A 32-year-old man with an uncommon cardiomyopathy

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Abstract (Key clinical message)

We report the case of a young patient with scleroderma-associated cardiomyopathy, which is currently poorly understood clinically. Scleroderma-associated cardiomyopathy is uncommon in young adults and lacks a specific therapeutic strategy, necessitating attention in clinical practice. Additionally, genetic testing should be emphasized in this disease to facilitate diagnosis and treatment.

Keywords

Scleredema, cardiomyopathy, skin thickening

Introduction

Scleredema is a rare connective tissue disease of unknown pathogenesis, and may be associated with autoimmune phenomena or allergic responses [1]. It is characterized by the progressive development of skin thickening and tightness on the neck and upper part of the body [2]. The prognosis varies according to the etiology and therapeutic options. In addition to skin lesions, scleredema involves endocrine/metabolic disorders, cardiovascular disorders, hematologic disorders, gastrointestinal disorders, and other systemic dysfunctions [3]. In particular, previous cases reported that scleredema associated cardiomyopathy, and its pathogenesis may be driven by the lymphocyte response [4,5]. It is still under investigation in clinical practice whether scleredema patients develop cardiomyopathy. We report a case of scleredema in a 32-year-old male with cardiomyopathy. The purpose of this case report is to raise awareness of scleredema-associated cardiomyopathy and contribute further insight to explore and establish the foundation for the cause of this uncommon cardiomyopathy.

Case history/examination

A 32-year-old male patient was admitted to our hospital for the purpose of examination and treatment of progressively deteriorating symptoms from two days chest pain and persisting chest tightness and breath shortness over a year lone.

Prior to this admission, the patient was firstly admitted to a local hospital for symptoms of chest tightness, shortness of breath and dyspnea following physical activity. His blood creatinine level was 126umol/L (reference range, 62 to 115 umol/L), the glomerular filtration rate was 65.11ml/min, the troponin T level was 37 pg /mL (reference range <17.5 pg /mL) and the N-terminal pro-brain natriuretic peptide (NT-proBNP) was 2264.0pg/mL (reference range, <125 pg /mL). The rest of the labs were normal. The patient was prescribed with aspirin, benazepril hydrochloride, spironolactone, atorvastatin, amiodarone, and metoprolol tartrate while admitted to the local hospital. After five days of treatment, the patient was discharged with relief from chest tightness. However, two days after discharge, he came back to another higher-graded hospital's clinic in Chongqing for second visit with the same symptoms.

The electrocardiogram (ECG) (Figure. 1) conducted at the second hospital showed sinus rhythm with T-wave abnormalities. Additionally, transthoracic echocardiography revealed an enlarged left heart with a septal thickness of 12 mm (normal range, 8 to 11), generally reduced left ventricular wall motion, reduced left ventricular systolic function, reduced diastolic function, and an ejection fraction of 49% (normal range, 55 to 70), as well as mild mitral and tricuspid regurgitation. Prescription continued as previously administered. However, the symptoms constantly to be recurrent, this was the reason the patient was admitted to our hospital in the hope of further clarifying the diagnosis and treatment.

The patient's medical history included hypertension and claims of normal blood pressure control, with no known history of diabetes mellitus. The skin on the neck was noted to be hardened from early 2021 without other noticeable redness, swelling, or pain. A skin pathology biopsy was carried out in July 2021 at a local hospital's clinic because the skin sclerosis had expanded to the back and scleredema was diagnosed. He admitted a history of smoking for more than 20 years and denied any history of drinking.

Methods

On examination in our hospital, the patient's vital signs are normal. There were no noticeable aberrant lung or cardiac murmurs. The skin of the neck and back was diffusely hardened and thickened with a smooth surface and normal hairs. His hands, feet, or upper or lower limbs were not involved. There were no finger ulcers, calcification, or sclerosis (Figures 2A and 2B). The patient's fasting glucose and glycated hemoglobin A1(HbA1c) were both high, and a clear diagnosis of type 2 diabetes was made available by further implementing the glucose tolerance test (OGTT) (a standardized OGTT of 75 g for 2 hours was performed after an overnight fast). Total cholesterol (TC), Triglyceride (TG), and Low-density lipoprotein cholesterol (LDL-C) concentrations were high, and High-density lipoprotein cholesterol (HDL-C) concentrations were low. Antistreptolysin-O (ASO), antistreptolysin kinase (ASK), anti-Scl-70, anti-Jo-1, anti-PM-SCL antibody, anti-RP3 antibody, anti-keratin antibody, erythrocyte sedimentation rate, and rheumatoid factor were all negative in the blood. The value of α-Galactosidase A(α-Gal-A) tested by dried blood spot (DBS) was 4.74 (normal range, 2.40 to 17.65). Thyroid function tests and serum protein electrophoresis results were normal. Other laboratory test results are shown in Table 1.

