Transient anti PM-Scl75 antibody positive acral ischemia syndrome in a 15 years-old girl

Abstract
In 1862, the French doctor Maurice Raynaud published his dissertation in Paris titled "Sur l'asphyxie locale et la gangrènesymétrique des extrémités" (On local asphyxia and symmetrical gangrene of the extremities). In it, he described a series of cases in which there were episodes of acral ischemia. The phenomenon later named after him typically involves changes in skin color from white to blue-livid to red, caused by a vasospasm of acral arteries (white phase) followed by reactive vasodilation. Acral ischemia is present in different clinical conditions as stated in this manuscript. We report a case of a transient anti PM-Scl75 antibody positive acral ischemia syndrome in a 15 years-old girl.

Key wors: Thrombosis, embolism,blockage, oxygen deprivation, ischemia

Introduction
Ischemia (derived from the Ancient Greek ἴσχειν/ἔχειν is-chein/echein, meaning 'to hold back' and αἷμα haima, meaning 'blood') is a condition characterized by reduced blood flow or a complete cessation of blood flow to a tissue, body part, or organ, often associated with pain and leading to functional impairment 2,9,13,17,20,21,22,23,24). The most common cause of ischemia is a change in blood vessels, such as narrowing or blockage, which can occur in conditions like thrombosis or embolism (2,9,13). Narrowing of blood vessels is called stenosis, as seen in atherosclerosis and peripheral arterial disease (2). Functional constrictions can also occur, as in Raynaud's syndrome or as a physiological response in circulatory shock (2,9,13,20). Ischemia can occur transiently and may have no lasting effects on the affected tissue. If the ischemia lasts longer than the tissue can tolerate, or if the reduced blood supply is severe enough to cause permanent tissue damage, it is referred to as critical ischemia. Ischemia disrupts cellular metabolism and leads to oxygen deprivation in the affected area (1,2,9). Prolonged inadequate blood supply to nerve tissue can lead to a cascade of events, including high intracellular calcium concentrations contributing to uncontrolled release of the neurotransmitter glutamate, ultimately leading to excitotoxic damage to surrounding tissue cells. These processes can result in cell death and, in the case of ischemic heart disease where a portion of the heart muscle is inadequately perfused, can lead to a heart attack. Pressure-related ischemia with tissue damage can lead to pressure ulcers. The tolerated duration of ischemia without permanent tissue damage varies from organ to organ. It is a few minutes for the brain, several hours for many transplantable organs such as the heart or kidneys depending on cooling and nutrient solution, and up to twelve hours for extremities.

Case Report
We report on a teenager patient, who was in our outpatient treatment with a mild acral ischemia syndrome with transient anti-PM-Scl75 positivity of questionable relevance. There was currently no evidence of inflammatory myopathy or scleroderma. ANA were positive, but specific antibodieswere negative. The child had no back pain, was HLA-B27 negative and showed no evidence of spondylarthritis.In the cold season chronically recurrent reddened and partly livid discolored fingers withoutperniones and without damage.
The intermediate history showed that the patient presented again at our department accompanied by her mother. She reported that since then she has regularly had reddened fingers and hands, especially in the winter months, and sometimes bluish discolored fingers and hands when exposed to cold, but without typical Raynaud's phenomenon. She had occasional pain in her fingers, but no swelling or restricted movement. However, sometimes rough skin was present. She had sometimes problems with gripping firmly. There have been no open sores or crusts. Her feet were sometimes a little red, but never painful. She weared gloves in the winter; according to her mother, this could still be optimized. She denied muscle weakness or muscle pain. She had recently some pain in her right arm. She was regularly active in sports with fitness training at the gym, usually 2-3 times a week. She did not take any medication. She was in the 9th grade of comprehensive school and was doing moderately well there. She aspired to become a preschool teacher.
The mother reported that she herself has Sjögren's syndrome and a pronounced Raynaud's

phenomenon; she therefore received regular Ilomedin infusions.

Physical examination findings were as follows:Height166.0 cm, weight 67.1 kg, blood pressure 116/73 mmHg, heart rate 55/min, body temperature 36.2° Celsius. 15-year-old girl in good general and nutritional condition. The fingers and hands were overall noticeably red, with palmar erythema, not cool, mild delayed capillary refill. Nail fold capillaries under magnification were inconspicuous. No butterfly or periungual erythema. No Gottron's signs.The feet and toes were found inconspicuous, withoutlivid or reddish discoloration. Otherwise, the skin wasinconspicuous, without rash. The conjunctiva and oral mucosa are free of irritation. The throat and tonsils are unremarkable. There was no peripheral lymphadenopathy. Heart sounds were clear and regular, no pathological heart murmur. Lungs were clear and well-ventilated on auscultation.The abdomen was soft, no tenderness, no hepatosplenomegaly. Peripheral joints were freely movable, without swelling or pain on movement. Gross muscle strength was consistently unremarkable.
Joint sonography showed results as following:The MCP and PIP joints are inconspicuous on both sides. The thyroid gland is sonographically inconspicuous in terms of size, shape, and texture, and there is no hyperperfusion.

