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. We report a case of a transient anti PM-Scl75 antibody positive acral ischemia syndrome in a 15 years-old girl.

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. 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. Narrowing of blood vessels is called stenosis, as seen in a therosclerosis and peripheral arterial disease. Functional constrictions can also occur, as in Raynaud's syndrome or as a physiological response in circulatory shock. 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. 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. 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. Further research should focus on triggers why acral ischemia occurs and should evaluate further targets for treatment, especially in children.

References:

1. Farajzadeh S, Khalili M, Dehghani S, Babaie S, Fattah M, Abtahi-Naeini B. Top 10 acral skin manifestations associated with COVID-19: A scoping review. Dermatol Ther. 2021 Nov;34(6):e15157. doi: 10.1111/dth.15157. Epub 2021 Oct 21. PMID: 34628708; PMCID: PMC8646918.
2. Ubbink DT, Janssen HA, Schreurs MM, Jacobs MJ. Capillary microscopy is a diagnostic aid in patients with acral ischemia. Angiology. 1995 Jan;46(1):59-64. doi: 10.1177/000331979504600108. PMID: 7818158.
3. Rosés-Gibert P, Gimeno Castillo J, Saenz Aguirre A, De la Torre Gomar FJ, Carnero González L, Martinez de Lagrán Alvarez de Arcaya Z, Gonzalez-Perez R. Acral lesions in a pediatric population during the COVID-19 pandemic: a case series of 36 patients from a single hospital in Spain. World J Pediatr. 2020 Dec;16(6):629-632. doi: 10.1007/s12519-020-00390-0. Epub 2020 Sep 8. PMID: 32901377; PMCID: PMC7478438.
4. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, Abril-Pérez C, Sabalza-Baztán O, Pardo-Granell S, Martínez I Cózar V, Botella-Estrada R, Évole-Buselli M. Assessment of Acute Acral Lesions in a Case Series of Children and Adolescents During the COVID-19 Pandemic. JAMA Dermatol. 2020 Sep 1;156(9):992-997. doi: 10.1001/jamadermatol.2020.2340. PMID: 32584397; PMCID: PMC7317654.
5. Nassih H, Lazrak Z, Younous S. Severe Acral Necrosis Complicating Thrombotic Microangiopathy in Two Toddlers. Case Rep Pediatr. 2020 Dec 15;2020:8869883. doi: 10.1155/2020/8869883. PMID: 33457033; PMCID: PMC7787831.
6. Khaddour K, Singh V, Shayuk M. Acral vascular necrosis associated with immune-check point inhibitors: case report with literature review. BMC Cancer. 2019 May 14;19(1):449. doi: 10.1186/s12885-019-5661-x. PMID: 31088420; PMCID: PMC6518656.
7. Biswal JK, Mohanty SK, Behera SN, Swain SK, Sahoo AK. Acute Limb Ischemia: A Catastrophic COVID-19 Sequel Leading to Amputation. Cureus. 2021 Jul 18;13(7):e16456. doi: 10.7759/cureus.16456. PMID: 34466301; PMCID: PMC8396422.
8. Wollina U, Hansel G, Gruner M, Schönlebe J, Heinig B, Köstler E. Painful ANA-positive scleroderma-like disease with acral ulcerations: a case of chronic gangrenous ergotism. Int J Low Extrem Wounds. 2007 Sep;6(3):148-52. doi: 10.1177/1534734607305308. PMID: 17909173.
9. Suenaga A, Ito T, Eto A, Furue M. Acral ischemia induced by nivolumab: A case report. J Dermatol. 2021 May;48(5):e223-e224. doi: 10.1111/1346-8138.15830. Epub 2021 Mar 2. PMID: 33650723.
