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The "red face": Not always rosacea

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Abstract Facial erythema (the "red face") is a straightforward clinical finding, and it is evident even to the untrained eye; however, a red face does not represent a single cutaneous entity. It may be due to a plethora of distinct underlying conditions of varying severity, including rosacea, demodicosis, dermatomyositis, lupus erythematosus, allergic contact dermatitis, drug-induced erythema, and emotional blushing. In clinical practice, dermatologists do not encounter only one type of facial erythema but rather a number of different shades of red. This review presents the clinical spectrum of facial erythemas and addresses the question of what lies beneath a red face by discussing the key clinical and histopathologic characteristics.

Introduction

Redness of the face is one of the most easily recognizable clinical signs in dermatologic patients; however, the corresponding diagnosis and etiology are not always so straightforward. A red face may be due to transient erythema (flushing), persistent erythema, or perilesional erythema, in the context of various cutaneous or systemic diseases including rosacea, demodicosis, contact dermatitis, polymorphous light eruption, acne, drug-induced (cortisone, brimonidine) erythema, lupus erythematosus, or mastocytosis.[1] Apart from the different etiology, the multiple types of facial erythemas may be associated with distinct histopathologic features that may assist in making the diagnosis. The red face is readily visible, although the underlying condition may remain hidden even to the trained eye. This review discusses the key clinical and histopathologic characteristics as a guide for diagnosing the "red face."

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Rosacea

Rosacea is a chronic inflammatory skin disease affecting the central face and a common diagnosis for facial erythema (Figure 1). Guidelines for the diagnosis of rosacea indicate the presence of one or more associated primary features, including flushing (transient erythema), nontransient erythema, papules, pustules, and telangiectasia, that may be typically associated with stinging, burning, and sensitive skin.[2,3] Facial erythema is extremely common in rosacea; it may be present in all subtypes of rosacea, and it affects up to 87% of patients with rosacea.[4] The condition may be without inflammatory lesions, and it may even be persistent.[5] Flushing may be precipitated by sun exposure, hot and humid atmosphere, stress, strenuous exercise (increased body temperature), alcohol, hot beverages/meals, or spicy foods. The antimicrobial peptides, neuropeptides, and transient receptor potential ion channels have been implicated in the induction of erythema and vasodilation in rosacea.[6] The transient receptor potential family of receptors are a group of nonselective cation channels activated by rosacea trigger factors as part of acute neurogenic inflammation.[6]

A medical history may reveal associated precipitating or exacerbating factors that should be avoided.[7] Also, because

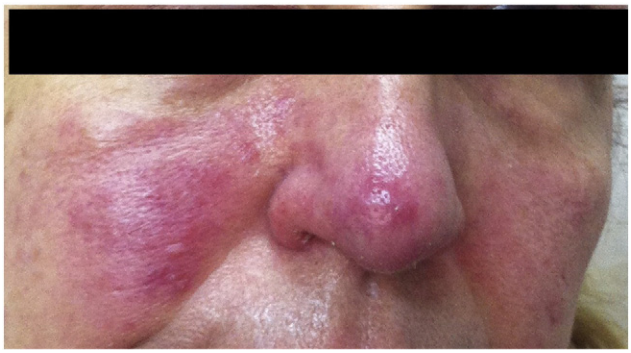

Fig. 1 Rosacea presenting with facial erythema and papules on the nose and cheeks.

rosacea is often associated with underdiagnosed ocular symptoms, asking the patients about foreign body sensation, photophobia (light sensitivity), blepharitis, and chalazia may point to a diagnosis of rosacea.[8,9] Of note, patients are unaware of connections between ocular symptoms and their skin rosacea and often may cite other factors perceived as the cause of their eye discomfort (allergies, contact lens irritation).[10] A referral to an ophthalmologist for slit-lamp examination may be helpful for patients with ocular symptoms.[9]

The diagnosis of rosacea is clinical, with biopsy only needed when other suspected diseases are to be excluded. Histologic features of rosacea include the presence of *Demodex* mites within the follicular infundibulum and nonspecific features, such as enlarged, dilated capillaries and venules of bizarre shapes in the upper portion of the dermis, a perifollicular[11] and perivascular lymphocytic infiltrate, edema of the superficial part of the dermis, and increased dermal mast cells.[12] The main diagnostic sign to differentiate rosacea from acne is the absence of comedones and dermal infundibular cysts.[12]

