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Case report

Cardiac involved and autopsy in two patients with systemic sclerosis: Two cases report

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ABSTRACT

Systemic sclerosis (SSc) is a connective tissue disease with high mortality. One of the most common causes of death in potential SSc patients is cardiac arrest. However, the pathogenesis of cardiac death is not very clear. As far as we know, there are few autopsy reports on this subject. Our autopsy report on two fatal cases of heart injury in SSc patients revealed evidence of myocarditis, focal myocardial necrosis, and myocardial fibrosis. Our findings suggest that chronic inflammation of the heart may lead to extensive fibrosis, which could contribute to the high mortality rate observed in SSc patients. Early detection of heart injury in SSc patients using existing technology is necessary to improve patient outcomes. Future research should focus on developing more effective methods for early detection and management of heart involvement in SSc.

1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by multiple organ involvement, with serious cardiac complications [1]. One of the most common cardiac involvement is pulmonary hypertension (PAH) and secondary right heart failure, which affects up to 15% of patients with SSc [2]. Heart disease is the main cause of cardiac death in SSc, and sudden cardiac death (SCD) is considered to be more common in SSc than in the general population. Diffuse myocardial fibrosis, myocarditis and ischemic heart disease are common in SSc, which can be reasonably assumed to increase the risk of SCD. In 50% of cases, cardiac arrest is the first manifestation of SCD [3], and the survival rate is very low. Only 10% of patients with cardiac arrest can survive to discharge [4].

Using the GEO database for disease comorbidity analysis can find that SSc is highly correlated with cancer [5]. However, the pathogenesis of SSc is not very clear, and the vascular abnormalities of microcirculation in patients with SSc are the key to diagnosis, prognosis stratification and long-term monitoring. Microvascular disease is a gradual process that eventually leads to vascular injury, inadequate repair and ischemia-reperfusion injury. In SSc, the relationship between morphology (i.e. microvascular disease) and functional impairment (i.e. decreased blood flow) has been proved by many studies [6–10]. Nailfold papilloscopy (NVC) is a non-invasive, reliable, inexpensive, reusable and running-in method for determining structural microvascular injury in SSc [11]. Laser speckle contrast analysis (LASCA) is a new safety technology to quantify blood perfusion (BP) in different body regions of patients with SSc and healthy control group. In conclusion, this study showed that the BP of SSc patients in the fingertip, perihoof and palm areas was significantly lower than that of healthy subjects, but there was no significant difference in the face and back of hand areas, which

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confirmed the selective participation in the microcirculation injury in SSc [12].

2. Cases presentation

2.1. Case 1

A 45-year-old male, a farmer, had a 3-year history of Raynaud's phenomenon presented with a history of progressive skin thickening, digital ulcers and skin loss spots on the extremities (Fig. 1a–c). He has a 10 year history of smoking, usually 10 cigarettes per day, and has quit smoking for 3 months. The patient denies a history of alcohol addiction. He was placed on traditional Chinese medicine and painkiller medication for 3 weeks but without improvement in a local hospital. Moreover, he developed hyperpyrexia

