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Case Report

Digital gangrene without sclerodactyly in the presence of anticentromere antibodies: A unique presentation of scleroderma

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ABSTRACT

Peripheral vascular disorders associated with anti-centromere antibody (ACA) present generally with sclerodactyly in connective tissue disorders (CTD). It is unusual for ACA-associated digital necrosis to develop without preexisting raynaud's phenomena or vascular risk factors. We report a novel case of a 60-year-old non-smoker, non-diabetic woman with ACA and isolated finger necrosis without any other features of CTD. This case underscores the importance of considering an autoimmune contribution to the development of digital necrosis even without any identifiable CTD. It highlights the need to consider ACA-associated digital gangrene to be considered as a distinct entity of an autoimmune disorder from scleroderma.

1. Introduction

Digital gangrene results in the limitation of functional activity of the fingers and toes leading to morbidity which may further progress to long-term disability. It usually occurs as a complication of various connective tissue disorders (CTD) like systemic sclerosis (SSc), anti-phospholipid syndrome, and systemic lupus erythematosus [1]. Sometimes as in limited scleroderma and CREST syndrome, the presence of digital gangrene in association with Anti-centromere Antibody (ACA) is also observed in Raynaud's syndrome with sclerodactyly and in Sjogren Syndrome [2]. There is paucity of data regarding digital ischemia associated with ACA without associated sclerodactyly, Raynaud's phenomenon or any other CTD. This subset of disease may be regarded as a different entity from scleroderma which involve tightening of the skin and vascular problems, commonly occurring between ages of 30 years and 50 years. This type of autoimmune disorder is rarely reported particularly from India. This is a novel case report in a 60-year-old woman who presented with digital gangrene and was positive for ACA in the absence of any features of scleroderma. Interestingly, the case presented without any preexisting Raynaud's phenomena and in absence of common vascular risk factors with isolated one affected finger leading to acute digital necrosis.

2. Case report

A 60-year-old non-diabetic female, presented in the out-patient department of Dermatology with the chief complaints of discoloration and blackening of the distal middle finger of the right hand for 10 days. It was painless and there was no history suggestive of Raynaud's phenomenon, arthritis, coronary artery disease, any addiction or similar episodes in the past. Patient had history of controlled hypertension on medication. Patient did not have any other comorbidity.

On examination of the affected lesion, the distal part of right middle finger including skin and nails were found necrosed (Fig. 1(a and b)). No sclerodactyly and peripheral vascular disease was evident. The patient was normotensive, and all systemic examination were within normal limits. The blood glucose levels and hemogram was within normal limits. Other haematologic investigations revealed mild dyslipidaemia and subclinical hypothyroidism. The patient was tested negative for rheumatoid factor, and cryoglobulinemia. Chest radiograph was normal. The venous colour doppler study of the right upper limb was within normal limits.

Notably, anti-nuclear antibody (ANA) testing by indirect immunofluorescence assay (IFA) on transfected Hep 2 cells (Immuno Concept®, Sacramento, CA, USA) showed multiple even sized granules in the nucleus along with stained chromatin plates (Fig. 1(c). Nucleoli and nucleoplasm staining were spared. It was identified as centromeric pattern as per AC-3 of the International Consensus on ANA Pattern [3] at