Diseases with facial erythema: Not always rosacea

A red face may be due to flushing or blushing, persistent erythema, or perilesional erythema (around papules and pustules). Flushing is defined as a transient erythema in the blush areas of the face, neck, and upper part of the chest, accompanied with a sensation of warmth. The most common reasons for flushing are fever, hyperthermia, menopause, and rosacea.[13] Blushing is a distinct type of transient erythema of a lighter pinkish hue that is not confined to the central face but extends to the peripheral cheeks and behind the cheeks in an homogeneous fashion. Blushing is attributed to stress or emotional events due to sympathetic activation.[6] Uncommon causes of flushing include the carcinoid syndrome, mastocytosis, and such tumors as medullary carcinoma of the thyroid and pancreatic islet-cell tumors.[9] Persistent erythema is defined as facial erythema that lasts for at least 3 months.[14] Facial erythema may present in the context of various cutaneous or systemic diseases apart from rosacea, as shown in Table 1.

Demodicosis involves the pilosebaceous units associated with the human *Demodex* mites (*Demodex folliculorum* and *D brevis*).[15] These normally saprophytic *Demodex* mites may lead to demodicosis, after changing into a pathogenic form, due to increasing density of the mite, immune system disorders, HIV infection, and corticosteroid use.[16] Demodicosis may present as pityriasis folliculorum or rosacea-like lesions, as well as perioral dermatitis-like lesions.[17] Pityriasis folliculorum presents with facial erythema with follicular plugs, scaling, and sandpaper-like appearance. There are thin whitish follicular scales located on the face, eyelids, ears, neck, and scalp. Histologically, there is perivascular and dense dermal infiltration of lymphocytes without granuloma formation.[18] Rosacea-like demodicosis presents with follicular scaling and follicular papular, inflammatory, granulomatous, and pruriginous lesions on the face (Figure 2). Biopsy results

Table 1 Diseases associated with the "red face"

Flushing (transient erythema)	Persistent facial erythema	Perilesional facial erythema
Rosacea	Rosacea	Rosacea
Common benign causes	Cutaneous diseases	Acne
Emotional blushing	*Demodicosis*	
Menopause	*Contact dermatitis*	
Hyperthermia	*Tinea*	
Fever	*Seborrheic dermatitis*	
Spicy foods	*PLE*	
Alcohol		
Systemic diseases	Systemic diseases	
Mastocytosis	*Dermatomyositis*	
Carcinoid syndrome	*Systemic lupus erythematosus*	
Tumors	Drug-induced	
Medullary carcinoma of the thyroid	*Cortisone*	
Pancreatic islet-cell tumors	*Brimonidine*	

PLE, polymorphous light eruption.

Table 2 Key features for the differential diagnosis of facial erythemas

Condition	Key differential features
Acne	Usually affects teenagers
	Presence of comedones
Demodex dermatitis (demodicosis)	Fine scaling
	>5 *Demodex* mites/cm^2 in microscopy
Seborrheic dermatitis	Appears during late puberty
	Affects also scalp, eyebrows
	May coexist with rosacea
Cortisone face	History of application of corticosteroids
Cutaneous lupus erythematosus	Affects the periphery of the face
	Possible extrafacial lesions
	Histology
	Immunofluorescence
Systemic lupus erythematosus	Butterfly facial erythema
	Other clinical manifestations: arthritis, nephritis
	Anti-ds DNA positive
PLE	Eruption on sun-exposed areas
	Onset several hours after sun exposure
	Typically occurs in spring and early summer

PLE, polymorphous light eruption.

indicate a perifollicular infiltrate of mononuclear cells, with possible granulomatous inflammation. There is a high *Demodex* density (>5 mites/cm^2) found with the standardized skin surface biopsy technique (Table 2).[17,19]

Contact dermatitis of the face may be a well-recognized entity in typical cases, but there are patients presenting with erythema of the face and no obvious use of an exogenous topically applied agent. Contact dermatitis includes irritant contact dermatitis, allergic contact dermatitis, phototoxic contact dermatitis, and photoallergic contact dermatitis.[13] Facial skin care products and improper cosmetics can be a cause of such a reaction in rare cases.[13] The use of soaps with alkaline pH of 9 to 10 for cleansing may be worsen a red face. Also, basic moisturizers are indicated for the red face, without any antiaging low-grade ingredients such as lactic acid, retinol, or glycolic acid.[13] A detailed patient history regarding the recent onset of application of a topical formulation or contact with a possible precipitating factor (eg, a helmet) will guide the correct diagnosis (Figure 3). Diagnosis may be further established with patch testing and phototesting.

