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DACRYOADENITIS AS A RARE INITIAL PRESENTATION IN A PATIENT WITH SUSPECTED CREST SYNDROME

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ABSTRACT

Systemic sclerosis (SSc) is a rare, chronic disease with diverse clinical presentations, and only a few cases with ocular manifestations have been reported in the literature. In this case report, we describe the case of a 51-year-old South Asian woman who initially complained of painless swelling in her left upper eyelid. An ultrasound examination of the left eye revealed an enlarged lacrimal gland with increased vascularity. The presence of dacryoadenitis, which was unresponsive to initial conservative management with oral antibiotics and warm compresses, along with positive antinuclear antibodies, prompted further investigation. Dacryoadenitis or orbital inflammation is a common presentation in systemic conditions such as Sjogren's syndrome, systemic lupus erythematosus, sarcoidosis, or granulomatosis with polyangiitis. However, it can also be a rare initial symptom in a patient with CREST syndrome. To our knowledge, this is only the second case in the literature of dacryoadenitis in the context of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome. This case highlights the significance of serological markers and peripheral clinical presentations in individuals with chronic orbital inflammation, emphasizing the importance of considering further systemic associations.

KEYWORDS

Systemic sclerosis, CREST syndrome, orbital inflammation, dacryoadenitis, ocular manifestations

LEARNING POINTS

- *Broad spectrum of clinical features:* Recognize that although CREST syndrome is primarily characterized by its hallmark features - calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia - it can also present with additional clinical features that may indicate the onset or presence of the syndrome.
- *Diagnostic challenges and differentiation:* Bilateral dacryoadenitis can be challenging to diagnose due to its overlapping symptoms with other orbital or systemic conditions. The case report may highlight the importance of differentiating it from conditions like orbital cellulitis, sarcoidosis, or lymphoproliferative disorders. Advanced imaging techniques (like magnetic resonance imaging or computed tomography scans) and careful assessment of clinical history (including systemic symptoms like fever or autoimmune conditions) are crucial for accurate diagnosis.

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- *Awareness of atypical presentations and follow- up:* The case report underscores the need for tailored management strategies for bilateral dacryoadenitis, from conservative treatments in mild cases to more aggressive therapies in severe ones, while also highlighting the importance of monitoring for complications and being vigilant about atypical presentations, such as those seen in patients with CREST syndrome.

INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is a chronic condition characterized by fibrosis initiated by autoimmune factors, affecting the skin and various internal organs. The complex pathophysiology of this disease involves early damage to endothelial cells, infiltration of inflammatory cells, and subsequent development of fibrotic responses *(Fig. 1)*[1]. SSc is a rare disease, with its advanced stages presenting distinct and readily diagnosable clinical features. However, the early stages of the disease are frequently overlooked, potentially leading to an underestimation of its prevalence[2]. It can manifest either as a systemic or localized condition. There are three well-recognized clinical variations: (i) limited cutaneous (formerly known as CREST syndrome), (ii) diffuse cutaneous, and (iii) sine scleroderma. Limited cutaneous SSc is distinguished by symmetrical skin thickening confined to the distal extremities and face. The earliest sign most commonly reported in the literature is the Raynaud phenomenon. The diagnostic criteria for SSc established by LeRoy and Medsger in 2001[3] for early identification include the presence of

