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BRIEF REPORT

Clinical characteristics and outcomes of digital gangrene in connective tissue disorders: a longitudinal single-centre experience from Jodhpur, India

Neeraja Vijayan[1] · Parag Vijayvergia[1] · Gopal Krishna Bohra[1] · Mahendra Kumar Garg[1] · Maya Gopalakrishnan[1]

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Abstract

Epidemiology, clinical presentation, and outcomes for digital gangrene in connective tissue disorders (CTD) remain underreported from tropical countries like India. In this series, we aimed to explore the clinical profile and outcomes of patients who presented with digital gangrene and a diagnosis of CTD. Hospital-based longitudinal observational study. Patients with digital gangrene and underlying diagnosis of CTD presenting to our tertiary-care centre in Jodhpur, India between1st January 2018 and 31st June 2021 were included. Clinical outcomes including mortality, limb outcomes, functional status and other systemic involvement were assessed. Of the 312 patients registered in the rheumatology clinic during this period, 22 (7%) patients were found to satisfy the inclusion criteria. Mean age was 46 years and 90% were females. The most common underlying diagnosis was Mixed connective tissue disorder (MCTD). Digital gangrene was the presenting symptom in 13 (60%) patients. Half of the patients received only corticosteroids as immunosuppression. Two died due to systemic complications. Complete resolution occurred in 17 (85%), autoamputation in 3, and infection requiring surgical drainage in one patient. All surviving patients reported good functional limb outcome on 6 months follow-up. MCTD is an important cause of digital gangrene in rheumatology practice. In patients presenting with digital gangrene, an active search for an underlying CTD is imperative, as this could result in timely initiation of appropriate limb-saving therapy. Corticosteroids alone with rapid tapering may be an appropriate option to consider in the initial management of digital gangrene in CTD.

Key Points

- *Mixed connective tissue disorder is an important cause of digital gangrene in rheumatology practice in western India.*
- *In patients presenting with digital gangrene, an active search for an underlying connective tissue disorder is imperative, as this could result in timely initiation of appropriate therapy and can prove limb saving.*
- *Corticosteroids alone with rapid tapering may be an appropriate option to consider in the initial management of digital gangrene in connective tissue disorders.*

Keywords Critical-limb ischemia · Mixed connective tissue disorder · Raynaud's phenomenon · Systemic lupus erythematosus · U1RNP

Background

Digital gangrene has been described as a complication of several connective tissue disorders (CTDs) including systemic sclerosis, antiphospholipid antibody syndrome (APS) and systemic lupus erythematosus (SLE). Digital gangrene may result in a significant morbidity with limitation of functional activity progressing to long-term disability. Prevalence of digital gangrene is estimated to be 8 to 9% in systemic sclerosis and around 2–5% in SLE [1–4]. Multiple mechanisms including small-vessel vasculitis, vasospasm, premature atherosclerosis, and hypercoagulability have been used to explain the mechanism of digital gangrene in CTDs [5]. Due to multiple underlying mechanisms and limited studies, the optimal management of digital gangrene in CTDs remains uncertain. While the role of anticoagulation

✉ Maya Gopalakrishnan
maya.gopalakrishnan@gmail.com

[1] Department of Internal Medicine, All India Institute of Medical Sciences, Basni Industrial Estate, Jodhpur 342005, India

in APS syndrome and vasodilators like dihydropyridine calcium channel inhibitors such as nifedipine and nitric oxide synthase inhibitors in vasospasm-related ulcers in systemic sclerosis are somewhat defined, the role of immunosuppression for small vessel vasculitis remains to be established [6]. In this series, we aimed to describe the clinical profile, risk factors and outcomes of adult patients who presented with CTD-associated digital gangrene in a 4-year period to our centre in India.