Tinea faciei presents with an erythematosquamous plaque with an elevated border and central clearance, but atypical presentation with a diffuse facial distribution may also occur. A full-body examination to identify the extension of the erythema with the characteristic elevated border may reveal additional areas of dermatophytosis (Figure 4). KOH scrapings and fungal cultures may confirm the diagnosis.[20]

Seborrheic dermatitis (SD) is a common, chronic, relapsing skin disease affecting the seborrheic areas of the body, including the scalp, face, and upper trunk (chest/presternal region).[21] The exact pathogenesis of SD is not clear. It has been proposed that SD is a primary inflammatory skin disease, an exaggerated response to *Malassezia* yeasts, or a form of eczema. SD affects individuals of younger age than patients with rosacea; SD occurs most commonly in infants within the first 3 months of life, adolescents, and young adults, with the incidence increasing again in patients older than 50 years.[21] SD is more common in men and boys, whereas rosa-

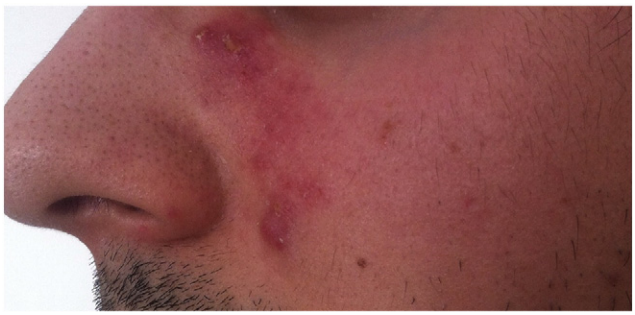

Fig. 2 Demodicosis. Solitary erythematous plaque with papules and scaling on the left cheek.

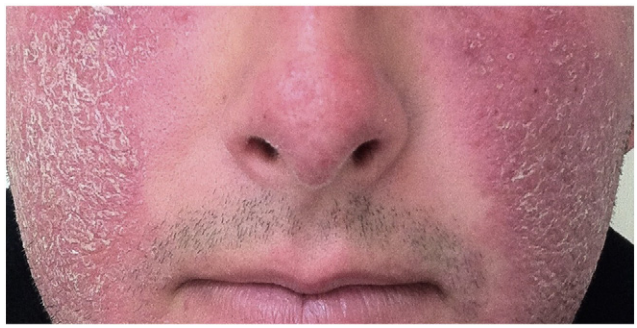

Fig. 3 Helmet contact dermatitis presenting with erythema, scaling, and oozing on the sites of contact with a newly purchased motorcycle helmet.

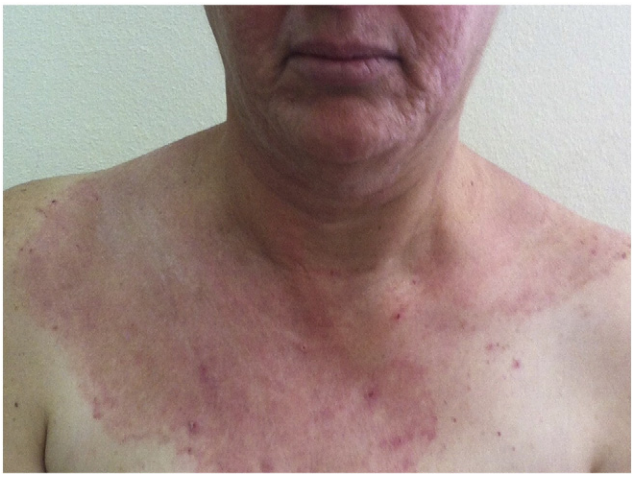

Fig. 4 Tinea faciei presenting with diffuse erythema of the face. Note the extending erythema on the upper trunk with a characteristic elevated border.

cea is more common in girls and women, and SD tends to improve during summer (with sun exposure), whereas rosacea does not (Table 2). Clinically, SD presents with erythematosquamous plaques with a predilection for the nasolabial folds and eyebrows, and it is advisable to also check the scalp, behind the ears, and on the chest of the patient, because these are areas commonly affected by SD and not by rosacea.[21]