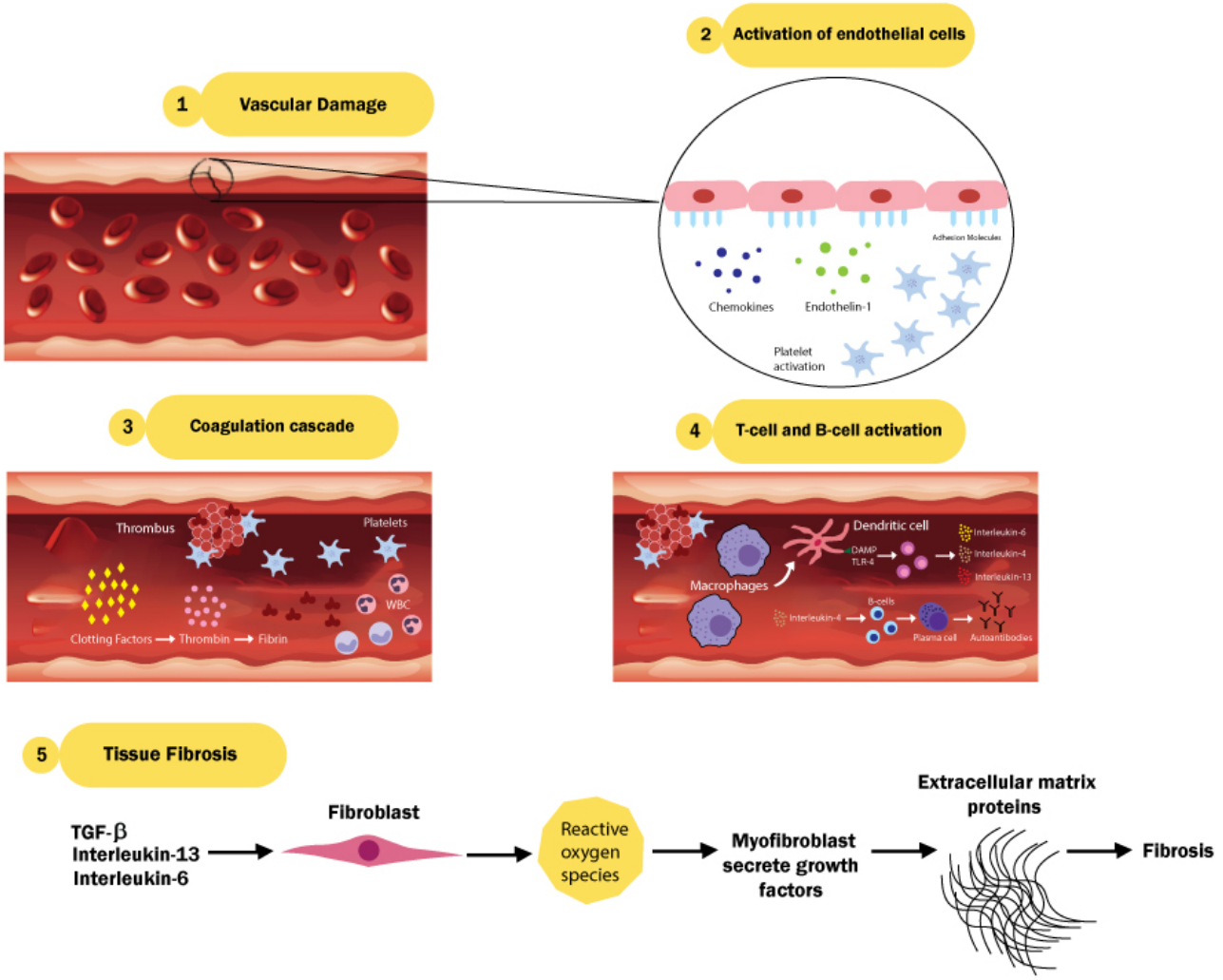

Figure 1. Molecular pathogenesis of initial systemic sclerosis. In early SSc vascular damage activates endothelial cells, leading to the expression of adhesion molecules, chemokine production, endothelin-1 release, and activation of coagulation cascade. Chemokines attract macrophages, while DAMPs activate dendritic cells. Activated T cells release IL-6, IL-4, and IL-13, stimulating B cells to produce autoantibodies. Fibroblasts, driven by TGF-beta, IL-13, and IL-6, generate ROS and become myofibroblasts, which secrete growth factors and extracellular matrix molecules, leading to fibrosis.

Abbreviations: SSc, systemic sclerosis; DAMP, damage-associated molecular patterns; TGF, transforming growth factor ; IL, interleukin; ROS, reactive oxygen species.

Raynaud phenomenon, specific autoimmune antibodies associated with systemic sclerosis, and scleroderma-like alterations observed through nailfold capillaroscopy[4]. Nail fold capillaroscopy is a dependable technique for detecting microvascular changes, such as reduced mean capillary density, capillary dilation, and increased tortuosity[5].

As SSc is uncommon and primarily does not affect visual organs, there has been only limited documentation of its ophthalmological effects, often stemming from isolated case reports and studies involving small groups of patients. The ophthalmic manifestations observed in SSc display considerable diversity, with certain manifestations such as eyelid skin abnormalities and dry eye disease (DED) being directly linked to SSc, while others remain subject to debate and are likely unrelated incidental findings[6].

The authors describe a case of dacryoadenitis with positive CREST syndrome-specific antibodies but no Raynaud phenomenon. The scarcity of SSc cases documented in current literature hampers the development of efficient diagnostic criteria, consequently impeding early diagnosis. Despite the low frequency of associations reported in the existing literature, heightened awareness can significantly improve management of such scenarios, ultimately leading to improved treatment outcomes.

CASE PRESENTATION

A 51-year-old woman with an unremarkable medical history reported painless upper unilateral left eyelid swelling for about a month. The swelling, initially small, had increased by the time of her presentation. During the physical examination, her best-corrected visual acuity in both eyes was determined to be 6/9. There was normal ocular muscle movement, and no signs of optic neuropathy were evident. The swelling appeared smooth and non-tender, with noticeable proptosis on the left side *(Fig. 2)*. Ultrasound results of the eye revealed a swollen left lacrimal gland with heightened vascularity, measuring approximately 1.1 x 1.4 x 1.4 cm, consistent with dacryoadenitis.