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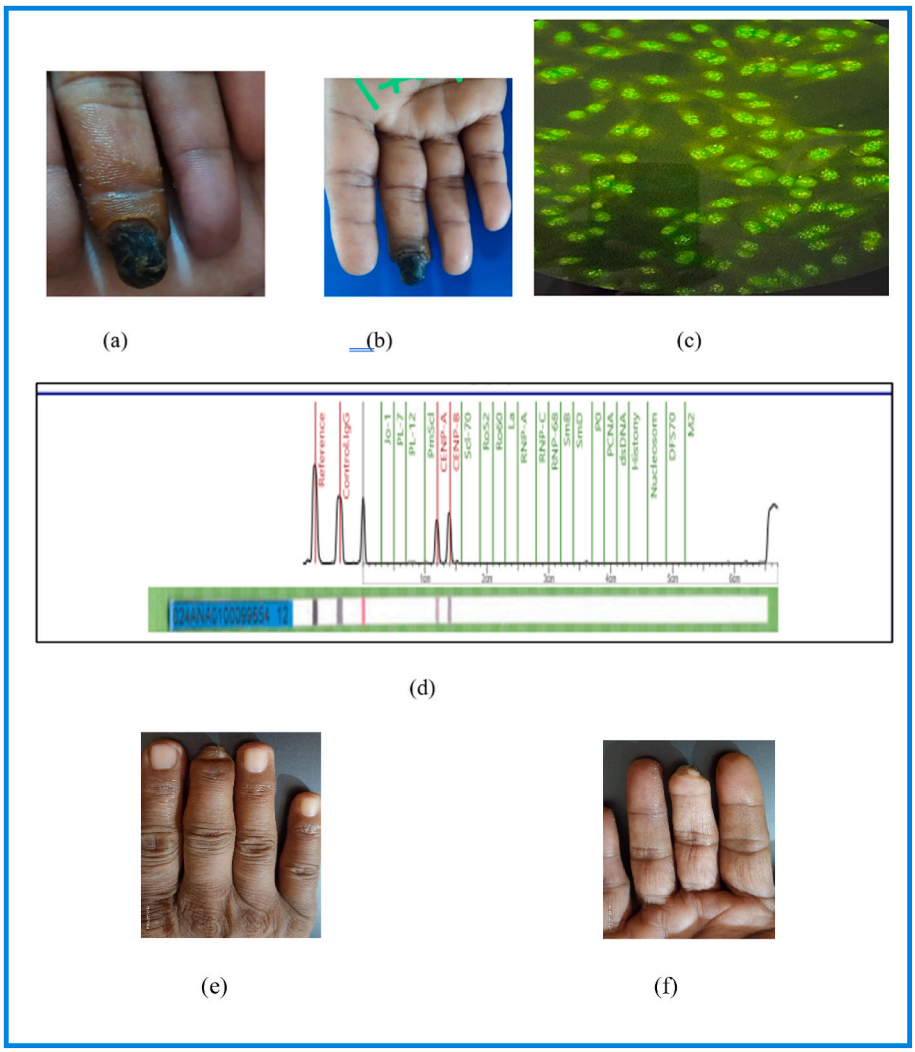

Fig. 1. (a) & (b): Photograph of the symptomatic finger having digital gangrene; (c) Anti centromeric antibody positive by Immunofluorescence assay; (d) CENP-A and CENP-B antigen bands in Line-Immune assay; (e) & (f) Photograph of the healed finger after follow up.

the screening titer of 1:80. The intensity of staining was comparable with that of positive control (+4). It was further tested in doubling dilutions with an end titre of 1:5120.

Further, Line-immunoassay (LIA) test (Test Line Clinical Diagnostics s.r.o, Brno, Czech Republic) for ANA was performed that showed intense lines at CENP A and CENP B (Fig. 1(d)) which was highly consistent with the centromeric pattern detected on ANA-IFA test. Antiphospholipid antibodies- Cardiolipin IgM & IgG, Beta-2 Glycoprotein IgM and IgG and Antineutrophilic cytoplasmic antibody (ANCA) by ELISA were found to be negative.

A working diagnosis of Raynaud's disease was made, and the patient was initiated on thyroxine, statins, mupirocin ointment, aspirin and sildenafil. The patient was referred to the rheumatology department for further workup. A battery of test conducted to exclude other causes of ACA association. Barium swallow studies showed normal oesophagus function. There was no evidence of calcinosis or dilated blood vessels on skin further excluding CREST syndrome. CT pulmonary angiogram and 2D ECHO excluded thromboembolism but suggested moderate pulmonary artery hypertension which is usually found in ACA positive cases. Final diagnosis of secondary Raynaud's disease due to autoimmune disorder was contemplated. The previous medications were supplemented with additional drugs, namely, telmisartan and nifedipine to address underlying hypertension and to improve the vascularity of the affected digit.

Gradually over the next six months follow up, the distal phalanx of the affected finger necrosed and fell off (Fig. 1(e and f)). However, no other finger or toe was affected in the course of follow up.

3. Discussion

Digital ischemia is one of the most common presentations of CTDs in young and middle-aged females. Other common causes apart from CTDs include chronic disorders like atherosclerosis, diabetes and vasculitis. Additionally, infectious conditions such as infective endocarditis and HIV may also present with digital necrosis in a few patients. The literature reports the association of ACA with peripheral vasculopathy and digital necrosis in patients diagnosed with systemic sclerosis (SSc) [4]. It is a novel finding in ACA positive patients without accompanying sclerodactyly to develop digital necrosis.