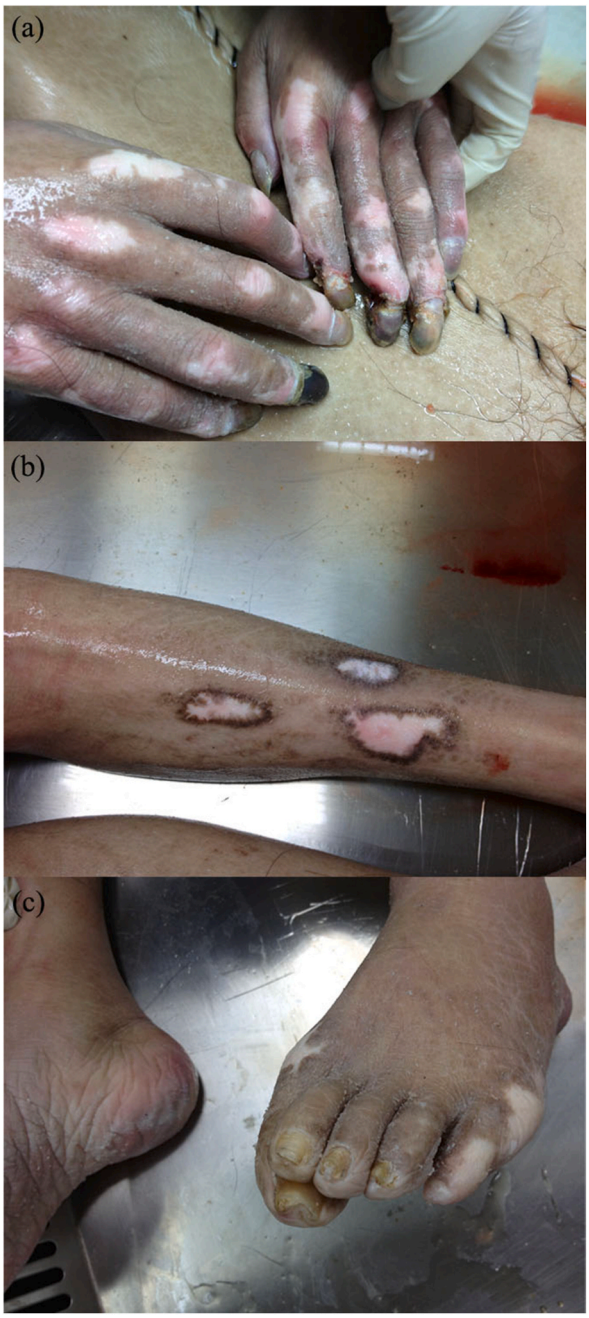

Fig. 1. Skin exfoliation of limb. Fig. 1a: Finger skin ulcers and hand skin peeling; Fig. 1b: Skin peeling in the anterior tibial region; Fig. 1c: Foot skin detachment.

(about 38–39 °C). After exclusion of infection, intravenous injection of 5–10 mg of dexamethasone per day was therefore initiated. Nevertheless, the treatments failed and the patient still suffered from hyperpyrexia. 3 months later, in addition to acronecrosis (Fig. 2) and hyperpyrexia, he developed a cough, dyspnea, fatigue, lower extremity edema, and anemia. At this time, the diagnosis is still not very clear, and the examination of emergency blood indicates elevated troponin and ST segment changes in the electrocardiogram. Acute myocardial infarction is considered, and it is recommended to refer to a superior hospital for treatment.

Subsequently, he was transferred to our hospital. After admission, the positive antinuclear antibody (ANA) was 1:100, along with positive Anti-Sjögren's-syndrome-related antigen A. He was diagnosed as SSc with artery involvements of coronary and limbs, accompanying acute myocardial infarction, third degree atrioventricular block, pneumonia, pericardial effusion, pleural effusion, and liver dysfunction. We urgently underwent percutaneous coronary intervention and immediately transferred to the ICU for continued life support after the diagnosis was confirmed. Subsequently, patients were treated with antiplatelet, lipid regulation, liver protection, heart rate control, diuresis, anti infection, and other treatments. After 2 days of treatment, the patient's symptoms such as dyspnea were relieved, but electrocardiogram monitoring suddenly indicated that the vital signs were unstable and the patient died.

The autopsy showed the heart was enlarged with a boundary dimension of 12 cm × 10 cm × 6 cm and a weight of 315 g, consistent with slightly thickened walls of aorta and coronary artery, as well as thickened mitral valve with myocardial necrosis and fibrosis. Diffused proliferation of the fibrous tissue accompanied with several focal myocardial necrosis was observed in the myocardium. Microscopic examination showed the myocardial swelling and the interstitial edema (Fig. 3). Large amounts of inflammatory cells, mainly including lymphocytes, macrophages, eosinophils, and foam cells were found in the myocardial interstitium and around the small arteries. The same phenomenon was found in the epicardium and endocardium, combined with significant overgrowth of fibrous tissue and thickening of the endocardium. Granulomatous inflammation is also seen in the mediastinum (Fig. 4). Diffuse fibrosis was found in both lungs, along with large amounts of caseous necrosis in the right lung. Ziehl-Neelsen special stain confirmed a positive outcome for mycobacterium tuberculosis (TB).