Laboratory findings:
Complete blood count (EDTA blood): Leukocytes: 4.12 - Tsd./ul (4.19 - 9.43); Erythrocytes: 4.42 Mio./ul
(3.93 - 4.9); Hemoglobin: 12.6 g/dl (10.8 - 13.3); Hematocrit: 37.6 % (33.4 - 40.4); MCV: 85.1 fl (76.9 - 90.6); MCH: 28.5 pg (24.8 - 30.2); MCHC: 33.5 g/dl (31.5 - 34.2); Platelets: 196 Tsd./ul (194 - 345)
Automated differential blood count (EDTA blood): Neutrophils (rel.): 50.2 % (39 - 73.6); Neutrophils (abs.):
2.07 Tsd./ul (1.82 - 7.47); Lymphocytes (rel.): 39.3 % (18.2 - 49.8); Lymphocytes (abs.): 1.62 Tsd./ul (1.16 - 3.33); Monocytes (rel.): 7.5 % (4.1 - 10.9); Monocytes (abs.): 0.31 Tsd./ul (0.19 - 0.72); Eosinophils (rel.): 1.9 % (0 - 3.4); Eosinophils (abs.): 0.08 Tsd./ul (0.02 - 0.32); Basophils (rel.): 1 + % (0 - 0.6); Basophils (abs.): 0.04 Tsd./ul (0.01 - 0.05); Mean platelet volume (MPV): 11.4 fl (9.6 - 11.7); Immature granulocytes: 0.01 Tsd./ul (<0.03), Reticulocytes (EDTA blood): Reticulocytes (rel.): 0.9 % (0.9 - 1.5); Reticulocytes (abs.): 38.5 - Tsa./ul(42 - 65); Ret He: 31.6 pg (28.2 - 33.9); Reticulocyte production index: 0.6
Coagulation (citrate blood): PT/Quick: 115% (70 - 130); INR: 0.92 - (0.97 - 1.3); Thrombin time: 16 sec.
(<21); Fibrinogen: 254 mg/dl (212 - 433); D-Dimer: 0.29 mg/l (<0.39)

Clinical chemistry (serum/heparin blood): Sodium: 138 mmol/l (134 - 143); Potassium: 4.4 mmol/l (3.3 -
4.6); Chloride: 104 mmol/ (96 - 109); Protein: 6.9 g/dl (6.6 - 8.3); Glucose: 80 mg/dl (60 - 110); Uric acid: 3.8 mg/dl (2.2 - 6.4); Urea-N: 10 mg/dl (8 - 21); Creatinine: 0.7 - mg/dl (0.8 - 1.4); Total bilirubin: 0.1 mg/dl (<1.2); AST (GOT): 20 U/ (<30); ALT (GPT): 13 U/ (<30); Gamma-GT: 9 - U/ (10 - 22); Alkaline phosphatase: 52 U/ (47 - 199); LDH: 165 U/ (117 - 213); CK: 96 U/l (<123);Troponin Ths: < 3.00 ng/ (<14); NT-proBNP: 41 pg/ml (7 - 137); Alpha-amylase: 94 U/l (28 - 100);Lipase: 36 U/ (13 - 60); eGFR (CKD-EPI): n.def. - (>90); CRP: < 0.5 mg/dl (<0.5); Albumin: 4.64 + g/dl(3.2 - 4.5); Transferrin: 296 mg/dl (200 - 360); Ferritin: 17.2 ug/l (16 - 92); Iron: 63 ug/dl (60 - 140);Transferrin saturation: 15% (16 - 45), Thyroid diagnostics: TSH: 1.24 uU/ml (0.51 - 4.30), Immunology: C3c: 109.3 mg/dl (89.7 - 176.4); C4: 16.1 mg/dl (8.6 - 37.4); IgG: 1115 mg/dl (700 -
1600); IgA: 131 mg/dl (70 - 400); IgM: 122 mg/dl (40 - 230); IgE: 13.9 IU/ml (<200); Interleukin 2 receptor: 550 U/ml (158 - 623)