ACA is not only known to be the marker of vascular endothelial injury but it may also have a role in direct pathogenesis of it [5]. In a study, human endothelial cells exposed to sera containing ACA, were observed to have increased apoptosis and altered gene expression. This exposure enhanced the expression of genes associated with apoptosis and fibrosis progression, reducing gene expression that promotes angiogenesis [6].

ACA are autoantibodies to the proteins present on to a distinct chromosomal domain called centromere that usually reacts to its

Table 1
Summary of cases reported with ACA reactivity associated digital necrosis without sclerodactyly.

Report	Age (years) and sex	Pre-existing Raynaud's	Raynaud's duration	Region affected	Cutaneous evidence of scleroderma	Systemic Involvement	Co-morbidities	Smoker
Takahashi et al [5]	60 F	+	3 months	Fingers, toes	No	No	No	No
	74 F	+	54 years	Fingers	No	No	No	
	79 F	+	30 years	Toes	No	No	CVA	
Sachsenberg-Studer et al [10]	43 F	+	2 years	Fingers	No	No	None	Yes
	73 F	+	12 years	Fingers, toes	No	No	HTN	Never
	84 F	+	Unknown	Fingers, toe	No	No	HTN	Never
	86 F	+	Unknown		No	No	None	Never
Barr et al [11]	67 M	Possible	NR	Fingers	No	No	CAD, CAGB	No
Picillo et al [12]	34 F	+	12 years	Fingers, toe	No	No	None	Yes
Brown et al [13]	87 F	–	–	Fingers	No	No	CHF, HTN	Never
El Mahou et al [14]	72 M	+	NR	Fingers, toes	No	No	SCC	Ex-smoker
Bolster et al [15]	53 F	–	–	Finger	No	No	WPW, CABG	Never
Grace et al [16]	75 F	–	–	Finger	No	No	None	Never
Present Study	60 F	–	–	Finger	No	No	No	Never

CABG, coronary artery bypass graft; CAD, coronary artery disease; CVA, cerebrovascular accident; HTN, hypertension; NR, not reported; SCC: small cell lung cancer; WPW: Wolff Parkinson White syndrome.

kinetochore component. The number of dots in centromere pattern is similar to our total number of chromosomes which is forty-six. Most sera with ACA recognize three major centromere proteins (CENPs-A, -B and -C) with a recently recognized, CENP-E as an antigenic target in SSc [7]. However, in the present patient, only CENP-A and -B were recognizable. This could be due to limitation that the LIA performed for this patient could identify only these two types of CENP antigens. Hence, we could not exclude the possible association of CENP-C in this case.

Thrombotic vascular diseases are reported to have a high titre of ACA. The association between ACA and Raynaud's phenomenon has been well-established in prior studies [8]. In these patients, presence of ACA suggests an increased risk of rheumatic diseases. The present case is a typical situation where a ACA positive patient develops digital necrosis without scleroderma in absence of other commonly associated risk factors [9] like male sex, SSc, presence of anti-topoisomerase I antibodies, smoking, malignancy or previous thermal injury. Sachsenberg-Studer et al., have proposed the name RACAND syndrome for the triad of Raynaud's phenomenon, positive anticentromere antibodies and digital necrosis without sclerodactyly and sclerosis of internal organ considering it as a distinct entity from scleroderma with sclerosis [10]. Similar cases have been reported in past (Table 1) but none from India [5,10–16]. Some of these have shown Raynaud's phenomenon and/or associated comorbidities. To the best of our knowledge, this is the first case to be reported from India.

Here, the elderly patient developed gangrene of finger without other commonly associated risk factors or comorbidities and only ACA positivity which indicate the role of autoimmunity in the pathogenesis of such diseases without any recognizable sign and symptoms of CTD. Further, this could be regarded as a distinct entity of an autoimmune disorder than the scleroderma or any CTD presenting with ACA associated digital gangrene only.

CRediT authorship contribution statement

Urvashi Suman: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Lata Sheoran:** Writing – review & editing, Writing – original draft, Data curation. **Vikas Manchanda:** Writing – review & editing, Supervision, Resources. **Sonal Saxena:** Writing – review & editing, Supervision, Resources.

Patient consent

Written informed consent from the patient was taken before preparation of this manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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