The pathologists considered that the exact cause of death for the patient was a combination of diffuse myocarditis, focal myocardial necrosis, endocarditis, pericarditis, and myocardial fibrosis, which induced cardiac failure. The pulmonary fibrosis and the tuberculosis of the right lung was a secondary cause of death.

2.2. Case 2

A 59-year-old female, a general staff member, had stiff and rough skin appearance of her hand 5 years ago. Blood examination indicated a series of serological positivity including ANA and anti-Scl 70 antibody, and she was definitely diagnosed as SSc in our department. During the past 5 years, she was only treated with traditional Chinese medicine and never visited a rheumatologist. 2 days before admission, she developed a cough, sputum, a fever, and tachypnea. Then she was sent to the Pneumology Department. Computed tomography (CT) showed bronchial lesions with infection and interstitial pneumonia. Echocardiography showed

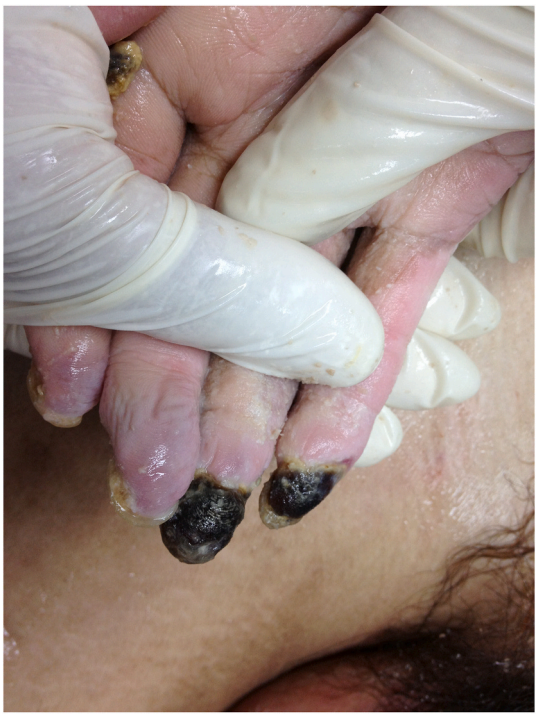

Fig. 2. Fingertip necrosis seen of patient.

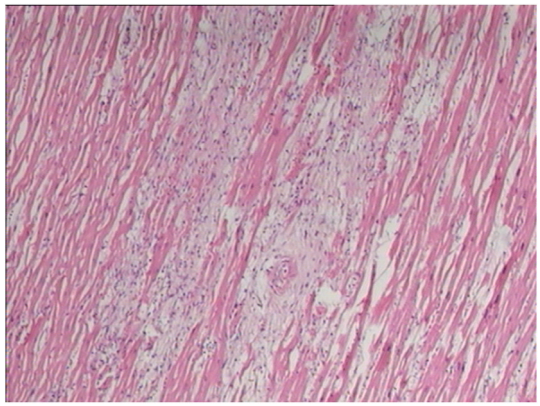

Fig. 3. Myocardial interstitial perivasculitis.

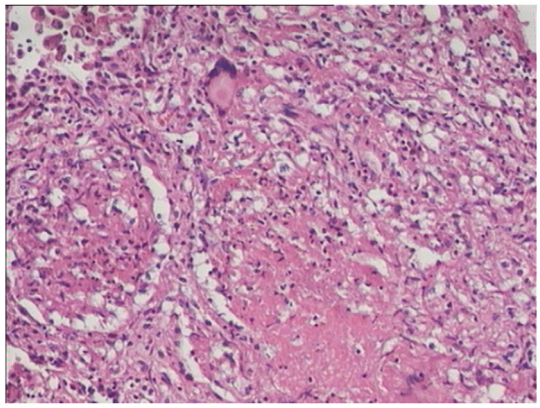

Fig. 4. Granulomatous inflammation of mediastinum.