Rheumatology diagnostics: Rheumatoid factor IgM (FIA): 1 IU/ml (<5); Rheumatoid factor IgA (FIA): 2.5 IU/ml (<20);anti-CCP (FIA): 2 U/ml (<7), Antinuclear antibodies (screening tests): ANA (IFT): 1:1280 (<1:80); ANA-Screen (FIA): Ratio (<1.0);CTD-Screen (FIA): 0.50 Ratio (<1.0)

ANA differentiation (quantitative): anti-dsDNA (RIA): IU/ml (<7)
Autoantibodies miscellaneous: anti-tTG IgA (FIA): 0.40 U/ml (<7)

Diagnosis of a hemostasis disorder: vWF antigen: 83.8% (44 - 145); LA 1: 29.6 sec (<45); LA 2: 29.8 sec (<38); LA Ratio: 0.99 (<1.5); Anticardiolipin antibodies IgG: 1.8 U/ml (<10); Anticardiolipin antibodies IgM:
0.4 U/ml (<7); 32 glycoprotein antibodies IgG: 2 U/ml (<8); 32 glycoprotein antibodies IgM: 0.6 U/ml (<8)

Calcium and bone metabolism: 25-OH-vitamin D3: 10.7 ng/ml (deficiency < 10 ng/ml; inadequate supply 10-30 ng/ml; adequate supply 30-100 ng/ml; toxicity > 100 ng/ml)

Urine status: Density (U, Stix): 1.01 - g/ml (1.015 - 1.025); pH (U, Stix): 5 (4.8 - 7.4); Leukocytes (U, Stix): neg #/ul (<10); Nitrite (U, Stix): neg (neg.); Protein (U, Stix): neg mg/dl (<10); Glucose (U, Stix): norm mg/dl (<15); Ketones (U, Stix): neg mg/dl (<5); Urobilinogen (U, Stix): norm mg/dl (<1); Bilirubin (U,
Stix): neg mg/dl (<0.2); Erythrocytes (U,

Urine analysis (FACS): Erythrocytes (U, FACS): 3 #/ul (<25); Leukocytes (U, FACS): 40 + #/ul (<20); Squamous epithelial cells (U, FACS): 21 #/ul (<40); Hyaline cylinders (U, FACS): 0 #/ul (<1); Bacteria (U, FACS): 353 + #/ul (<30); Crystals (U, FACS): 0 #/ul (<1); Yeasts (U, FACS): 3 +#/ul (<1); Pathological cylinders (U, FACS): 0 #/ul (<1); Round epithelial cells (U, FACS): 4 #/ul (<10); Gram information (U, FACS)

Discussion:

Our case describes a 15-year-old previously healthy girl with mild acral ischemia syndrome and a positive ANA titer with early positive detection of anti-PM-Sc175 antibodies. Currently, there were no indications of a manifest collagenosis, especially no evidence of inflammatory myopathy or scleroderma-like changes, and there were currently no specific antibodies, including PM-Scl or specific immunological activation. However, she had mild acral ischemia, but without a fully developed Raynaud's phenomenon (1-24). Protection from cold exposure with appropriate gloves was recommended. A mild acral ischemia could be interpreted as incomplete Raynaud phenomenon (1, 5,7,11,20). Acral ischemia was found in COVID-19 (1,15,24), chronic gangrenous ergotism (8), t-cell lymphoma (14), essential thrombocythemia (13), thrombotic microangiopathy (5), Hodgkin lymphoma (22), application of immune checkpoint inhibitors (6), nivolumab (9) and epinephrine (16) and closed injury (21). It remains a rare acral vascular event in children and teenagers like in our case.

Collodion baby is a rare congenital disorder in which affected infants are born with a thick, tight, shiny, translucent membrane covering their bodies (25). Most babies with a collodion membrane also have other associated disorders, such as nonbullous congenital ichthyosiform erythroderma and lamellar ichthyosis. In one case report, the authors described a collodion baby who developed a rare complication of acral contracture, ischemia, and nail dystrophy (25). Treatment with tazarotene 0.1% gel led to rapid improvement, with the patient eventually regaining normal nail plates and full motor function in both hands and feet (25). This case represents the first reported use of topical tazarotene for managing this rare condition in a neonate (25).

