Case Report

Dermatology

Dermatology 2013;227:226–230
DOI: 10.1159/000353926

Received: April 29, 2013
Accepted after revision: June 25, 2013
Published online: October 1, 2013

Cutaneous Reactive Angiomatosis with Combined Histological Pattern Mimicking a Cellulitis

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Key Words
Cutaneous reactive angiomatosis · Reactive angioendotheliomatosis · Diffuse dermal angiomatosis · Intralymphatic histiocytosis

Abstract
Cutaneous reactive angiomatoses (CRA) encompass a distinct group of rare benign reactive vascular proliferations that include reactive angioendotheliomatosis, diffuse dermal angiomatosis and reactive intralymphatic histiocytosis. The etiology of these conditions, often associated with either localized or systemic diseases, is poorly understood. We report a 72-year-old woman who presented giant diffuse cellulitis-like plaques on the right lower limb and the pelvis and a reduction of her general condition with fever. Light microscopy studies revealed combined features of reactive angioendotheliomatosis, diffuse dermal angiomatosis and reactive intralymphatic histiocytosis. A small arteriovenous fistula of the right lower leg was thought to act as trigger. Systemic corticosteroids resulted in the clinical remission of the skin lesions. Our observation provides strong evidence that reactive angioendotheliomatosis, diffuse dermal angiomatosis and reactive intralymphatic histiocytosis, previously regarded as distinct forms of CRA, may show overlapping histopathological features and most likely represent facets of the same disease.

Introduction

The term 'cutaneous reactive angiomatosis' (CRA) is used to describe a rare cutaneous reaction characterized by a benign reactive vascular proliferation [1]. At least 6 forms of CRA with different histopathological patterns have been described (table 1). Histologically, they are associated with a proliferation of endothelial cells, either with intravascular or extravascular, lobular or diffuse distribution, together with pericytes or histiocytes. The best-known forms are reactive angioendotheliomatosis and acroangiodermatitis of Mali (pseudo-Kaposi sarcoma). Reactive angioendotheliomatosis as well as its variant called glomeruloid reactive angioendotheliomatosis [2] are characterized by a proliferation of endothelial cells within vascular lumina resulting in the obliteration of the involved vessels. The glomerular aspect of glomeruloid reactive angioendotheliomatosis can be morphologically similar to a glomeruloid hemangioma of the POEMS syndrome, but the latter is considered a different entity [1]. Diffuse dermal angiomatosis is associated with a diffuse proliferation of endothelial cells that are arranged interstitially between collagen bundles of the reticular dermis [3]. Acroangiodermatitis, also known as pseudo-Kaposi sarcoma, includes 2 variants: the Mali type associated with venous hypertension, and the Stewart-Bluefarb type associated with either an arteriovenous malformation or an acquired iatrogenic arteriovenous fistula in patients with chronic renal dysfunction [4]. In the so-called reactive intralymphatic histiocytosis (IH) there is an intraluminal accumulation of cells carrying the histiocytic marker CD68 [5]. Finally, angiopericytomatosis (angiomatosis with cryoprotein) shows periluminal pericytes immunohistochemically positive for smooth muscle actin [6].

Although different histopathological patterns of CRA are well recognized, the clinical presentation of CRA is frequently the same and is associated with multiple erythematopurpuric flat plaques, sometimes evolving in a necrosis and ulceration with propensity to involve the limbs [7, 8]. The cutaneous signs often appear together with fever and shivering. Hence, the overall clinical picture may closely mimic an infectious cellulitis [9].

Case Report

A 72-year-old woman was admitted for evaluation of sudden fever and chills, with simultaneous appearance of giant cellulitis-like erythematous plaques on the right lower leg with following rapid spread to the pelvis and left upper leg. Her history disclosed that she had vulvar and vaginal extramammary Paget's disease that was treated with vulvec-