Design and methods

The study was designed as a hospital-based ambispective clinical study of all adults (> 18 years) who presented to the Department of Medicine (inpatients and outpatients) and outpatients rheumatology clinic service between 1st January 2018 and 31st June 2021 with digital gangrene and a diagnosis of connective tissue disease. Ethical approval was obtained from the institute ethics committee (AIIMS/IEC/2020/3070). Records of these patients were accessed using the hospital information system and discharge details. Data regarding demographic details (age, gender, address), diagnosis, relevant investigations, interventions, and outcomes were collected using standard data collection sheets. The patients were contacted telephonically for consent and requested to come for physical follow-up wherein written informed consent was obtained, and clinical details collected. Data was entered in Microsoft excel spreadsheets, descriptive statistics are presented as mean with standard deviation in case of continuous variables and median with interquartile range in case of categorical variables.

Results

Demographic details and limb involvement

Twenty-two patients of 312 (7%) were identified fitting the inclusion criteria in the study period. Mean age of the patients was 46.6 years. In 13 (59%) patients, digital gangrene was the initial clinical clue that culminated in a diagnosis of CTD while the rest of the patients were already diagnosed with an underlying rheumatological condition. Of the 22, 7 had gangrene involving only upper limbs, 7 involving only lower limbs while 8 had gangrene involving both fingers and toes. Digital gangrene was preceded by Raynaud's phenomenon in 15 patients. Table 1 summarises the clinical profile and outcomes in CTD-associated digital gangrene. Figures 1 and 2 depict the various presentations of digital gangrene.

Underlying diagnosis

The most common underlying CTD diagnosis was MCTD ($n=7$). MCTD was diagnosed in all patients with Kahn's or Alacron-Segovia's criteria. Other underlying diagnosis included SLE ($n=4$), systemic sclerosis ($n=3$), Rheumatoid arthritis (RA) ($n=2$), primary antiphospholipid syndrome (APS) ($n=2$) and ANCA-associated vasculitis (n = 1). One patient presented at 20 weeks of gestation with lower limb gangrene, with history of similar episode in past pregnancy. She had positive Antinuclear Antibody (ANA) twice separated by a period of 3 years and hence was diagnosed as undifferentiated connective tissue disorder (UCTD, criteria in Appendix 1).

Two patients had clinical and laboratory features of vasculitis but did not qualify the diagnostic criteria of any of the vasculitis, hence were classified as possible undifferentiated vasculitis syndromes.

Antibody profile

On assessment of the autoantibody profile, ANA was detected in 63% ($n=14$) followed by anti-U1RNP ($n=10$) and anti-Ro 40% ($n=9$). Other antibodies included lupus anticoagulant ($n=3$), p-ANCA ($n=2$) and anti Scl-70 ($n=3$) while in 2 patients, no autoantibodies were detected (Table 1).

Systemic involvement

Patients were also screened for systemic involvement. Pulmonary manifestations were found to be present in more than half of the patients ($n=13$). Most common among these was interstitial lung disease ($n=9$), and pulmonary arterial hypertension ($n=4$). One patient had diffuse alveolar hemorrhage and one was receiving continuation phase of antitubercular therapy for pulmonary tuberculosis.

Renal involvement was present only in 3 patients, one presented with pulmonary-renal syndrome and evolved into CKD requiring haemodialysis. The other 2 patients were diagnosed with SLE with lupus nephritis.

Musculoskeletal and skin involvement: Myositis was present in 3 patients in our series (with MCTD). Synovitis was present in 6 while 3 patients had findings suggestive of erosive arthritis. Three patients had presented with acute cutaneous flare of lupus (malar rash) and one with livedo reticularis respectively while others did not have any dermatological manifestations.