An electrocardiogram showed high left ventricular voltage and mild widening of QRS waves (Figure 3A). The dermis thickness on the patient's neck and back was measured using ultrasonography. The thickness of the dermis was measured in the thickest area and the normal area for comparison, and it was discovered that the skin on the neck and back (8–10 mm) was considerably thicker and more echogenic than the typical skin around the waist (4 mm) (Figure 3B). A transthoracic echocardiogram (Figure 4A) on admission showed an enlarged left heart, left ventricular end-diastolic internal diameter of 65mm, left ventricular end-diastolic volume of 220ml, left ventricular hypertrophy, left ventricular posterior wall thickness of 12mm, septal thickness of 12mm, left ventricular apical appendage thrombus formation (2.1*1.5 cm), and severely reduced overall left ventricular function (EF 30%). Coronary computed tomography angiography (CTA) revealed no significant abnormalities in the coronary vessels but indeed revealed an enlarged whole heart and left ventricular

myocardial hypertrophy (ranging from 14mm to 18mm thick). Cardiac magnetic resonance imaging (CMRI) showed thrombosis in the left ventricular apical region and left heart insufficiency, considering metabolic cardiomyopathy with delayed enhancement of the inner apical septum and inferior lateral wall with flocculent patches (Figure 5). Skin biopsy of the back demonstrates thickening of the dermis and enlargement of the intra-dermal collagen fiber gap, along with alcian blue staining positive deposits between the swollen collagen fibers, which was consistent with the diagnosis of scleredema (Figure 6A,6B).

Treatment was initiated concurrently after the required tests. Low molecular weight heparin (LMWH) was injected subcutaneously to treat the patient's left ventricular thrombosis, rosuvastatin calcium tablets and alirocumab were administered to lower lipids, along with sacubitril valsartan sodium tablets, spironolactone, and furosemide tablets to improve cardiac function and diuretic therapy. Dapagliflozin and metformin hydrochloride tablets were used to decrease blood sugar levels, and metoprolol tartrate tablets to regulate blood pressure and control ventricular rate. Uremic clearance granules, Bailing capsules, and Shenkang injection were used to protect the kidney, and febuxostat to lower uric acid.

Outcome and Follow-up

After approximately two weeks of treatment, the patient was discharged with well-controlled blood pressure, reduced levels of blood glucose, lipids, and uric acid compared to prior levels, as well as normalized blood creatinine concentrations (Table 1). The transthoracic echocardiography at discharge showed a left ventricular end-diastolic internal diameter of 63 mm, a left ventricular end-diastolic volume of 204 ml, and an ejection percentage of 34%. There were no signs of thrombus formation in the left ventricular apical area (Figure 4B). Patients continue to receive regular follow-up. One year after discharge, the patient's blood pressure and blood glucose were well controlled, and symptoms of chest tightness, chest pain, and shortness of breath were relieved compared to the previous period. Additionally, there was no aggravation of skin hardness.

Discussion

Scleredema adultorum, also known as Buschke disease, is a rare skin disease with characterized by thickened, nonpitting sclerosis and hard skin nodules [6-8]. It is typically found on the face, neck, shoulders, and trunk, and rarely affects the hands and feet. The etiology of scleredema adultorum is currently unclear, and histopathological findings include a thickened dermis with mucin deposits between thickened collagen bundles [9]. There are three types of scleredema, including post-infection, associated with blood dyscrasias (e.g., paraproteinemia), and connected with diabetes mellitus, which is the most typical cause [10]. Chronic obesity, hyperglycemia, and a dysfunctional metabolism may all contribute to scleredema diabeticorum, the etiology of which remains unspecified. Blood glucose plays a critical role in scleredema diabeticorum, and dermal collagen is irreversibly glycosylated, leading to excessive accumulation of mucin and collagen [11]. This patient was diagnosed with diabetes mellitus at our hospital, and significant dermal thickening and mucin deposition were observed (Figure 3B, Figure 6). His diagnosis of scleredema diabeticorum was clearly established. Unlike previous cases, the skin lesions in this patient were detected prior to developing diabetes mellitus. Early detection of diabetes is therefore critical for the diagnosis and prevention of scleredema in patients.