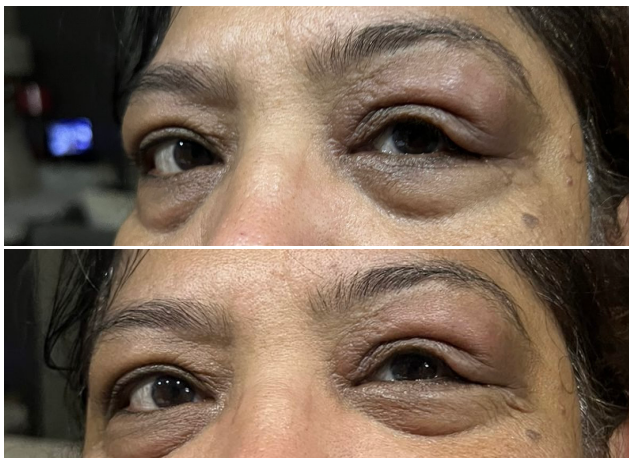

Figure 2. Left upper eyelid swelling reported in patient.

The patient was initially treated empirically with antibiotics due to a suspected infectious etiology, but her symptoms failed to improve, prompting further investigation. Results from a complete blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), creatine kinase levels, urinalysis, and tests for other infectious causes (viral and bacterial) were all negative.

At her subsequent follow-up, the patient did not report any additional symptoms or complaints. During the physical examination, she denied tenderness on palpation over the eyelid, excessive tearing, a dry sensation, or restricted lid closure. The fundus examination was unremarkable. However, on systemic examination, small pitting lesions on the fingertips were observed. The patient mentioned she had similar lesions 3 years ago, which resolved after a week-long oral steroid therapy, although the lesions do recur intermittently. She had no complaints of skin dryness or joint stiffness. Given her strong family history of autoimmune diseases in her father and daughter, a presumptive diagnosis

Figure 3. Scoring For Limited Sclerosis by American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) in 2013. Abbreviations: SSc, systemic sclerosis; RNA, ribonucleic acid; HTN, hypertension.

of an autoimmune disease was formed, with differentials including SSc, Sjogren's syndrome, and IgG4-related systemic disease, all of which can present with similar orbital pathologies. Laboratory tests were conducted for antinuclear antibodies (ANA), rheumatoid factor (RF) 10.20 U/ml (range <20 U/ml), and anti-neutrophil cytoplasmic antibodies (ANCA). The ANA test results were strongly positive (190.27 U/ml; range: <20.00 U/ml), with normal levels of IgG, calcium (10.7 mg/dl; range: 8.5-10.5 mg/dl), and CRP. Consequently, a referral to Rheumatology was made.

The patient's RF, angiotensin-converting enzyme (ACE 28.50, range: <40 nmol/ml/min), and antineutrophil cytoplasmic antibodies (p-ANCA and c-ANCA) were within normal limits. To rule out other potential complications and differentials, the patient underwent a positron emission tomography/computed tomography (PET/CT) scan. The scan revealed an inconspicuous, poorly defined, and asymmetrical area of soft tissue with reduced density along the upper and outer aspect of the left eyeball. This area measured approximately 20 mm from front to back, 15 mm from top to bottom, and 8 mm at its widest point. The scan indicated an uneven and slightly elevated F-fluorodeoxyglucose (FDG) uptake, with a maximum standardized uptake value (SUV max) ranging from 5 to 5.25, suggesting possible enlargement of the left lacrimal gland and confirming the diagnosis of dacryoadenitis. In contrast, the right lacrimal gland measured less than a centimeter in diameter in all dimensions and exhibited no abnormal FDG uptake, indicating unilateral orbital involvement. Additionally, laboratory tests for anti-Rho and anti-LA were conducted to exclude the possibility of Sjogren's syndrome, which yielded negative results.

An enzyme immunoassay (EIA) revealed that the patient's ANA antibody pattern was consistent with a centromere pattern (AC-3) and an endpoint titer of 1:32000, indicative of CREST or limited SSc. The patient was started on oral steroids (deflazacort 18 mg) for 20 days and was gradually weaned off as her symptoms began to resolve. She was advised to undergo a biopsy of the swelling to confirm the diagnosis, but she declined. The patient was seen on the 15th and 30th days of follow-up with no recurrence or complaints.