Table 1 Clinical, laboratory characteristics and patient outcomes

Sl No	Age	Diagnosis	Upper/ lower limb gangrene	Antibodies	Raynaud's phenomenon	Systemic manifestations	Management received	Outcome
1	31	MCTD	Both	Anti U1RNP	Yes	ILD-UIP, Raynaud's phenomenon, myositis, synovitis, Autoimmune hepatitis	Steroids Mycophenolate mofetil, Azathioprine	Recovered
2	28	MCTD	Upper limb	Anti U1RNP, Anti Ro	Yes	Myositis, synovitis, ILD	Steroids and methotrexate (for myositis)	Recovered
3	28	MCTD	Lower limb	Anti U1RNP, Anti Ro	Yes	Raynaud's phenomenon, synovitis, malar rash	Steroids	Recovered
4	52	MCTD	Lower limb	ANA, Anti U1RNP	Yes	ILD, Raynaud's phenomenon	Steroids	Recovered
5	45	MCTD	Upper limb	ANA, Anti U1RNP, Anti Ro	Yes	PAH, Synovitis	Steroids	Recovered
6	68	MCTD	Upper limb	ANA, Anti U1RNP, Anti Scl-70	Yes	ILD, Raynaud's phenomenon, synovitis	Steroids Mycophenolate Mofetil	Recovered
7	57	MCTD	Upper limb	ANA +, Anti U1RNP	No	Synovitis	Steroids	Recovered
8	35	SLE with p-ANCA vasculitis	Lower limb	p-ANCA, ANA, U1RNP, Anti Ro	No	None	Steroids	Recovered
9	24	SLE with APS	Lower limb	ANA, Anti dsDNA, lupus anticoagulant, Anti SSA, SSB	No	Anterior tibial artery thrombosis, cutaneous lupus	Steroids, anticoagulation	Recovered
10	31	SLE	Both	ANA, Anti-Ro and Anti La	Yes	Lupus nephritis, arthritis	Steroids, Cyclophosphamide	Recovered
11	39	SLE	Upper limb	ANA, Anti U1RNP, PM-SCL	Yes	Lupus nephritis, ILD, Serositis, cutaneous lupus	Steroids, Mycophenolate Mofetil	Recovered
12	36	APS	Lower limb	Lupus anticoagulant	No	Pulmonary TB on ATT	Steroids Anticoagulation	Recovered
13	47	APS	Both	Lupus anticoagulant	No	Recurrent pregnancy loss, Type 2 diabetes	Anticoagulation	Recovered
14	30	Systemic sclerosis	Upper limb	Anti-Ro, Anti Scl-70	Yes	ILD-NSIP	Steroids, Mycophenolate Mofetil	Recovered
15	52	Diffuse Cutaneous Systemic sclerosis	Both	ANA, Anti Ro	Yes	ILD – Hypersensitivity pneumonitis, PAH	Steroids, Mycophenolate Mofetil	Previous history of left arm amputation
16	18	Systemic sclerosis-MCTD overlap	Both	ANA, Anti U1RNP, Anti Scl-70, anti- cardiolipin	Yes	PAH	Steroids, Cyclophosphamide	Recovered
17	31	Rheumatoid Arthritis with systemic sclerosis overlap	Both	ANA	Yes	Raynaud's phenomenon, keratoconjunctivitis sicca, livedo reticularis, ILD	Steroids, methotrexate	Expired
18	44	Rheumatoid arthritis	Lower limb	ANA +	No	PAH	Steroids, Cyclophosphamide	Recovered

Table 1 (continued)

Sl No	Age	Diagnosis	Upper/ lower limb gangrene	Antibodies	Raynaud's phenomenon	Systemic manifestations	Management received	Outcome
19	70	ANCA vasculitis	Both	p-ANCA, ANA	Yes	Raynaud's phenomenon, Hypothyroidism	Steroids	Recovered
20	29	Undifferentiated vasculitis With Pulmonary renal syndrome	Both	None	No	Diffuse Alveolar hemorrhage	Steroids, Mycophenolate Mofetil	CKD STAGE V ON MHD, Expired
21	48	Undifferentiated Vasculitis	Upper limb	None	Yes	ILD, MRSA palmar abscess	Steroids	Recovered
22	25	Undifferentiated CTD	Lower limb	ANA	Yes	None	Steroids but discontinued in 4 weeks	Progression of gangrene to involve all 5 digits of both feet Amputation of toe done

ANA, Antinuclear antibody; *ANCA*, Antineutrophil cytoplasmic antibody; *APS*, Antiphospholipid syndrome; *CKD*, Chronic kidney disease; *CTD*, connective tissue disorder; *ILD*, Interstitial lung disease; *MHD*, Maintenance hemodialysis; *MCTD*, Mixed connective tissue disorder; *MRSA*, Methicillin resistant staphylococcus aureus; *NSIP*, non-specific interstitial pneumonia; *PAH*, pulmonary artery hypertension; *UIP*, usual interstitial pneumonia