pulmonary hypertension up to 65 mmHg, compatible with mild to moderate tricuspid regurgitation and left ventricular diastolic dysfunction. Electrocardiography (ECG) revealed sinus rhythm with prolongation of PR interval, left anterior fascicular block and intraventricular block. The clinical diagnosis was pulmonary infection, scleroderma with pulmonary fibrosis, and pulmonary hypertension. Subsequently, the patient received anti infection treatment with piperacillin sulbactam and meropenem needles, supplemented by cough relief and expectorant therapy. The patient's temperature was stable, and symptoms of cough and expectoration were slightly relieved. However, 10 days later, the patient suffered a sudden cardiac arrest and died after rescue, so he underwent an autopsy.

The autopsy showed similar result with case 1 except for TB. The heart was larger with a dimension of 13 cm × 10 cm × 7 cm and a weight of 480 g. An abundance of inflammatory cells were found in the myocardial interstitium (Fig. 5a), endocardium (Fig. 5b), epicardium (Fig. 5c), and around the small arteries of the myocardium (Fig. 5d), combined with significant overgrowth of fibrous tissue and thickened endocardium. The thickened mitral valve was notable, with large overgrowth of fibrous tissue, combined with fibrinoid necrosis. The aorta and coronary artery showed no abnormality. Diffuse fibrosis was observed in both lungs, with proliferation of small arteries. The walls of pulmonary arteries thickened with fibrosis and smooth muscle cells. A considerable amount of inflammatory cells appeared around the bronchus in both lungs.

The pathologists considered cardiac failure and respiratory failure as the exact causes of death, which respectively induced by diffuse myocarditis, focal myocardial necrosis, endocarditis, pericarditis, myocardial fibrosis, pulmonary artery fibrosis, diffuse pulmonary fibrosis and bronchitis.

3. Discussion

SSc is a connective tissue disease characterized by a series of manifestations, including vascular involvement, systemic microvascular disease, skin and visceral fibrosis, and is compatible with the presence of circulating autoantibodies and pro-inflammatory cytokines [13]. Our patients also showed Renault phenomenon and other major features, which are the most common and earliest disease manifestations in 95% of cases, as other authors have studied [14].

Among them, cardiac involvement is usually considered to be myocardial fibrosis with slow progression [15]. The highly prevalent

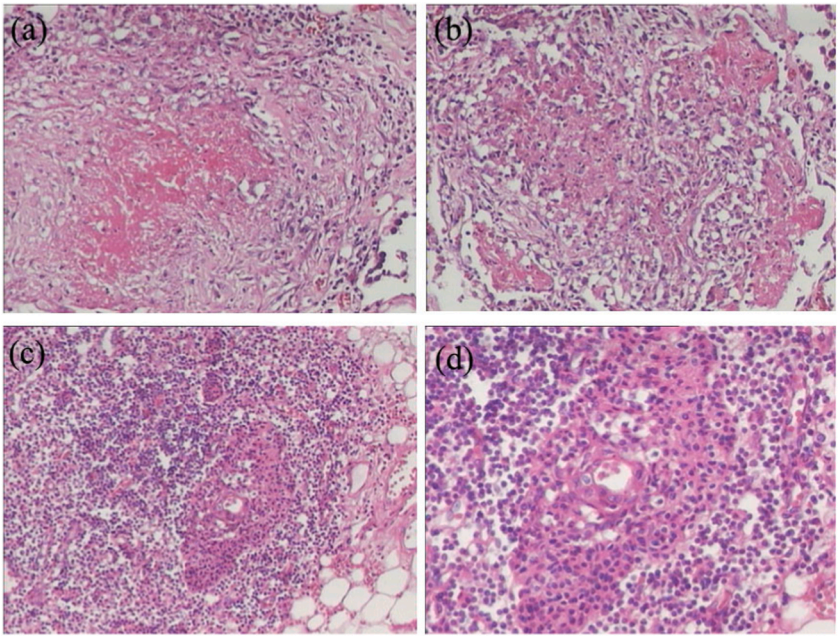

Fig. 5. Perivascular inflammation. Fig. 5a: Inflammatory infiltration of myocardial interstitium; Fig. 5b: Endocarditis infiltration; Fig. 5c: Inflammatory infiltration of epicardium; Fig. 5d: Inflammatory infiltration around myocardial arterioles.