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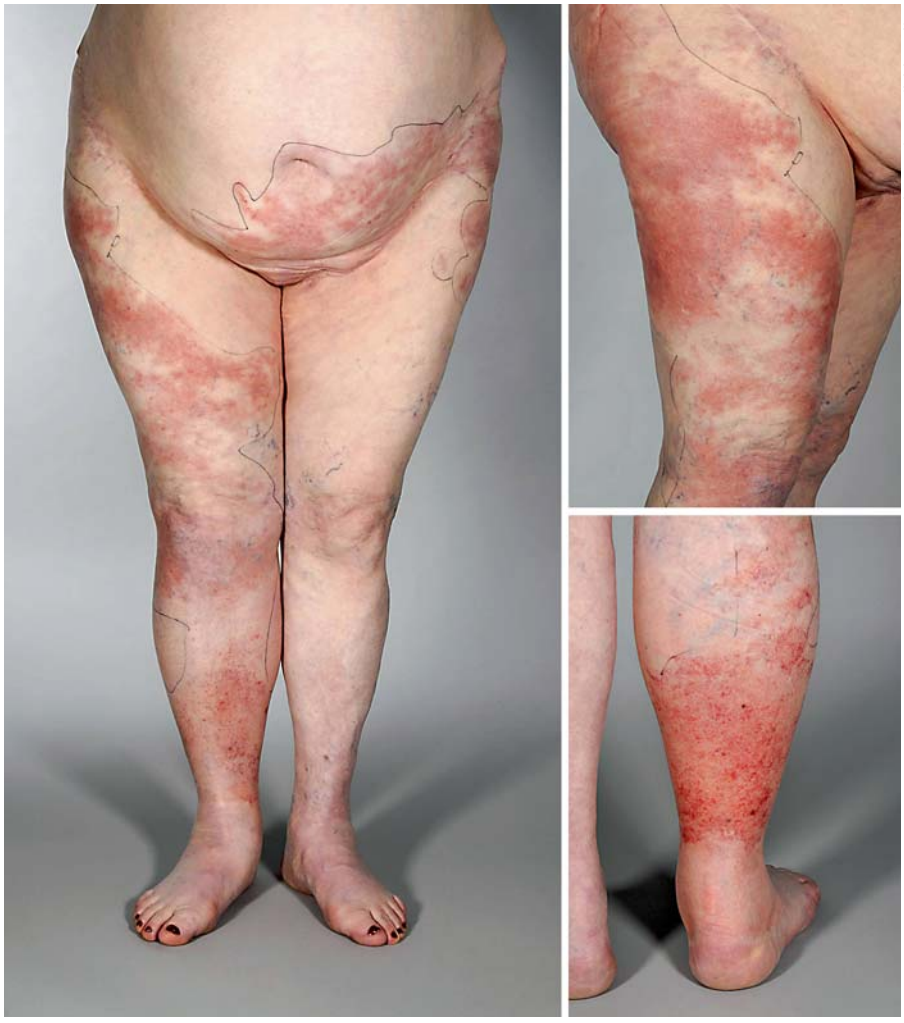

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Fig. 1. Infiltrated flat skin lesions with erythematoviolaceous hue and purpuric appearance involving the right leg, the pelvis and partially the left leg.

tomy and radiotherapy from 1992 to 2002; furthermore, she was anticoagulated with phenprocoumon because of a tachycardic atrial fibrillation. On admission, she was in a reduced health condition. The right leg was edematous with red-violet, palpable and confluent lesions expanding to the pelvic region and partially to the left leg (fig. 1). Laboratory examination revealed leukocytosis of 17×10^9/l (normal: $4–10 \times 10^9$/l), high C-reactive protein (338 mg/l; normal: <5 mg/l) and a blood sedimentation rate of 64 mm/h. The liver and renal tests were normal.

Clinical features were suggestive of a bacterial cellulitis and the patient was first treated with intravenous piperacillin, tazobactam and clindamycin, and subsequently orally with co-amoxicillin for a total of 14 days. Although the patient became afebrile, no amelioration of the cutaneous symptoms was observed.

Repeated clinical evaluations, urinalysis, chest radiology, MRI of the pelvis and the legs as well as abdominal sonography showed no clear focus of infection or evidence for a Fournier gangrene or a necrotizing fasciitis.

Light microscopy studies of a biopsy specimen obtained from the right leg disclosed deep dermal vessels surrounded by an inflammation and clogged up with cells characterized by an eosinophilic large cytoplasm (fig. 2). Immunohistochemically, these cells were positive for CD31 and CD68 with partially extravascular and interstitial arrangement (fig. 3); D2-40 was negative. These features were concomitantly consistent with the diagnoses of reactive angioendotheliomatosis, its diffuse form diffuse dermal angiomatosis as well as with IH.

The MRI showed a small arteriovenous fistula of the right lower leg as the possible disease causing CRA. No other coexisting CRA-associated systemic disease with thrombotic or occlusive vascular tendency was found (table 1). The pelvic surgery with radiation, performed 8 years before, cannot be excluded as a causal disease, but the long refractory period and the beginning of the symptoms far away from the pelvic region are not confirming arguments. No infectious trigger was found in the very extensive internistic analyses, which included heart echography.