Management

All patients received supportive therapy with maximum tolerated doses of nifedipine and 75 mg of aspirin. All patients also received immunosuppressive therapy with pulse methylprednisolone followed by oral prednisolone at a dose of 1 mg/kg with weekly tapering at 10 mg/week at the time of diagnosis of digital gangrene. One patient with RA was previously on methotrexate and steroids, the former was continued while dose of the latter was increased. Patients who were diagnosed with primary APS received anticoagulation additionally. There was complete cessation of gangrenous extension within 6 weeks in all our patients, without surgical intervention or limb loss. On subsequent follow-up, 12 of our patients required additional immune suppression in lines of mycophenolate mofetil ($n=6$), cyclophosphamide ($n=3$), methotrexate ($n=2$) and azathioprine ($n=1$).

Outcomes

One patient with undifferentiated vasculitis (patient 20) developed diffuse alveolar hemorrhage and succumbed to the disease 6 months after presenting with digital gangrene. This patient had digital gangrene concurrently at the time of diagnosis of rapidly progressive renal failure which later progressed to chronic kidney disease.

Patient 17 with rheumatoid vasculitis was readmitted with recurrence of digital gangrene at 1 year, and was planned for intravenous cyclophosphamide, but she developed sudden cardiac arrest and expired during hospital stay.

Follow-up and complications

On long-term follow-up in a rheumatology clinic, we observed complete resolution of digital gangrene in 17 of our patients (85%), autoamputation in 3 patients and surgical amputation in one. One patient developed soft tissue infection of the gangrenous digit 3 months after the diagnosis of gangrene with Methicillin Sensitive *Staphylococcus aureus* isolated from the same. She improved with incision and drainage and systemic antibiotics. One patient included in the series with MCTD had presented with acute febrile illness and was diagnosed with COVID-19 pneumonitis (mild severity). Patient 22 delivered a healthy term infant but declined immunosuppressive therapy with steroids or other drugs. Her gangrene worsened involving bilateral lower limbs and she had to undergo toe amputation in the left leg 3 months post-partum. All surviving patients reported good functional status and limb outcomes at 6 months follow-up.

