Rosacea

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Rosacea is a common skin disease, accounting for 0.5–1% of all cases seen in a dermatologic department [1]. Its nature remains largely obscure, but recent and old studies suggest a multifactorial etiology. The present review aims to give an account of recent findings rather than providing an exhaustive survey of the past literature. The reader is directed to the vast bibliography in the recent review by Wilkin [2].

CLINICAL FEATURES

Rosacea is a multiphasic disease characterized by four stages of pathologic events: the sequence is not obligatory and few patients complete the course of the disease. In most cases its progress is arrested in the second stage.

Frequent episodes of flushing (first stage) [3] are followed by persistent erythema (erythrosis) and telangiectases (second stage). Only a minority of the erythrotic patients develop papules and pustules (acne rosacea). Rhinophyma is the fourth and last stage, affecting only a restricted fringe of patients, usually men with erythrosis confined to the nose.

The age of prevalence varies according to the stage considered. In a series of mine [4], the erythrotic patients were 38–40 years old and the papulo-pustular patients were 47–54 years old. Rosacea is said to be more common among women, but this is true only for the first stages of the disease, possibly because women may seek cosmetologic advice more often than men.

Flushing is an accessional redness of the face and frequently of the lateral aspects of the neck and the presternal area. In some cases also the shoulders are involved. Emotional stress, drinking alcohol and hot drinks, or even an ordinary meal trigger the flushing reactions. They differ from ordinary blushing in that these reactions are more frequently and easily induced. By no means is flushing an exclusive sign of rosacea. It occurs under many other circumstances, listed extensively by Wilkin [5]. Sometimes two such conditions coincide: menopausal hot flashes may accompany rosacea flushing and rosacea stigmata may occur in carcinoid syndrome [6,7].

Most of the flushers develop erythrosis and telangiectases on the same flushing areas. Telangiectases are usually fine on the cheeks and malar areas, whereas they tend to be coarse on the nose, especially on the pinnae. On rare occasions erythrosis is accompanied by lymphoedema [8]. On the lateral aspects of the neck and/or the mastoid area, the telangiectases are interfollicular and exceedingly fine (erythrosis interfollicularis colli; EIC) [9]. Under the chin, a rhomboidal area is constantly spared and is neatly delimited by EIC. Whether this is due to a particular architecture of the cutaneous vasculature or to the protection the chin offers against sunlight (vide infra) is unknown. Thorough reviews on skin vasculature [10] do not provide useful information.

Only a minority of people with erythrosis develop papules and pustules. Papules are either sparse or in crops, sometimes asymmetric, but invariably more numerous than pustules. The neck is usually spared, except for a few isolated pustules. The bald scalp may be extensively involved [11].

In rare circumstances papules follow a chronic course and show a yellow-brown lupoid color that justifies old denominations such as "rosacea-like tuberculid of Lewandowsky" or "lupoid miliaris." I have never seen such lupoid papules below the chin, but they do occur in unusual areas such as the perioral zone and the bald scalp.

Rhinophyma develops in a small number of erythrotic patients who flush and have coarse telangiectases frequently only on the nose. They rarely have pustules, and when they do the pustules are invariably isolated. Rhinophyma is a hypertrophy of both sebaceous glands and connective tissue along with a lymphedematous component. Mentophyma, otophyma, and zygophyma are very uncommon but devastating equivalents.

Rosacea can be found in regions of the body other than the face and neck. Besides the bald scalp, the chest, back, and limbs may be affected [12]. Even the palms have been observed to show isolated pustules [4].

Eyes are quite often affected. Mild lesions include sties, chalazia, blepharitis, conjunctival hyperemia, superficial punctate keratopathy, episcleritis, and iritis. Severe lesions consist of corneal neovascularization, scarring and thinning, or even corneal perforation. Blepharitis and conjunctival hyperemia are by far the most common occurrences. Sties and chalazia are often disregarded as rosacea stigmata, but rosacea has been found in 61% of patients with chalazia [13]. Iritis and keratopathies are definitely rarer. The pH of tears from sufferers does not differ from that of control subjects [14]. Also keratoconjunctivitis sicca has been found to be significantly associated with ocular rosacea [15].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is, in many cases, nothing more than an academic exercise. Genuine clinical entities like rosacea have such precise features that diagnosis most often is not in doubt. Nonetheless, conditions that are not genuine as clinical entities or that are genuine clinical entities in iatrogenic pathomorphosis or in concurrence with rosacea may confound diagnosticians. I shall discuss herein only those conditions, leaving aside alternatives that are unlikely ever to be taken into consideration.