histopathological evidence indicates that cardiac involvement, heart failure and malignant arrhythmia or conduction disorder are relatively rare at autopsy. However, primary myocardial damage is often manifested clinically as acute heart failure or fulminant myocarditis, asymptomatic conduction defect and ventricular arrhythmia, whereas patients with secondary myocardial fibrosis often present with diastolic dysfunction with local and diffuse disease [1]. However, in the autopsy of our case, a combination of inflammation and fibrosis was notable, including cardiomyocyte cell edema, inflammatory cellular infiltration in the myocardial interstitium, endocardium and epicardium, focal myocardial necrosis combined with fibrous tissue hyperplasia, and considerable overgrowth of fibrous tissue in the endocardium. Therefore, we hypothesize that the extensive fibrotic process may be secondary to chronic diffuse inflammation of the heart, as in our cases. Otherwise, it is enough to result in death if the inflammation is acute.

Previous studies [16–18] have suggested that there are two aspects of SSc-induced cardiac injury. One is primary cardiac injury, involving the endocardium, myocardium and pericardium, preceded by cardiac microvascular injury and endothelial cell activation. Further injury then occurs, including vasospasm and moreover, regional hypoperfusion and reperfusion injury. In addition, due to collagen deposition, the later-developed myocardial fibers tend to distribute with a mosaic-like appearance, affecting the conduction system of heart and leading to arrhythmia and conduction disturbance. Another type of secondary cardiac injury is caused by renal vascular lesions, interstitial lung disease, and pulmonary hypertension.

The prevalence of left ventricular dysfunction in SSc patients was 5.4%. Age, male, finger ulcer, myositis and lung involvement were independently associated with the increased prevalence of left ventricular dysfunction [19]. SSc patients showed no decrease in maximal vasodilation response, indicating that there was no irreversible functional impairment at the level of coronary artery. In patients with low coronary artery blood flow reserve, the reduction and acceleration of basic myocardial resistance index reflect the compensatory vasodilation mechanism, which may be triggered by the ischemic signal generated by abnormal myocardial microcirculation [20]. The standard serum cardiac biomarkers of myocardial fibrosis (especially NT-proBNP) and magnetic resonance index were associated with adverse cardiovascular outcomes of SSc [21]. These related studies provide support for the mechanism of SSc involvement in cardiovascular disease.

It is important to detect the cardiac damage of SSc as early as possible. However, most patients with cardiac disease are subclinical, especially early in the early stages of the disease [22]. It calls for a careful physical examination to detect such as palpitations, discouragement and murmurs. In addition, laboratory tests including cardiac enzyme tests, electrocardiogram, ultrasonic cardiogram (US), X-ray, computed tomography (CT) and magnetic resonance (MR) can be considered to find evidence of cardiac damage. If necessary, more extensive evaluation should be performed to detect the disease more specifically. Impairment of left atrial mechanics is an early sign of myocardial involvement in SSc, which reflects the change in left ventricular (LV) diastolic function in SSc [23]. In case 2, US images indicated trivial tricuspid regurgitation, pulmonary hypertension, and impaired left ventricular diastolic function, along with an aberrant outcome in ECG. However, the disease remained absent due to normal cardiac enzyme findings (Creatine Kinase 77 IU/L, CK-MB isoenzyme 13 IU/L).

Tissue Doppler Imaging (TDI) is more suitable for assessing the cardiac function than traditional 2D echocardiography as it is not affected by the rate, loading, and morphology of heart. The research conducted by Dağ et al. [24] approved this argument, who performed tissue Doppler echocardiography examination in 30 SSc patients without clinical cardiac symptoms and 30 controls. They

found that there was a significant difference with regard to right ventricular free wall tissue, Doppler late diastolic waves, pulmonary arterial systolic pressure, right ventricular ejection fraction, and right ventricular diastolic dysfunction values.