In addition to affecting the skin, scleredema may also affect the heart, joints, tongue, bone marrow, and eyes [12]. In early reports of scleredema, myocardial involvement has been identified by focusing on alterations in the ECG [13,14]. Cardiac involvement can manifest in various ways, including cardiomyopathy and heart failure. Leinwand et al. [15] reported a case of a middle-aged female patient with scleredema. The results of the heart autopsy revealed that the patient had a rubbery rigidity in the ventricular wall. A 2001 case report described typical histologic features of sclerosing edema in a myocardial biopsy from an elderly male patient [4]. In our patient, although no myocardial biopsy was performed, cardiac involvement was evaluated by CMRI, and CMRI shows lamellar delayed enhancement of the inter-apical septum and inferior lateral wall. A previous case report [5] used CMRI to evaluate myocarditis in a patient with scleredema, but its results did not show delayed enhancement. There were few reports of cardiomyopathy associated with scleredema,

and the causes of cardiomyopathy were variable. Since scleredema in our case occurred before the patient's cardiac involvement, it should be further determined whether the patient's cardiomyopathy resulted from a delayed start of scleredema. We will continue to follow up with the patient and complete the myocardial biopsy examination.

Notably, whole exome sequencing for hereditary cardiovascular disease was performed on our patient. The results indicated that the cysteine and glycine-rich protein 3 (CSRP3) gene pathogenicity for this patient was categorized as a Variant of Uncertain Significance (VUS). Mutations in the CSRP3, which encodes the muscle Lim Protein (MLP), are key contributors to cardiomyopathy. Previous studies have found that mutations in the human CSRP3 gene are associated with hypertrophic cardiomyopathy (HCM) [16,17]. However, as a gene classified at an intermediate level among HCM genes, there is insufficient evidence for the pathogenicity of CSRP3 and its pathogenicity remains unclear [18]. According to a study from 2020[19], the CSRP3 p. (Cys150Tyr) variant was associated with the pathogenicity of HCM, but it was different from the present case variant locus CSRP3c.301T>C (p. Ser101Pro).

Although this VUS result suggests that the gene involved is associated with the patient's clinical indication, there is currently insufficient information to determine whether the variant itself is pathogenic. It can still complicate clinical diagnosis. We further carried out genetic tests on the patient's family tree to clarify the pathogenicity of the gene. The results of the test revealed that no one else in the patient's family carried the CSRP3 gene. Therefore, it is still not possible to determine whether the gene variant is pathogenic or not. We will conduct VUS and negative cases at intervals reanalysis to obtain evidence supporting the disease association.

In conclusion, it is unclear which factors contribute to cardiomyopathy in our patients. This might result from both the CSRP3 mutation and scleredema, rather than just one or the other. Further follow up on the patient's condition to clarify the etiology of cardiomyopathy. Scleredema has an insidious onset and a good prognosis with aggressive treatment. Early detection and notification of the associated cardiomyopathy in a scleredema patient are crucial to prevent adverse outcomes. Recognition and treatment of scleredema associated cardiomyopathy are still lacking in clinical practice. Therefore, collaboration with multidisciplinary departments is essential for comprehensive understanding and treatment.

Author Contributions

Yuting Zou: conceptualization, investigation, methodology, resources, writing - original draft, writing - review & editing. Shan Li: conceptualization, investigation, methodology, writing - original draft. Tong Chen: investigation, methodology, supervision.Yi Li: conceptualization, investigation, methodology, resources, supervision, writing - review & editing.

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Consent

Written informed consent was obtained from the patient himself to publish this report in accordance with the journal's policy.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Carrington PR, Sanusi ID, Winder PR, Turk LL, Jones C, Millikan LE. Scleredema adultorum. *International journal of dermatology* . 1984;23(8):514-522. doi: 10.1111/j.1365-4362.1984.tb04202.x.

2. Miguel D, Schliemann S, Elsner P. Treatment of Scleroedema Adultorum Buschke: A Systematic Review. *Acta dermato-venereologica* . 2018;98(3):305-309. doi: 10.2340/00015555-2846.

3. Rongioletti F, Kaiser F, Cinotti E, Metze D, Battistella M, Calzavara-Pinton PG, Damevska K, Girolomoni G, André J, Perrot JL, Kempf W, Cavelier-Balloy B. Scleredema. A multicentre study of characteristics, comorbidities, course and therapy in 44 patients. J*ournal of the European Academy of Dermatology and Venereology* : JEADV. 2015;29(12):2399-2404. doi: 10.1111/jdv.13272.

4. Wu EB, Fuller LC, Hughes RA, Chambers JB. Images in cardiovascular medicine: Rare cause of cardiomyopathy. *Circulation* . 2001;103(23):2867. doi: 10.1161/hc2301.091931.

5. Nakatsuji M, Ishimaru N, Ohnishi J, Mizuki S, Kanzawa Y, Kawano K, Nakajima T, Kuroda M, Sano N, Kinami S. Scleredema with biopsy-confirmed cardiomyopathy: A case report. *Journal of scleroderma and related disorders* . 2021;6(3):311-315. doi: 10.1177/23971983211013977.