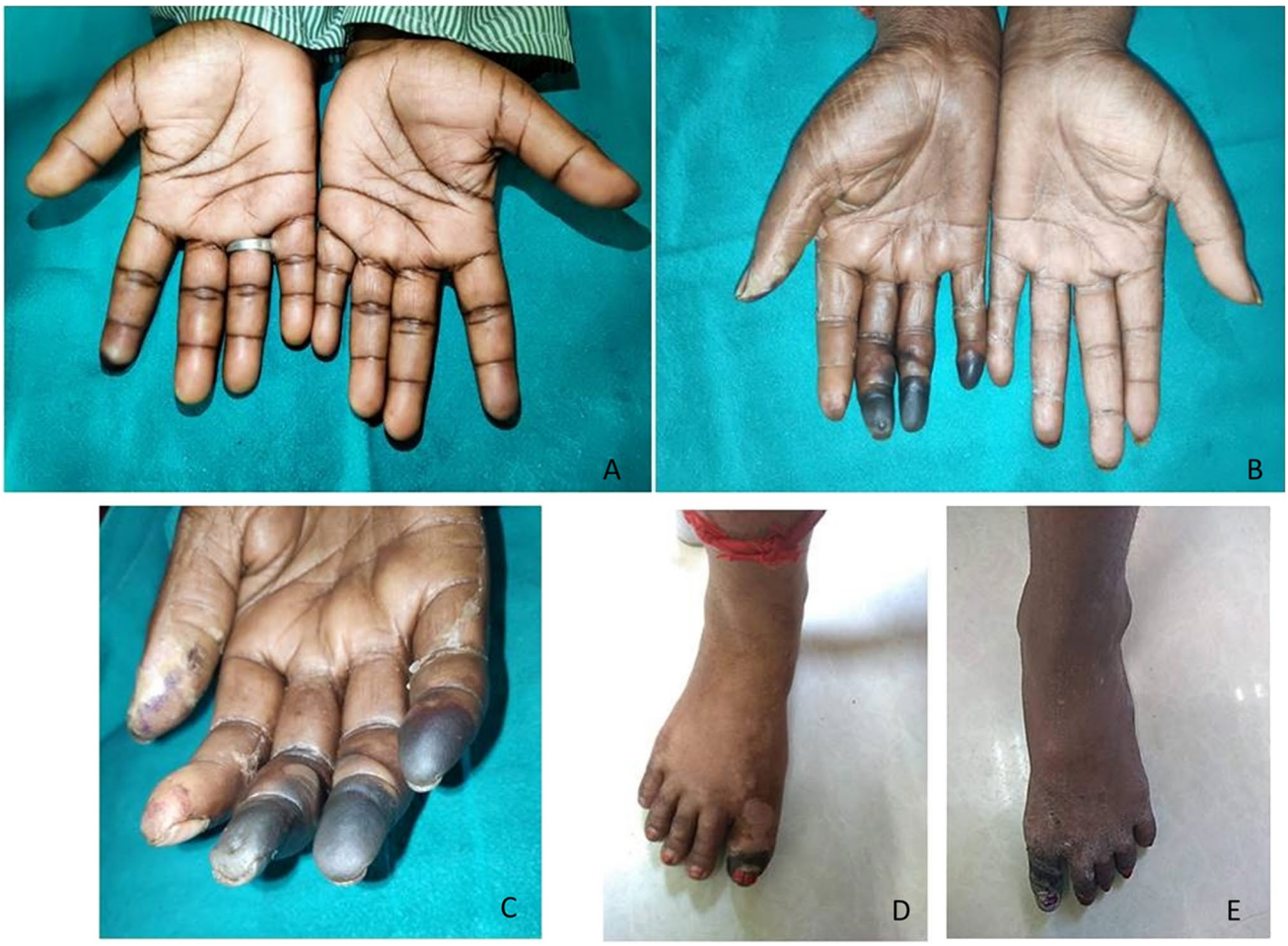

Fig. 1 **A** Swollen fingers in mixed connective tissue disorders with digital gangrene over tip of 4.th digit in the right hand. **B** and **C** Skin thickening and digital gangrene in a patient with systemic sclerosis. Hyperpigmentation in the right hand and digital ulcers over thumb **C**. **D** and **E** Digital gangrene involving lower limb in a patient with RA-systemic sclerosis overlap. Ankle swelling right > left

Discussion

Digital gangrene has been described in association with CTDs, with a varied prevalence of 1% in SLE to 8.9% in systemic sclerosis [2, 4]. In our setting, the hospital-based prevalence was 5.3%. For the 22 patients, with digital gangrene during a 4-year period, the mean age was 46 years, which was higher than the previously reported mean age of 30–35 years [1–3].

The most common underlying diagnosis in our case series was MCTD ($n = 7$), in contrast to previous studies which place systemic sclerosis as the most common contributor to digital gangrene. The idea of a "mixed connective tissue disorder" (MCTD) was introduced in 1969 by Sharp et al., and gangrene has been reported in MCTD as early as 1975 [7]. MCTD is characterized as a rare disorder, with an estimated prevalence of 6.4 per 1,00,000 population in the USA [8, 9], no data exists for the Indian population, with highest prevalence reported by Lawrence et al. in 2007 with their data of 16 MCTD patients among a cohort of 441 patients with CTD [10]. The actual prevalence of digital gangrene in MCTD remains unknown. Therefore, as new data is emerging from the developing world, it appears that the clinical characteristics and distribution of digital gangrene are different from western cohorts with MCTD and SLE being the commonly associated disorders rather than systemic sclerosis [10–12]. A cohort of lupus patients from India estimated the prevalence of digital gangrene in SLE as 5% [13] notably higher than previous data ranging from 0.6 to 1.2% suggesting that digital gangrene maybe commoner in South Asian region. Our prevalence of 7% among all connective tissue disorders (including rheumatoid arthritis) is similar to this.