Diagnosing peripheral ischemic diseases can be challenging for vascular specialists due to the difficulty in distinguishing between different conditions based on clinical symptoms. Capillary microscopy is a noninvasive diagnostic tool that allows visualization of the morphology and perfusion of digital capillaries. In a study of 522 patients referred to the vascular laboratory over six years, the authors aimed to improve diagnostic certainty for acral ischemic complaints (26). By comparing patients with clinically evident Raynaud's phenomenon and control subjects, differentiation criteria were established (26). Capillary microscopy demonstrated a sensitivity of 67%, specificity of 84%, and accuracy of 81% in detecting Raynaud's phenomenon (26). Disturbed capillary morphology was highly indicative of Raynaud's disease secondary to systemic disorders (specificity 100%), with an accuracy of 74% (26). Capillary microscopy provided a diagnosis in 69% of patients with atypical acral ischemia (26). Digital blood pressure measurements were not helpful in diagnosing Raynaud's phenomenon (26). Overall, capillary microscopy proved to be a valuable tool in diagnosing acral ischemic syndromes.

Approximately 6% of individuals with COVID-19 will develop skin manifestations (27). Analyzing data from this group could offer valuable insights for managing the disease (27). A systematic review aimed to examine the different types of rashes associated with COVID-19 and their correlation with disease severity (27). Among 2056 patients included in the study, the most common rash types were chilblain-like lesions (54.2%), maculopapular rashes (13.6%), and urticaria (8.3%) (27). Chilblain-like lesions were more prevalent in younger individuals (average age 21.5) and were often associated with milder disease that did not require hospitalization (27). On the other hand, acro-ischaemia and livedo reticularis were linked to more severe outcomes, such as ICU admission and mortality (27). Acral lesions were the most frequently affected area (83.5%), with symptoms like pruritus, pain, and burning reported by some patients (27). A significant portion of individuals had asymptomatic lesions, and rash was the sole symptom in a fifth of cases (27). Some patients tested positive for COVID-19 through PCR or antibody testing, while others tested negative or were not tested (27). In summary, COVID-19 can present with various types of rashes, which may impact symptoms and disease progression (27). The specific rash morphology could potentially help predict the course of the illness.

PM-Scl antibodies are autoantibodies from the group of antinuclear antibodies (28-35). They are particularly important in the diagnosis of a polymyositis-scleroderma overlap syndrome (PM-Scl overlap syndrome) (28-35). PM-Scl antibodies are directed against a protein complex in the nucleoli, the function of which is still unknown (28-35). This protein complex consists of at least 11 proteins (33,34). A 100kDa protein and a 75kDa protein are the epitopes against which antibodies are most commonly detected (29). PM-Scl antibodies are very rarely found in association with acral ischemia, scleroderma, polymyositis, or a PM-Scl overlap syndrome (28-35). Since the finding is often falsely positive, these antibodies are attributed low sensitivity in the diagnosis of collagen vascular diseases and myositis. It is suspected that patients with PM-Scl antibodies represent a special subgroup of acral ischemia, myositis and scleroderma patients (33,35). These patients have a relatively favorable prognosis compared to patients with other scleroderma markers (34).
Approximately half of patients diagnosed with the polymyositis/scleroderma (PM-Scl) overlap syndrome have been found to possess autoantibodies targeting a nuclear/nucleolar particle known as PM-Scl (35). This particle consists of multiple polypeptides, two of which have been identified as autoantigens. A human cDNA clone encoding the complete 75-kD autoantigen of the PM-Scl particle (PM-Scl 75) could be isolated from a MOLT-4 lambda gt-11 library in one study (35). The deduced amino acid sequence of the cDNA clone revealed a protein consisting of 355 amino acids and weighing 39.2 kD; the in vitro translation product of this cDNA migrated at around 70 kD in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) (35). The anomalous migration of the polypeptide in SDS-PAGE was attributed to the acidic residue-rich COOH half. The authenticity of the cDNA encoding PM-Scl 75 was confirmed through the reactivity of PM-Scl sera with in vitro translation products and recombinant fusion proteins derived from the cDNA (35). Furthermore, rabbit antibodies generated against the recombinant fusion protein exhibited reactivity in immunofluorescence, immunoblotting, and immunoprecipitation assays, mirroring the characteristic features observed with human anti-PM-Scl sera (35).

Conclusion

In our patient, the level of PM-Scl antibodies was high, supposing any correlation to polymyositis-scleroderma overlap syndrome (PM-Scl overlap syndrome). Further evaluation will show clearer relations to this extrem rare disease in teenagers. Further research should also focus on immunological triggers and molecular aspects why acral ischemia occurs and should evaluate further targets for treatment, especially in children.

Consent
As per international standards, parental written consent has been collected and preserved by the author(s).

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