DISCUSSION

Dacryoadenitis, characterized by inflammation of the main or accessory lacrimal glands, often arises from infections and typically affects only one eye. These infections may stem from the conjunctiva, skin, trauma, or bacteremia. Viral nonsuppurative dacryoadenitis is frequently caused by viruses such as Epstein-Barr, adenovirus, herpes simplex, and herpes zoster, while bacterial infections, including those from *Staphylococcus aureus*, *Streptococcus pneumoniae*, and Gram-negative rods, can lead to suppuration. In cases where a patient presents with bilateral dacryoadenitis, it is important to consider other underlying causes, such as autoimmune diseases like thyroid eye disease, granulomatosis with polyangiitis, Sjogren's syndrome, and IgG4-related disease. Additionally, neoplastic conditions like lymphoma, adenoid cystic carcinoma, and pleomorphic adenoma may also be responsible. Therefore, dacryoadenitis warrants a thorough exploration of various etiologies to ensure accurate diagnosis and appropriate management[7].

SSc, also known as scleroderma, is a connective tissue disease characterized by fibrosis (thickening and hardening) of the skin and internal organs. This autoimmune condition has different presentations depending on the disease variant affecting the individual. Limited systemic sclerosis also known as CREST syndrome, is linked with specific manifestations such as calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly (a tapering deformity of the finger bones), and telangiectasia[8]. The staining patterns in ANA tests can help distinguish autoimmune diseases by revealing which antibodies have interacted with specific cellular regions. Anti-centromere antibodies are typically associated with limited cutaneous systemic sclerosis and serve as a diagnostic feature for this condition[9]. However, although it is less common, these antibodies can also be present in Sjogren's syndrome, primary biliary cirrhosis, and diffuse cutaneous systemic sclerosis [10,11].

Due to the small number of cases of the disease, it is very challenging to develop diagnostic criteria for SSc. The current diagnostic criteria by the American College of Rheumatology/European League Against Rheumatism (2013) *(Fig. 3)* states that a score of ≥9 is required for definite diagnosis of SSc[12]. The existing literature highlights the scarcity of these case reports and enunciates that by the time patients seek medical attention, they often present with advanced disease pathology which leads to higher mortality rates. Given the potential for false positives, the most crucial aspect of managing dacryoadenitis is ensuring thorough follow-up. If there is no improvement, a more detailed evaluation should be considered. We have highlighted the significance of an atypical presentation in our report, describing early signs suggestive of CREST syndrome in our patient who is currently undergoing targeted treatment. Our patient has a score of 6 with the evidence of fingertip lesions and positive anti-centromere 3 antibodies. Additionally, ocular involvement was noted in this case, which could be suggestive of an overlap with the systemic disease spectrum. The eye has a unique anatomical and immune system, making it vulnerable to immunologic disorders, vascular irregularities, and various inflammations. It may serve as an indicator for the onset or worsening of immune reactivation in numerous rheumatic diseases. Additionally, ocular symptoms can precede the diagnosis of the underlying rheumatic disease[9]. The ophthalmologic organs are primarily composed of connective tissue, which may explain the pathogenesis behind ocular manifestations being the presenting symptoms in some cases of SSc[6,13].

There are various ocular manifestations reported in a study by Waszczykowska A. et al on SSc, which include dry eye disease, periorbital edema, ectropion or ciliary madarosis[14]. An article by Kozikowska M. et al tabulates the presence of different ocular symptoms in SSc patients[13].

According to the survey conducted by Szucus G, et al., DED emerged as the primary ocular disorder, capable of causing cataracts and changes in eyelid skin[6]. Swollen and hardened eyelids often accompany microorganism colonization and inflammation along the eyelid margins, leading to infections. In advanced stages, individuals may experience limited mobility of the eyelids. Among patients with systemic sclerosis, the progression of fibrosis can lead to occlusion of tear ducts and decreased tear production and drainage, impairing the removal of pathogens from the conjunctival sac[14]. Our patient had a similar fibrotic progression which led to her presentation of dacryoadenitis.

In our case report, we have highlighted the variable presentation of autoimmune diseases. Our patient had ophthalmological manifestations, leading to the discovery of anti-centromere antibodies and nail pitting, which are highly suggestive of SSc. In addition to further research aimed at refining diagnostic criteria for early confirmation and timely management of SSc, there is a need to raise awareness among clinicians about the diverse presentations of this disease.

CONCLUSION

While orbital inflammatory disease is not typically associated with systemic sclerosis, it is crucial to differentiate it from other potential causes. This distinction is essential as effectively managing both the systemic disease and orbital inflammation can improve prognosis, often necessitating the use of oral nonsteroidal preparations. Increased awareness about the atypical presentations of systemic sclerosis and its potential association with orbital inflammatory disease is essential. Physicians are encouraged to consider systemic causes in patients presenting with unexplained ocular manifestations, as prompt recognition and appropriate management can significantly result in better prognosis and patient outcomes.

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