Clinical and histological features with periodic acid-Schiff and Gram stains, the absence of cytological atypia as well as the clinical evolution permitted to reasonably exclude the possibility of a bacterial cutaneous infection, a neutrophilic dermatosis, a benign or malignant vascular tumor, a Masson's hyperplasia or an intravascular lymphoma. There were no signs of a re-

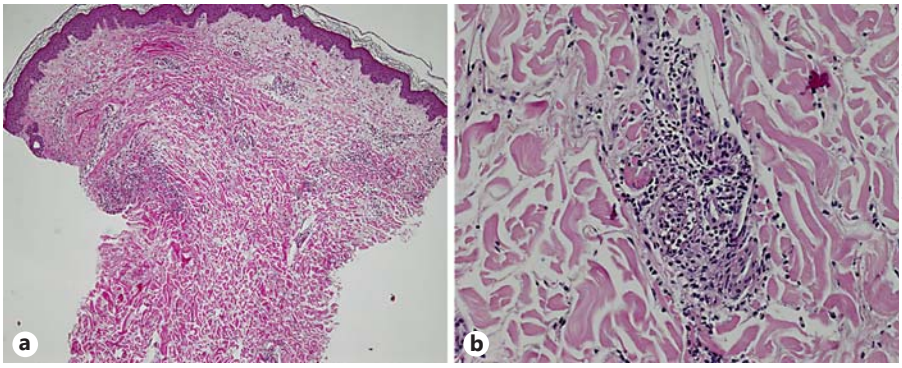

Fig. 2. a Biopsy specimen of the right leg showing a superficial and deep perivascular and interstitial dermatitis. HE. ×100. **b** Accumulation of several cytoplasm-rich cells inside the lumina of dermal vessels. The cell proliferation also expands around the vessels in a diffuse interstitial pattern. No cellular atypia. HE. ×400.

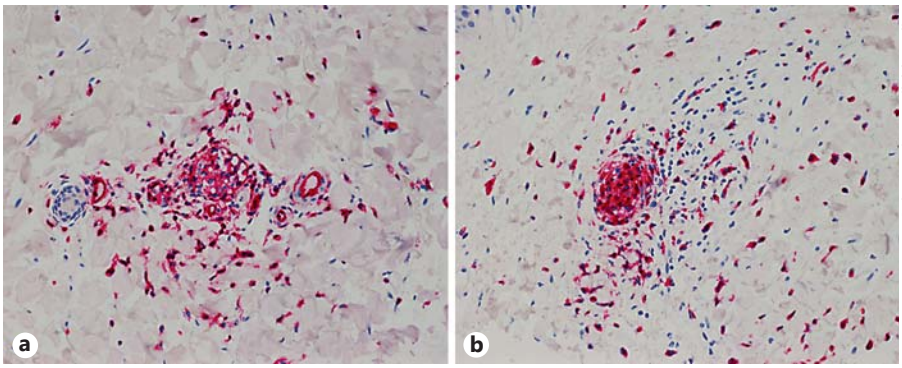

Fig. 3. Immunohistochemistry of the biopsy specimen consistent with an endothelial (CD31+, **a**) and histiocytic (CD68+, **b**) proliferation of cells inside and outside dermal vessels. ×400.

Table 1. Features and characteristics of the 6 forms of CRA [1]

Characteristics	RAE	DDA	AAD	IH	GAE	AP
Clinical presentation	Violaceous or erythematous papules and plaques, localized or extensive, occasionally ulcerated and necrotic	As RAE	As RAE (usually on the distal legs)	As RAE	As RAE	As RAE
Histological features	Endoluminal proliferation	Interstitial clusters in the dermis	Periluminal lobular proliferation with thick-walled vessels in the papillary dermis	Intraluminal proliferation (± occlusion)	Intraluminal glomerulus-like tufts of capillaries	Periluminal proliferation (± thrombi)
Proliferating cells	Endothelial (± pericytes)	Endothelial	Endothelial (± pericytes)	Histiocytes	Endothelial	Pericytes
Immunohistochemistry	CD31+ CD34+ Other endothelial markers + (± α-actin)	CD31+ CD34+ Other endothelial markers +	CD31+ CD34+ Other endothelial markers + (± α-actin)	CD68+	CD31+ CD34+ Other endothelial markers + (± α-actin)	α-Actin + (± CD31, CD34, other endothelial markers, CD68)
Characteristics and clinical context	Associated with bacterial endocarditis, cholesterol emboli, arteriovenous shunt, antiphospholipid syndrome, renal disease, RA, leukocytoclastic vasculitis, monoclonal gammopathy, hepatitis	Described as the diffuse variant of RAE Associated with arteriosclerosis, arteriovenous shunt	Associated with chronic venous insufficiency (Mali type) or arteriovenous malformation (Stewart-Bluefarb type)	Associated with RA, monoclonal gammopathy, chronic infections	Described as the glomeruloid variant of RAE Associated with cold agglutinins, lymphoma	Associated with cryoglobulinemia, myeloma

RAE = Reactive angioendotheliomatosis; DDA = diffuse dermal angiomatosis; AAD = acroangiodermatitis (pseudo-Kaposi sarcoma); IH = intravascular histiocytosis; GAE = glomeruloid angioendotheliomatosis; AP = angiopericytomatosis (angiomatosis with cryoproteins); RA = rheumatoid arthritis.