Hot flashes during menopause are frequently associated with rosacea flushing, occurring in the same period of life; flushing reactions due to drinking alcohol may coincide with or aggravate those occurring in genuine rosacea.

The erythrotic stage of rosacea presents some difficulties in

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Abbreviations:
DMSO: dimethyl sulfoxide
EIC: erythrosis interfollicularis colli

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diagnosis, the most common of which is corticosteroid rosacea [16]. Topical corticosteroids may change a number of facial dermatoses to erythrotic rosacea. This is mostly the case of seborrheic dermatitis. Its confinement to the hairy scalp or to the retroauricular and endoauricular regions may clarify the diagnosis. This is also the case of systemic lupus erythematosus, which lacks scarring and keratosis. Sometimes epidermal atrophy and magnification of telangiectases due to corticosteroids make such a diagnosis extremely difficult. Direct immunofluorescence does not help as much in these cases, showing a linear deposition of immunoglobulins at the basal zone in much the same pattern as rosacea does [11,17–20]. A thorough investigation of systemic manifestations, and additional laboratory tests are needed.

Haber's syndrome is one of the most curious examples of a critical quotation in dermatologic literature. After the original report by Sanderson and Wilson [21] no other genuine descriptions of such "disease" have been published. The cases of Seiji and Otaki [22] and the one of Kikuchi [23] have been shown not to be Haber's syndrome but cases of Dowling-Degos disease [24–26]. I believe that Haber's syndrome is simply Dowling-Degos disease with accompanying erythrotic rosacea.

Papulo-pustular rosacea is quite easy to diagnose. Some very rare perioral localization may be confused with perioral dermatitis. Perioral dermatitis, which is quite rare now, shows vesicopustules rather than papulo-pustules, and prefers a younger age group than rosacea. Also, its unusual periocular distribution may be seldom confused with rosacea, which constantly spares that region.

Demodicidosis does not seem to be as different from rosacea as Ayres [27] asserted, and the mite *Demodex folliculorum* is a common finding in papulo-pustular rosacea (vide infra). Only pruritus and fortnightly exacerbations would be differential criteria [28].

Rosacea-like tuberculid of Lewandowsky belongs to the group of clinical entities the authenticity of which is discussed. It can not be differentiated from granulomatous rosacea. Their similar response to metronidazole suggests that they are probably the same disease.

After their abrupt withdrawal, corticosteroids may change a number of diseases to a severe papulo-pustular rosacea. Atrophy of the skin, extension of the lesions beyond the areas usually involved by primitive rosacea, and its thick, grayish cretaceous scales, which incidentally are plenty of mites, are distinctive criteria. On a background of "blushing and flushing" [16], corticosteroids have, in a few weeks, induced or facilitated the changes that "nature" spends years to provoke in true rosacea, namely, collagen and elastin damage, vascular changes, and *Demodex* proliferation.

Acne vulgaris is another of the classical differential diagnoses. The absence of comedos and the different age of prevalence would seem to distinguish it easily from rosacea, but this is by no means true. Even in adolescents, acne vulgaris may be associated with vascular changes that might be defined as "prerosacea" [16]. The condition is quite common and it is most important to recognize because of its extreme reactivity to topical treatments for acne.

ETIOPATHOGENESIS

Exhaustive reviews of the different factors that have been thought to play a role in rosacea have been done by others [1–3]. Nonetheless, a crucial though obvious point is neglected in other reviews, many of which merely enumerate such factors.

As mentioned early in this essay, rosacea is a multiphasic disease and it seems likely that a different etiology is at work in each of its stages. In other words, factors inducing a functional disorder such as flushing are very likely to be different from factors that cause an organic pathology such as papulo-pustules.

