological consultation was requested to assess non-healing, painless open sores on her left heel and lateral malleolus (Figs 1-2). Her medical history includes similar
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ulcers that started on the right plantar surface, tips of her fingers and toes at the age of four. The previous ulcers led to spontaneous mutilation of her fingers and toes (Fig. 3). Her history is negative for other dermatological or systematic diseases. She has achieved all developmental milestones with height and weight proper for her age with an exception for teeth eruption. The patient’s parents are a consanguineous couple with negative family history.

Physical examination confirmed the presence of deep ulcers with local signs of infection and widespread necrosis, and confirmed complete absence of teeth (Fig. 4). Neurological examination showed decreased sensation to pain and temperature in her lower limbs. Her motor abilities were limited due to pain and edema. Angiographic evaluation with Doppler ultrasonography of her lower limbs showed no abnormalities. Assessment of other organs was completely negative. A dental consultation was sought. However, no specific pathology was detected to explain her hypodontia.

Her labs at admission are summarized in Table 1. A skeletal survey revealed a 1-cm lytic lesion in the body of her left radial bone (Fig. 5). We conducted electro-physiologic studies and it showed evidence of sensory peripheral neuropathy. Consequently, a wide differential diagnosis of autoimmune diseases and neuropathies was considered including diabetic neuropathy, viral infections, anti-phospholipid syndrome, amyloidosis, hereditary motor and sensory diseases, ectodermal dysplasia and hereditary sensory and autonomic neuropathy. As detailed in Table 1, the patient’s blood tests did not show signs of diabetes (normal FBG and Hemoglobin A1c) or signs of viral infections (normal white blood cells differential and viral IgM antibodies). Also, her biopsies did not show signs of amyloidosis and she did not meet any of the clinical or laboratory criteria for antiphospholipid antibody syndrome. Furthermore, she did not show any signs of concurrent autoimmune diseases and several markers of autoimmunity (anti-nuclear antibodies, antineutrophil cytoplasmic antibodies and rheumatoid factor) were negative. Eventually, based on the characteristic clinical picture and all the

Figure 1: Ulcers on the left heel and lateral malleolus at presentation.

Figure 2: Ulcer on the left heel before admission to the hospital.

Figure 3: Ulcers on the tips of the right hand’s fingers.
Figure 4: Complete absence of teeth at presentation.

Figure 5: Lytic lesion in the left radial bone.

Figure 6: Loss of both legs due to gangrenous ulcers and self-amputations.

The aforementioned investigations, which led to excluding other potential diagnoses (Table 1), a diagnosis of Thévenard’s disease; a type of Hereditary Sensory and Autonomic Neuropathy, was established.

The patient was given supportive and antibacterial treatment (IV third generation cephalosporin). In 2 weeks, the patient developed a gangrene in her left leg and underwent amputation. In the meantime, the patient is only receiving supportive treatment and nursing services as she lost both legs and her fingers (Fig. 6). Those services are severely limited due to accessibility to healthcare issues in Syria due to the crisis, and the unrested financial status of the family. In better circumstances, the patient should have received specialized care earlier on with genetic counseling, would have been more frequently followed up, and would have received better nursing care and had prosthetics.

DISCUSSION

Ulcero-mutilating Acropathology is a rare disease that leads to significant morbidity and disability. Our case presented in a child, with no family history, teeth involvement, which has not been reported before, and hands involvement that is exceptionally rare. It is noteworthy that approaching this case, in terms of diagnostic measures and treatment plan, can be more challenging in low-resource settings.

The classic presentation of the disease—defined as deep, non-healing ulcers on the distal aspects of lower extremities leading to infections and amputations—has been constantly mentioned throughout all the reported cases. However, occasionally, new features and organ-involvement were described. For instance, hand involvement was reported on rare occasions as widespread superinfections leading to septic shock, destruction of the interphalangeal joints and mutilation of the distal phalanges [6]. Despite the scarcity of well-studied cases, it is thought that upper extremities’ involvement follows the development of initial lesions, typically on plantar surfaces, which is the case in our patient as well where feet ulcers and toes mutilations started a year before ulcers on the distal phalanges started to appear. This might hold a prognostic significance as early-detection and approach to any open sores might decrease complications and overall morbidity and mortality.
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Table 1: Summary of all the laboratory tests that were conducted as part of the patient’s work up (A–D)

| Lab (serology) | Value | Reference |
|----------------|-------|-----------|
| Hemoglobin (Hb) | 7.5 | |
| White blood cells count (WBCs) | 9.2 | |
| Creatinine (Cr) | 0.5 | |
| Blood urea nitrogen (BUN) | 6 | |
| Fasting blood glucose (FBG) | 75 | |
| Hemoglobin A1c | 4.6 | |
| Erythrocyte sedimentation rate (1h/2h) | 74/106 | |