Ciurzynski et al. [25] prospectively studied 111 SSc patients and 21 age-matched controls. They assessed left (LV) and right ventricular (RV) diastolic function by transthoracic echocardiography, and measured tissue inhibitor of metalloproteinases 1 (TIMP-1) serum level of the patients. After at least 1-year observation, they found that 34% SSc patients presented with impaired LV relaxation. Besides, the mean E/A ratio was lower in patients with SSc than that in controls. The mean serum level of TIMP-1, compared to the baseline examination, was significantly elevated in the follow-up group, which on the other hand, was positively correlated with E/E. What they found suggested that the LV and RV relaxation was impaired in SSc patients, and left ventricular diastolic function deteriorated after the follow-up period. Moreover, there might be a correlation between TIMP-1 serum levels and echocardiographic parameters. In the case of this disease, to some extent, there might be a potent link for LV diastolic function and matrix remodeling to a certain extent in patients with SSc.

According to the literature, the overall prognosis of patients with SSc cardiac involvement is poor. The patients we report here have a long course of disease. At the time of admission, many tissues and organs have been damaged, such as skin, lung, heart and kidney. Previous reports on two patients with SSc showed that endocardium and myocarditis can be detected by myocardial biopsy and MR, which indicates that these two methods can also be used to assess patients' cardiac injury. Studies have confirmed that the use of biological agents is not only stable and effective for the skin and internal organs involved, but also effective for the microvascular lesions of early dcSSc [26]. In addition, the exploration of epigenetic modification mechanism has become more mature. With the development of probe technology, targeted drug treatment can be more applied to the treatment of SSc patients [27]. However, although we prescribed corticosteroids and immunosuppressive drugs to the patients, and even transferred them to the intensive care unit for further support treatment, the survival time of the patients is still not long.

There are indeed some limitations in this study. Firstly, as this is a sporadic disease, cardiac involvement in SSc is currently limited to case reports and lacks data from large cohort studies, so the research evidence is insufficient; The second point is that this study was conducted for scleroderma patients in our hospital, who are Han Chinese in the south, and there are certain geographical limitations. The third point is that the conclusion will be derived based on some existing literature, and the direct causal relationship is weak.

In conclusion, cardiac damage in patients with SSc is not uncommon. Regular cardiac screening at the time of diagnosis and during follow-up is necessary to improve identification of cardiac damage in SSc patients, potentially leading to improved survival rates.

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Availability of data and supporting materials

Not applicable.

Authors' contributions

HY, QW, XZ and HZ participated in the conception and design of this report and were involved in drafting and revising the manuscript. XW performed the final revisions of the manuscript. All authors read and approved the final manuscript.

Consent for publication

Written informed consent was obtained from the immediate family of patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