Psychogenic factors have been claimed to be of great importance. Wilkin has given an exhaustive account of the theoretical concepts and experimental results of a number of writers [2]. More recently, patients with rosacea have been studied with respect to their personality, and most of them revealed neuroses of the neurotic or psychasthenic type. In 91%, a connection was suspected between their skin disease and stress situations [29]. Unfortunately, this belief is shared by the large majority of dermatologic patients.

The psychologic profile of the rosacea patient presents as an anxious, insecure, immature personality with crises of embarassment, guilt, and shame [30]. Because these traits are common in patients with other skin diseases such as urticaria and alopecia areata [30], it should be admitted that rosacea patients have a predisposition to facile blushing. However, the cause of predisposition consists remains unknown.

Although a familiarity may be found in some 30% of the patients, no significant association with HLA-A, HLA-B and -C phenotypes was found [31], discriminating between patients in the flushing-erythrotic stages and papulo-pustular patients.

In any case, psychogenic factors are unlikely to play a role other than in inducing or facilitating flushes. Flushing is the earliest symptom in rosacea [32], but it does not have a peculiar mechanism of production [2]; in other words, flush in rosacea patients is not qualitatively different from other flushes, but shares their heterogeneous pathophysiology [33]. Different biochemical pathways are probably available, and each subject selects one or more of them on unknown bases.

Gastrointestinal disturbances may also concur in inducing flushing. Hypochloridria, gastritis, and abnormalities in jejunal mucosa have been found and later denied [8,34]. A mild lipase secretion deficiency has been reported [35]. In my experience, patients with rosacea show gross abnormalities in stomach, duodenum, or gall-bladder as frequently as the general population; approximately 13%. However, minor gastrointestinal problems are difficult to identify, and may be important in certain patients. Release of vasoactive intestinal peptides may explain why the ingestion of ethanol facilitates flushing reactions in rosacea patients [33,36] of a type otherwise attributed to bradykinin [37] or to enkephalin and/or endorphin release [38]. In an unpublished study of mine, gastrin was found to be normal in flushing rosacea patients, whereas it was expected to be in excess because pentagastrin, its synthetic analog, had been shown to induce flushing [39].

There is no evidence that frequent, intense flushes alone lead to a loss of vascular tone resulting in the permanent vasodilation [5] typical of the erythrotic stage. In fact, Borrie [40,41] was unable to find any abnormality in testing facial vessels of rosacea patients with adrenaline, noradrenaline, histamine, and acethylcholine. I and my collaborators tested patients in all stages of rosacea and normal age-matched and sex-matched subjects by locally applying vasoactive agents such as ethylnicotinate, privine, and dimethyl sulfoxide (DMSO), and found that in rosacea facial vessels maintain their capacity for dilation and constriction. Fluids leak from them at a higher rate than they do in the general population. A significant finding was a delayed clearance of the DMSO-induced wheal in patients with erythrotic and papulo-pustular rosacea. These results suggest that the damage is in the dermis around the vessels as well as in their walls, and may coincide with the elastotic changes. In fact, a delayed clearance of the DMSO-induced wheal has been also found on the sun-damaged nape without any rosacea-like lesion, in a clear parallel with the severity of its elastotic degeneration [42].

There is little doubt that sunlight combines with repeated flushing to provoke erythrotic rosacea. The distribution of telangiectases, including those of the EIC and of the presternal area, with the typical sparing of the submental region, and the benefits of the shadow projected by the chin; the prevalence of the disease in subjects with blue eyes and fair skin [1]; along with its peculiar onset in April through May [1] seem to be sufficient evidence.

Ultraviolet radiation, however, has been said not to play an essential role in rosacea. When tested with a high-pressure mercury lamp, only 20 patients with rosacea versus 14 control subjects were found to have an increased reaction to UV. This difference was not statistically significant [43]. Many years ago, also Brod-

thagen [44] and Söbye [1] found no abnormal reaction to light in rosacea patients, but Brodthagen's failure in inducing rosacea at the sites of light testing can only be regarded as naive.

Other radiation may damage collagen and elastin fibers. Infrared rays have been poorly studied thus far. In my experience, as in Söbye's [1], erythrotic rosacea is fairly common in people occupationally exposed to heat. The worst rosaceas I have ever seen were in steel-workers.