B. Summary of all the laboratory tests that were conducted as part of the patient’s work up

| Lab (serology) | Value | Reference |
|----------------|-------|-----------|
| Anti–double-stranded DNA (IgG) | 5 | ~20 |
| Anti-nuclear antibody (ANA) screening test (IgG) | Negative | |
| Antineutrophil cytoplasmic antibody C ANCA-C (ANTI PR3) | 3 | ~5 |
| Antineutrophil cytoplasmic antibody P ANCA-P (ANTI-MPO) | 2 | ~5 |
| Cardiolipin antibody (IgG) | 8.12 | 10 |
| Cardiolipin antibody (IgG) | 7.01 | 10 |
| Beta-2 glycoprotein 1 (IgG) | 5.31 | <10 |

C. Summary of all the laboratory tests that were conducted as part of the patient’s work up

| Lab | Value | Reference |
|-----|-------|-----------|
| Thyroid stimulating hormone | 2.14 | 0.3–7.6 |
| Anti-Sjögren’s-syndrome-related antigen A Anti SS (a) | Negative | |
| Anti-Sjögren’s-syndrome-related antigen B Anti SS (b) | Negative | |
| ANA | Negative | |
| Anti-cytomegalovirus antibodies (IgM) | Negative | |
| Anti-cytomegalovirus antibodies (IgG) | 574 H | <4 >7 |
| Anti-toxoplasmosis antibodies (IgM) | Negative | |
| Anti-toxoplasmosis antibodies (IgG) | Negative | |
| Anti-rubella antibodies (IgM) | Negative | <0.8 >1.2 |
| Anti-rubella antibodies (IgG) | 552 H | |

D. Summary of all the laboratory tests that were conducted as part of the patient’s work up

| Lab | Value | Reference |
|-----|-------|-----------|
| Anti-hepatitis B surface antigen HBsAg (ICT) | Negative | |
| Anti-hepatitis C Virus (ICT) | 0 | |

Osseous deformities have not been well described, and the underlying pathogenesis is also yet to be fully understood. The most frequently reported bone involvements were intra-articular destruction, metatarsal dislocation, necrosis and mutilation. Our patient showed normal bones except for a lytic bone lesion in the tibia.

To date, there is no cure for this syndrome. However, experimental studies showed that interventions that reduce the accumulation of neurotoxic metabolites might be beneficial. For instance, oral supplementation of L-serine caused improved performance in rat models, and clinical studies are ongoing to assess its efficacy in patients with Hereditary Sensory and Autonomic Neuropathy Type 1 [7, 8]. Such experimental therapies, if proven safe and effective, can be considered as potential therapies for patients with Thévenard’s disease as well.

Approaching these cases in low-resource settings adds to the diagnostic and therapeutic challenges. In our case, we could not conduct genetic testing due to financial and logistic hardships. Also, the patients’ family struggled with affording care and had to pay out-of-pocket for numerous tests before reaching the diagnosis. The burden might be heavier in the future as the patient will need constant nursing care and follow-up visits to the clinic, especially after the amputations. Therefore, it is vital to remind clinicians of this disorder to help earlier detection, better-control complications and further-delay disability. It is also important to emphasize that regular examination and rapid response to any new lesions are primordial and should always be combined with education and support to the patient and the family.

ETHICAL APPROVAL

An ethical approval was not required for this project.

CONSENT

The patient’s parents gave written consent for the publication of this case and its use for academic affairs.

GUARANTOR

Dr. Houda Al Assil serves as the guarantor for this paper.
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CONFLICT OF INTEREST STATEMENT
None declared.

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