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References

[1] C. Bruni, L. Ross, Cardiac involvement in systemic sclerosis: getting to the heart of the matter, Best Pract. Res. Clin. Rheumatol. 35 (3) (2021), 101668.
[2] C.P. Denton, D. Khanna, Systemic sclerosis, Lancet 390 (10103) (2017) 1685–1699.
[3] E. Marijon, et al., Warning symptoms are associated with survival from sudden cardiac arrest, Ann. Intern. Med. 164 (1) (2016) 23–29.
[4] L. Ross, et al., Sudden cardiac death in systemic sclerosis: diagnostics to assess risk and inform management, Diagnostics (Basel) 11 (10) (2021).
[5] M.K. Islam, et al., Network based systems biology approach to identify diseasome and comorbidity associations of Systemic Sclerosis with cancers, Heliyon 8 (2) (2022), e08892.
[6] V. Lambrecht, et al., Reliability of the quantitative assessment of peripheral blood perfusion by laser speckle contrast analysis in a systemic sclerosis cohort, Ann. Rheum. Dis. 75 (6) (2016) 1263–1264.
[7] B.R. Shirazi, R.J. Valentine, J.A. Lang, Reproducibility and normalization of reactive hyperemia using laser speckle contrast imaging, PLoS One 16 (1) (2021) e0244795.
[8] V. Smith, et al., An EULAR study group pilot study on reliability of simple capillaroscopic definitions to describe capillary morphology in rheumatic diseases, Rheumatology (Oxford) 55 (5) (2016) 883–890.
[9] V. Smith, et al., Systemic sclerosis: state of the art on clinical practice guidelines, RMD Open 4 (Suppl 1) (2018) e000782.
[10] S. Soulaidopoulos, et al., The role of nailfold capillaroscopy in the assessment of internal organ involvement in systemic sclerosis: a critical review, Autoimmun. Rev. 16 (8) (2017) 787–795.
[11] M. D'Oria, et al., Correlation between microvascular damage and internal organ involvement in scleroderma: focus on lung damage and endothelial dysfunction, Diagnostics (Basel) 13 (1) (2022).
[12] A. Sulli, B. Ruaro, M. Cutolo, Evaluation of blood perfusion by laser speckle contrast analysis in different areas of hands and face in patients with systemic sclerosis, Ann. Rheum. Dis. 73 (11) (2014) 2059–2061.
[13] C. Ferreli, et al., Cutaneous manifestations of scleroderma and scleroderma-like disorders: a comprehensive review, Clin. Rev. Allergy Immunol. 53 (3) (2017) 306–336.
[14] N. Anbiaee, Z. Tafakhori, Early diagnosis of progressive systemic sclerosis (scleroderma) from a panoramic view: report of three cases, Dentomaxillofacial Radiol. 40 (7) (2011) 457–462.
[15] L.Y. Nie, et al., Cardiac complications in systemic sclerosis: early diagnosis and treatment, Chin. Med. J. (Engl) 132 (23) (2019) 2865–2871.
[16] L.A. Bissell, et al., Incidental significant arrhythmia in scleroderma associates with cardiac magnetic resonance measure of fibrosis and hs-TnI and NT-proBNP, Rheumatology (Oxford) 58 (7) (2019) 1221–1226.
[17] N. Bose, A. Chiesa-Vottero, S. Chatterjee, Scleroderma renal crisis, Semin. Arthritis Rheum. 44 (6) (2015) 687–694.
[18] M. Mohameden, P. Vashisht, T. Sharman, Scleroderma and Primary Myocardial Disease, in: StatPearls, StatPearls Publishing, 2022.
[19] Y. Allanore, et al., Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis, Ann. Rheum. Dis. 69 (1) (2010) 218–221.
[20] T. Pintér, et al., Mechanism of coronary flow reserve reduction in systemic sclerosis: insight from intracoronary pressure wire studies, Rheumatology (Oxford) 50 (4) (2011) 781–788.
[21] R.B. Dumitru, et al., Cardiovascular outcomes in systemic sclerosis with abnormal cardiovascular MRI and serum cardiac biomarkers, RMD Open 7 (3) (2021).
[22] S.I. Mavrogeni, et al., Cardiovascular Magnetic Resonance Imaging clarifies cardiac pathophysiology in early, asymptomatic diffuse systemic sclerosis, Inflamm. Allergy - Drug Targets 14 (1) (2015) 29–36.
[23] A. Porpáczy, et al., Impairment of left atrial mechanics is an early sign of myocardial involvement in systemic sclerosis, J. Card. Fail. 24 (4) (2018) 234–242.
[24] Ş. Dağ, et al., Relation of asymmetric dimethylarginine and cardiac involvement in systemıc sclerosis, Acta Reumatol. Port 39 (3) (2014) 228–235.
[25] M. Ciurzyński, et al., Heart diastolic dysfunction in patients with systemic sclerosis, Arch. Med. Sci. 10 (3) (2014) 445–454.
[26] V. Smith, et al., Stabilization of microcirculation in patients with early systemic sclerosis with diffuse skin involvement following Rituximab treatment: an open-label study, J. Rheumatol. 43 (5) (2016) 995–996.
[27] J. Henderson, J. Distler, S. O'Reilly, The role of epigenetic modifications in systemic sclerosis: a druggable target, Trends Mol. Med. 25 (5) (2019) 395–411.