Polymorphous light eruption is a common photodermatosis presenting with monomorphous lesions such as papular or papulovesicular lesions or urticarial plaques with pruritus (Figure 5A, B). Characteristic features include localization of the eruption on sun-exposed areas, onset several hours after sun exposure, and typical occurrence in spring and early summer. Skin biopsy is indicated to rule out cutaneous lupus, and phototesting and a negative immunofluorescence result contribute to the diagnosis of polymorphous light eruption (Table 2).[14]

Acne may present with facial redness, mostly due to perilesional erythema around the inflammatory papules and pustules (Figure 6). Acne affects usually patients of younger age than rosacea; it may be associated with residual scarring, and acne patients do not report stinging or burning of the skin. A cardinal differential diagnosis point is the presence of comedones in acne.[19]

Ulerythema ophryogenes is a rare benign cutaneous disorder characterized by erythema and follicular hyperkeratosis on the cheeks and lateral eyebrows, together with progressive atrophy and loss of eyebrows (Figure 7). Symptoms appear during early childhood.[22]

Dermatomyositis is a systemic autoimmune disease characterized by periocular violaceous erythema (heliotrope rash), edema, and facial erythema. The "shawl sign" with poikiloderma (erythema, hypopigmentation, hyperpigmentation, and telangiectasias) on the upper back is characteristic (Figure 8A, B). There may be erythematous papules on the dorsal hands with sparing of the interdigital web spaces, photosensitivity, and localization of skin lesions on photoexposed areas. Histopathologic findings, autoantibodies, electromyography, and the presence of other systemic manifestations guide diagnosis.[14]

Cutaneous lupus erythematosus may present with erythematous lesions on the face. Histopathologic findings, immunofluorescence, and antinuclear antibodies aid diagnosis; however, a subset of patients with rosacea may also have positive antinuclear antibodies (Table 2).[23] Significantly higher prevalence of *Demodex* mites have been reported in rosacea (51%, 55%) compared with eczematous dermatitis (28%) and cutaneous lupus erythematosus (3%, 31%).[11,24] A study of 27 patients with rosacea compared with 30 patients with facial cutaneous lupus erythematosus reported a lower mean CD4-to-CD8 ratio with immunohistochemistry in lupus.[11] Follicular plugging and abundant mucin deposition were also significantly associated with lupus.[11]

Systemic lupus erythematosus may present with malar butterfly erythema on the malar areas of the face. Diagnosis

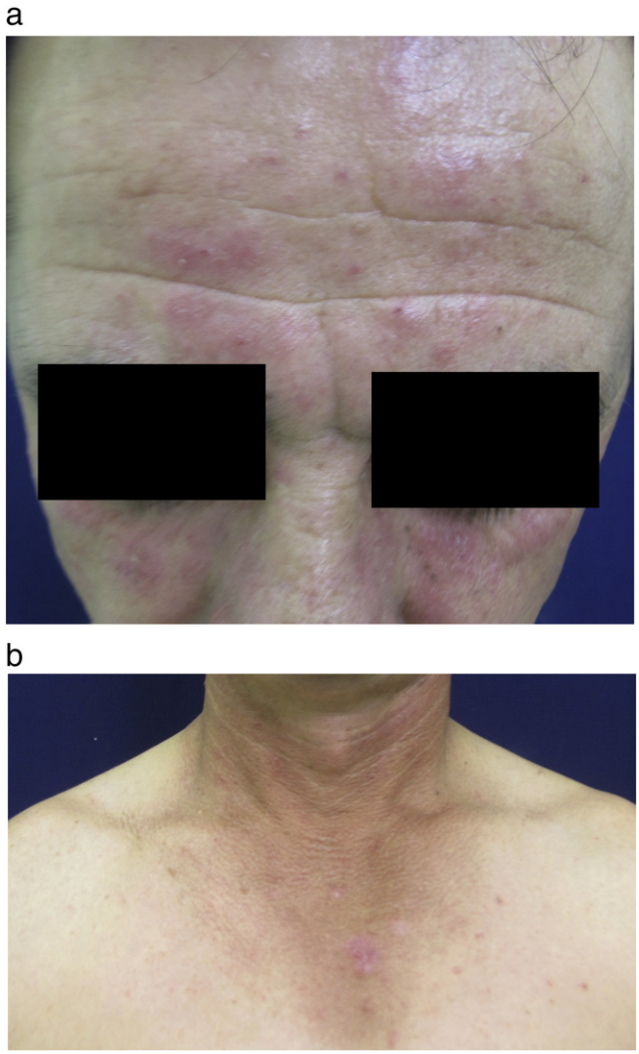

Fig. 5 Polymorphous light eruption. A, Erythematous papules in the face after first sun exposure of the season. B, Associated pruritic papules and erythema on the "V" area of the neck in the same patient.