6. Haustein UF. Scleroderma and pseudo-scleroderma: uncommon presentations. *Clinics in dermatology* . 2005;23(5):480-490. doi: 10.1016/j.clindermatol.2005.01.019.

7. Foti R, Leonardi R, Rondinone R, Di Gangi M, Leonetti C, Canova M, Doria A. Scleroderma-like disorders. *Autoimmunity reviews* . 2008;7(4):331-339. doi: 10.1016/j.autrev.2007.12.004. doi: 10.1016/j.autrev.2007.12.004.

8. Alhunaif SA, Alsarheed A, Almutairi R, Almutairi G. Atypical Case of Combined Types I and II Scleredema Mimicking Morphea on Histopathology.*Cureus* . 2023;15(1):e34077. doi: 10.7759/cureus.34077.

9. Gandolfi A, Pontara A, Di Terlizzi G, Rizzo N, Nicoletti R, Scavini M, Galimberti G, Bosi E. Improvement in clinical symptoms of scleredema diabeticorum by frequency-modulated electromagnetic neural stimulation: a case report. *Diabetes care* . 2014;37(11):e233-234. doi: 10.2337/dc14-0730.

10. Turchin I, Adams SP, Enta T. Dermacase. Scleredema adultorum, or Bushke disease. *Canadian family physician Medecin de famille canadien* . 2003;49:1089, 1093.

11. Muhaidat J, Al-Qarqaz F, Alshiyab D. Unilateral Linear Induration of the Skin: A Case Report of an Unusual Presentation of Scleredema.*The Journal of clinical and aesthetic dermatology* . 2020;13(12):E53-e55.

12. Rimon D, Lurie M, Storch S, Halon D, Eisenkraft S, Laor A, Cohen L. Cardiomyopathy and multiple myeloma. Complications of scleredema adultorum. *Archives of internal medicine* . 1988;148(3):551-553.

13. Johnson ML, Ikram H. Scleroedema of Buschke. An uncommon cause of cardiomyopathy. *British heart journal* . 1970;32(5):720-722. doi: 10.1136/hrt.32.5.720.

14. Vallee BL. Scleredema: a systemic disease. *The New England journal of medicine* . 1946;235(7):207-213. doi: 10.1056/nejm194608152350701.

15. Leinwand I. Generalized scleroderma; report with autopsy findings.*Annals of internal medicine* . 1951;34(1):226-238. doi: 10.7326/0003-4819-34-1-226.

16. Ehsan M, Kelly M, Hooper C, Yavari A, Beglov J, Bellahcene M, Ghataorhe K, Poloni G, Goel A, Kyriakou T, Fleischanderl K, Ehler E, Makeyev E, Lange S, Ashrafian H, Redwood C, Davies B, Watkins H, Gehmlich K. Mutant Muscle LIM Protein C58G causes cardiomyopathy through protein depletion. *Journal of molecular and cellular cardiology* . 2018;121:287-296. doi: 10.1016/j.yjmcc.2018.07.248.

17. Bos JM, Poley RN, Ny M, Tester DJ, Xu X, Vatta M, Towbin JA, Gersh BJ, Ommen SR, Ackerman MJ. Genotype-phenotype relationships involving hypertrophic cardiomyopathy-associated mutations in titin, muscle LIM protein, and telethonin. *Molecular genetics and metabolism* . 2006;88(1):78-85. doi: 10.1016/j.ymgme.2005.10.008.

18. Ingles J, Goldstein J, Thaxton C, Caleshu C, Corty EW, Crowley SB, Dougherty K, Harrison SM, McGlaughon J, Milko LV, Morales A, Seifert BA, Strande N, Thomson K, Peter van Tintelen J, Wallace K, Walsh R, Wells Q, Whiffin N, Witkowski L, Semsarian C, Ware JS, Hershberger RE, Funke B. Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes. *Circulation Genomic and precision medicine* . 2019;12(2):e002460. doi: 10.1161/CIRCGEN.119.002460.

19. Salazar-Mendiguchía J, Barriales-Villa R, Lopes LR, Ochoa JP, Rodríguez-Vilela A, Palomino-Doza J, Larrañaga-Moreira JM, Cicerchia M, Cárdenas-Reyes I, García-Giustiniani D, Brögger N, Fernández G, García S, Santiago L, Vélez P, Ortiz-Genga M, Elliott PM, Monserrat L. The p.(Cys150Tyr) variant in CSRP3 is associated with late-onset hypertrophic cardiomyopathy in heterozygous individuals. *European journal of medical genetics* . 2020;63(12):104079. doi: 10.1016/j.ejmg.2020.104079.

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