Unlike previous case reports where gangrene was reported independent of disease flares, all 4 of our SLE patients had presented with signs of acute flare, with lupus nephritis and or acute cutaneous lupus suggesting that vasculitic activity might be the predominant mechanism in gangrene in these patients. Raynaud's phenomenon preceded digital gangrene

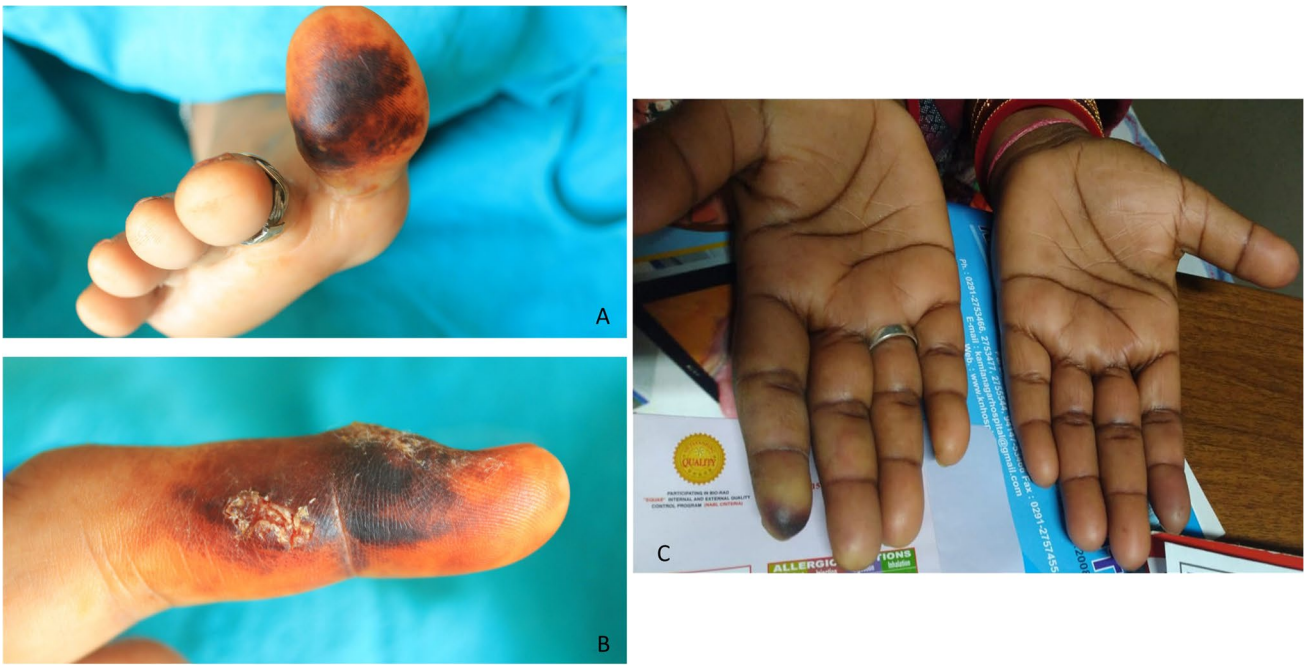

Fig. 2 **A** Digital gangrene over great toe in a patient with APS, **B** Digital gangrene with ulcer over index finger in a patient with MCTD, **C** MCTD with digital gangrene over right index finger, puffy fingers

in 15 of our patients, commonly in those diagnosed with MCTD ($n=6$) and systemic sclerosis ($n=3$).

Digital gangrene was the initial presenting symptom in 12 of our patients, 4 of whom were diagnosed with MCTD, 2 each with SLE and primary APS and one systemic sclerosis and ANCA vasculitis respectively. We wish to highlight the importance of screening and thorough evaluation of young patients who present with digital gangrene require any underlying for CTD for early initiation of immune suppression which can prevent limb and organ threatening complications. We encountered 3 patients whose diagnosis remained elusive after extensive investigations and were hence classified as "Undifferentiated CTD"; similar findings were reported by Ravi et al. in a case report [14].