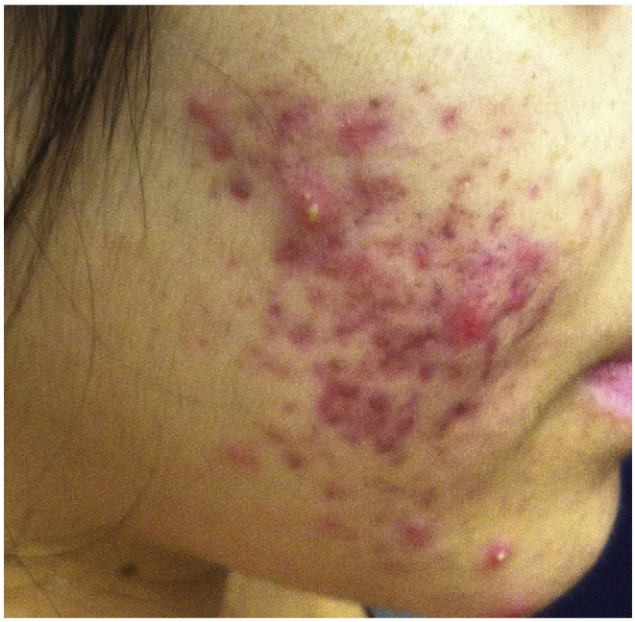

Fig. 6 Acne with perilesional erythema, papules, pustules, and scarring on the cheeks.

of systemic lupus erythematosus is based on the presence of specific published systemic and immunologic criteria.[25,26]

Mastocytosis is a group of rare disorders due to abnormal growth and accumulation of clonal mast cells. Mastocytosis includes cutaneous mastocytosis (solitary mastocytomas, urticarial pigmentosa, diffuse cutaneous mastocytosis) and systemic mastocytosis. Systemic mastocytosis is characterized by flushing and extracutaneous involvement with abdominal pain, diarrhea, and unexplained syncope. There is a characteristic serum tryptase elevation (>20 ng/mL).[11]

Drug-induced red face: From corticosteroids to brimonidine

Cortisone face may develop in case of long-term use of a topical corticosteroid or after its abrupt discontinuation after long-term application. It presents with erythema, telangiectasias, and papules on the areas of corticosteroid application

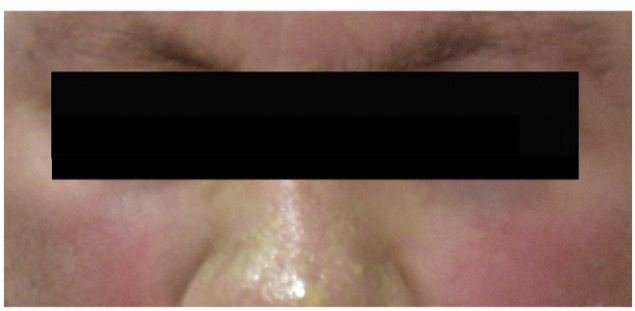

Fig. 7 Ulerythema ophryogenes. Erythema on the face and atrophy and loss of lateral eyebrows.