10. Ríos A, Pinzón LF, Rodríguez JM, Parrilla P. Acral ischemia secondary to pheochromocytoma. Cir Esp (Engl Ed). 2018 Nov;96(9):589-591. English, Spanish. doi: 10.1016/j.ciresp.2018.02.019. Epub 2018 Apr 25. PMID: 29704976.
11. Bergersen TK, Walløe L. Acral coldness - severely reduced blood flow to fingers and toes. Handb Clin Neurol. 2018;157:677-685. doi: 10.1016/B978-0-444-64074-1.00040-9. PMID: 30459032.
12. Stringer T, Femia AN. Raynaud's phenomenon: Current concepts. Clin Dermatol. 2018 Jul-Aug;36(4):498-507. doi: 10.1016/j.clindermatol.2018.04.007. Epub 2018 Apr 10. PMID: 30047433.
13. Hanoun M, Röth A, Dührsen U, Brock FE. Acral ischemia as a presenting manifestation of essential thrombocythemia. Int J Hematol. 2011 Sep;94(3):219-220. doi: 10.1007/s12185-011-0914-8. Epub 2011 Aug 20. PMID: 21858443.
14. Klanidhi KB, Monian SA, Chakrawarty A. Acral vascular syndrome Lennert type T cell lymphoma-a case report. J Egypt Natl Canc Inst. 2021 Mar 4;33(1):8. doi: 10.1186/s43046-021-00063-7. PMID: 33661406.
15. Clawson RC, Tabata MM, Ko JM. Management of a Child vs an Adult Presenting With Acral Lesions During the COVID-19 Pandemic: A Practical Review. Cutis. 2021 Mar;107(3):139-142. doi: 10.12788/cutis.0203. PMID: 33956605.
16. Hartzell TL, Sangji NF, Hertl MC. Ischemia of postmastectomy skin after infiltration of local anesthetic with epinephrine: a case report and review of the literature. Aesthetic Plast Surg. 2010 Dec;34(6):782-4. doi: 10.1007/s00266-010-9528-4. Epub 2010 May 13. PMID: 20464394.
17. Liu RH, Becker B, Gunkel J, Teng J. Rapid improvement in digital ischemia and acral contracture in a collodion baby treated with topical tazarotene. J Drugs Dermatol. 2010 Jun;9(6):713-6. PMID: 20645539.
18. Gao JC, Huang A, Desai A, Safai B, Marmon S. "COVID toes": A true viral phenomenon or a diagnosis without a leg to stand on? JAAD Int. 2022 Dec;9:1-6. doi: 10.1016/j.jdin.2022.06.012. Epub 2022 Jun 19. PMID: 35756912; PMCID: PMC9213024.
19. AlRasbi S, Al-Badi AH, Al Alawi AM. Paraneoplastic acral vascular syndrome: case presentation and literature review. BMJ Case Rep. 2021 Jan 15;14(1):e237258. doi: 10.1136/bcr-2020-237258. PMID: 33452070; PMCID: PMC7813368.
20. Ubbink DT, Janssen HA, Schreurs MM, Jacobs MJ. Capillary microscopy is a diagnostic aid in patients with acral ischemia. Angiology. 1995 Jan;46(1):59-64. doi: 10.1177/000331979504600108. PMID: 7818158.
21. Janák D, Ručka D, Kudlička J, Rohn V, Lindner J, Kittnar O. Acute Digital Ischemia Associated with Closed Injury. Prague Med Rep. 2015;116(3):239-43. doi: 10.14712/23362936.2015.64. PMID: 26445396.

22. Villano F, Peixoto A, Riva E, Di Matteo C, Díaz L. Digital Ischemia as an Unusual Manifestation of Hodgkin's Lymphoma. Case Rep Hematol. 2018 Aug 19;2018:1980749. doi: 10.1155/2018/1980749. PMID: 30210881; PMCID: PMC6120276.
23. Marshall M. Akutes akrales Ischämie-Syndrom [Acute acral ischemia syndrome]. MMW Munch Med Wochenschr. 1982 Jul 9;124(27):68-70. German. PMID: 6810161.
24. Andersen MB, Lund ML, Jacobsen S, Kümler T, Simonsen S, Ravn P. [Acral ischaemia with multiple microthromboses and imminent gangrene in a 73-year-old woman with COVID-19]. Ugeskr Laeger. 2020 Jun 22;182(26):V05200379. Danish. PMID: 32584760.