Though no specific antibody profile has been previously implicated in digital gangrene, 40% of our patients had significant U1RNP titres since MCTD was the commonest underlying diagnosis. Additionally, we found that anti-Ro was also detected in 35% with differing underlying diagnosis of SLE ($n=3$), MCTD ($n=2$) and Systemic sclerosis ($n=2$). Whether Anti-Ro positivity predisposes to development of digital gangrene, its role in the disease pathogenesis or as a biomarker of association can serve as grounds for further research.

Fifty-five percent of patients with gangrene had an underlying pulmonary disease, the commonest being Interstitial lung disease. This was followed by musculoskeletal ($n=6$) and renal involvement ($n=3$). So far, no data exists regarding an increased predisposition to any organ involvement in patients with digital gangrene in CTD. We propose to preserve a low threshold to screen for pulmonary involvement in patients with CTD-associated digital gangrene.

Digital ulcers which are considered as a continuum with digital gangrene have been most widely studied in systemic sclerosis, with existing guidelines proposed by EULAR in 2016 for its management [15]. Based on a meta-analysis of 4 trials, intravenous iloprost has been found to be beneficial in healing digital ulcers; however, it had no role in their prevention [16]. On the contrary, PDE-5 inhibitors have been found to be effective in healing as well as preventing new digital ulcers while endothelin antagonists have been recommended only in those cases refractory to therapy [15, 16]. No clear guidelines exist for the use of immunosuppressive agents in CTD-associated digital gangrene till date.

Although the benefits for immunosuppression in digital gangrene is uncertain, most centres prefer to offer some immunomodulatory therapy in view of small vessel vasculitis as the underlying mechanism [1, 13]. All patients in our study series received steroids as first line therapy in the absence of contraindications. We wish to highlight that except for two patients in our study (RA-CREST overlap and Systemic sclerosis- MCTD overlap), none of our patients required additional immune-suppression for digital gangrene per se. However, 3 of our patients concurrently received immunosuppressive agents in the form of cyclophosphamide or mycophenolate mofetil for their systemic manifestations.

This was in stark contrast to all previous reports, wherein the protocol was to initiate cyclophosphamide along with steroids as first line agent [4, 11, 13]. Other agents of choice in previous reports included rituximab and IV prostanoids in refractory cases [1, 12]. Only one surgical intervention was required in our series (for MSSA abscess) while rates of surgical amputation were significantly higher in previous studies, like 44% in the lupus cohort [4].

We infer from our experience that corticosteroids may prove an effective first line agent in CTD associated with digital gangrene. Further immunosuppressive agents may be reserved for systemic and life-threatening manifestations of the underlying disease or progressive digital gangrene. As this study included a limited number of patients, there is an unmet need for randomized controlled trials exploring the role of immunosuppressive agents in CTD-associated digital gangrene to standardize the treatment protocols in such patients.

Conclusion

In conclusion, the most common underlying diagnosis for hose presenting with digital gangrene in CTDs in our settings is MCTD while age of presentation is older adults. This diverges from previous reports and hence clinicians need to be aware of this epidemiological aspect while managing CTD-associated gangrene. Also, in patients presenting with digital gangrene, an active search for an underlying vasculitis or connective tissue disorder is imperative as this could result in timely initiation of appropriate therapy and can prove limb saving. Corticosteroids alone with rapid tapering may be an option to consider in the management of digital gangrene in CTD, conserving further immune suppression for life-threatening systemic manifestations. Further follow-up and larger studies are required to confirm this observation. We suggest that all patients with CTD-associated gangrene need to be screened for systemic involvement early.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06265-1.

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Author contribution The study was conceived by MG. Data collection was done by NV, PV and MG. All authors were involved in patient care and management decisions. First draft was written by NV and revised by PV, MG and MKG. Technical inputs were provided by GKB and MKG. All authors read and approved the final manuscript.

Declarations

Disclosures None.

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Prior presentations A part of the work was presented as a poster by NV in the 35th annual conference of Indian Rheumatology Association (IRACON) in December 2019.