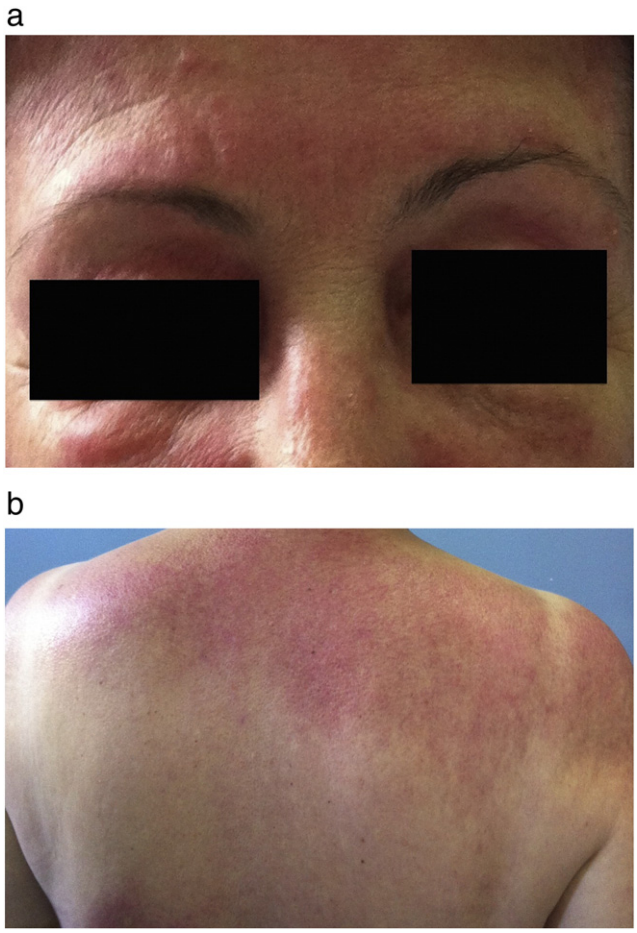

Fig. 8 Dermatomyositis. A periocular violaceous erythema (heliotrope rash) and edema and facial erythema. B, The "shawl sign."

(Figure 9). It is due to a folliculitis with neutrophilic infiltrate around or in the hair follicle. Diagnosis is based on the monomorphic nature of lesions and the reported history of chronic application of a corticosteroid-containing formulation.[19]

Brimonidine tartrate gel 0.5% is a topical α_2-adrenergic receptor agonist that has been approved by the European Medicines Agency in a once-daily application for the symptomatic treatment of facial erythema of adult rosacea[27]; however, it has been reported that facial erythema may be paradoxically worsened by the topical application of brimonidine in up to 20% of patients, usually within the first 2 weeks of application.[4,28,29] There are also reports of contact allergic dermatitis presenting with erythema and pruritus in the areas of application of brimonidine gel due to possible allergy to brimonidine or other inactive ingredients contained in the formulation such as phenoxyethanol.[30,31]

Conclusions

Erythema of the face is a common clinical sign, and apart from rosacea, it may be due to topically applied formulations; other cutaneous conditions, such as demodicosis, contact

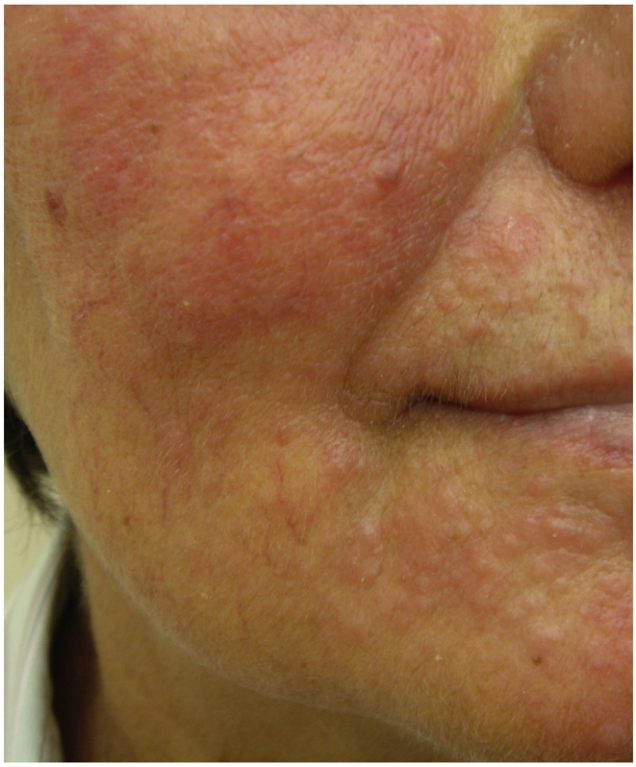

Fig. 9 Erythema and monomorphous papules on the face at the sites of chronic corticosteroid application.

dermatitis, seborrheic dermatitis, tinea faciei, or acne; or systemic diseases, such as dermatomyositis, lupus erythematosus, or mastocytosis. Before implementing treatment for the red face it is essential to establish a correct diagnosis and to understand the underlying pathophysiologic factors, because not every patient with facial erythema is the same. The approach to the patient with a red face includes a whole-body examination for the presence of skin lesions in other body areas, and a detailed medical history for the age of onset, accompanying symptoms, medication intake, topical formulations used, and possible exacerbation or improvement during summer. When there is no improvement of the facial erythema with common therapies, it is advised to perform a skin biopsy for histopathologic evaluation and appropriate laboratory evaluations to guide the correct diagnosis.

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