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Table 2. Previously described CRA cases with combined histological patterns [8, 11–13]

Publication	CRA forms	Location	Associated diseases	Therapy
Rieger et al. [12]	RAE and IH	Face, left elbow	RF+, monoclonal IgG	Cyclophosphamide
Rieger et al. [12]	RAE, IH and GAE	Elbows	RA, breast cancer	Triamcinolone, clobetasol propionate
McMenamin and Fletcher [8]	DDA and AAD	Lower legs, feet, arms	Polyarteritis nodosa, hemodialysis	Systemic steroids
Mensing et al. [13]	RAE and IH	Face, back, extremities	RF+, peripheral artery occlusive disease	Acetylsalicylic acid
Our case	RAE, DDA and IH	Legs, pelvis	Arteriovenous fistula	Prednisolone, clobetasol propionate

RF = Rheumatoid factor; for all other abbreviations, see table 1.

lapse of Paget's disease clinically, histologically and in the performed gynecological controls at the time of the examination and in the following 2 years.

The patient was subsequently administered prednisolone 0.5 mg/kg body weight per day with subsequent tapering for a total of 3 weeks together with topical clobetasol propionate and compression bandage and lymphatic drainage. The clinical course was favorable with reduction of the extension and the redness of the lesions, which disappeared few months thereafter. For the suspected small arteriovenous fistula of the right leg, no further management was initiated because of its hemodynamic irrelevance and its tendency to spontaneously disappear.

Discussion

The etiology and the pathomechanism of CRA remain poorly understood. CRA has often been described in association with many different systemic or local diseases such as rheumatoid arthritis, bacterial endocarditis, cryoproteinemia, lymphoproliferative disorders, peripheral atherosclerosis, or an arteriovenous shunt [10, 11] (table 1).

The common characteristic among these diseases is the tendency to develop either a vasculopathic occlusive process or an inflammatory vascular reaction that generates a localized hypoxic stimulus causing the endothelial neovascularization [1]. This could explain the supposed pathogenesis of different CRA forms as a continuum of the same regeneration mechanism after an occlusive or inflammatory vascular process [1, 12].

The neovascularization process in the organization of microthrombi involves different stages [12]. Each stage may reflect a different form of CRA [1, 12], which in the early stages is characterized by an intravascular proliferation of histiocytes and in the late stages by an endothelial and pericytic cell proliferation. The spectrum of lesions, seen mainly histologically, is dependent on the time of the biopsy and on the severity of the underlying pathological condition. Some recent cases, including ours, confirm this hypothesis by showing different simultaneous patterns of CRA [8, 13, 14] (table 2).

The clinical presentation of CRA is characterized by erythematopurpuric flat plaques and often appears together with fever and shivering. Therefore, the clinical picture may closely mimic an infectious cellulitis [9] and the inflammatory condition could be mistaken for an infection as in our case. Although some infections have been associated with CRA (mostly bacterial endocarditis with peripheral bacterial embolism as cause of the hypoxic stimulus [1]), others were rarely discussed as direct causal diseases. After observation of IH in a patient with exacerbated chronic tonsillitis [15], it was speculated that chronic bacterial infections may cause vascular damage and at the same time activation of histiocytic-monocytic cells through the excessive innate immune reaction. A periodontitis-induced leukocytoclastic vasculitis [16] and hepatitis with increasing hypercoagulability by cirrhosis and chronic liver diseases [1] were described in the past as indirect infection causes of CRA.

Management of CRA includes an accurate exclusion of the possible associated systemic diseases (table 1). Treatment of the underlying disease should automatically improve the associated CRA. No specific treatment for CRA is available. Furthermore, systemic steroids have been used successfully, as in our case, based on their inhibitory effect on neoangiogenesis [1]. Local compression may also be helpful in IH, as described [12]. Cessation of smoking led to a substantial improvement in patients presenting with diffuse dermal angiomatosis of the breast [17]. Finally, self-improvement and resolution of CRA are also possible [1].

In conclusion, our observation reminds the clinicians that in case of acute cellulitis-like plaques unresponsive to antibiotic therapy, the diagnosis of CRA should be considered. Its diagnosis is based on histopathological analyses supported by immunohistochemical studies with endothelial, histiocytic and pericytic markers. The observation of combined and mixed histological findings in our case provide further support to the idea that the different forms of CRA represent different facets of the same spectrum of reactive vascular lesions in relation with recanalization and/or neoangiogenesis of dermal vessels.

Disclosure Statement

The authors declare no conflict of interest and no financial support.

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