UVA may also be important, able as it is to reach the dermis, and the synergy of infrared and UV radiations should not be disregarded [45].

Repeated flushing reactions and sunlight overexposure may explain erythrosis and even facial "phyma" [7], but something more is needed to turn a disease that, up to this stage, is largely functional (or in any case involves little organic damage) into an inflammatory disease like papulo-pustular or granulomatous rosacea.

Both cell-mediated and humoral immunity play an important role. Studies with anti–human T cell monoclonal antibodies showed that the perifollicular lymphoid infiltrate is made of T cells, with a prevalence of the helper-inducer subset [46]. Other studies, on the contrary, found very few T cells amid histiocytes and IgM-bearing cells [47]. The importance of the humoral immunity is suggested also by the difficulty of sensitizing rosacea patients with dinitrochlorobenzene with respect to the general population [20], and by the finding of anticollagen immunoglobulins at the dermoepidermal junction [11,17–20] and/or in the dermis [19,20]. In addition, a number of antinuclear antibodies of various types were detected in the blood, either free [20] or bound to lymphoid cells [19].

Contrasting evidence is offered by the activity of metronidazole in papulo-pustular rosacea. Its mechanism remains unknown (vide infra) but, as proven in other granulomatous disorders, both experimental [48] and clinical [49], metronidazole may act as a selective suppressor of some aspects of the cell-mediated immunity.

The antigens the humoral immunity is directed against are partially known, and include light-altered collagen and nuclear components, along with the mite *Demodex folliculorum*.

Anticollagen antibodies have been found in both involved and uninvolved sun-exposed skin, suggesting that light degeneration of collagen (or possibly elastic fibers) is a prerequisite for mounting the immune response [19,20]. Also, the positivity of the basal zone may mean an activity towards sun-damaged collagen IV [19].

Nuclei of the epidermal, dermal, endothelial, and eccrine ductal cells in involved and uninvolved skin, both in sun-exposed and sun-protected areas, were found to be the target of antibodies, mainly IgM and IgE, eluted from circulating lymphoid cells [19]. Circulating antinuclear IgM were also found in an unexpected percentage of patients [20].

These findings had suggested that antibodies could react to UV-altered DNA, but pyrimidine dimers, induced by UVC radiation, were not found [50].

Antibodies (IgG) directed to *Demodex folliculorum* were also detected in rosacea skin [19]. *Demodex*-specific antibodies were also shown in 22% of rosacea patients and in goats and rabbits that had been sensitized with small amounts of demodectic (*D caprae*) antigen. Frequent cross-reactions were observed with antigens of house-dust mites and *Tyrophagus putrescentiae* [51].

The mechanism of production of rhinophyma is unknown. Its occurrence in subjects who flush almost exclusively on the nose, the fact that carcinoid syndrome induces facial "phyma," and even visceral adenomatosis [52], after intense and repeated flushes [7] suggest that rhinophyma may be accounted for by flushing itself or by the vasoactive substances responsible for it.

In conclusion, the available evidence, both clinical and experimental, suggests that rosacea patients are particularly prone to physiologic flushing reactions induced by psychosomatic and, possibly, gastrointestinal stimuli. In these subjects a chronic relative overexposure to light and/or to heat produces telangiectases through degenerative changes of the perivascular (and possibly vascular) collagen and elastic tissues. In a minority of these patients, a number of antigens, including *Demodex folliculorum* and altered collagen (and possibly elastic fibers), generate an immune response leading to the inflammatory changes that clinically appear as papules, pustules, and lupoid nodules.

TREATMENT

Flushing may be relieved by all drugs that are used for migraine, but its severity rarely makes any medication necessary.

Clonidine, for example, has been successfully used in migraine and menopausal hot flashes, but its efficacy in rosacea is discussed [53,54]. In addition, its withdrawal may induce dangerous rebound effects on blood pressure that make its use in rosacea flushers unadvisable. Atenolol, 50 mg/day, is well tolerated and virtually free from side effects, but its efficacy is inconsistent. Naloxone has been found to be effective, and the use of an oral opiate antagonist has been suggested for prevention [38]. Other drugs, such as methysergide, H1 and H2 antagonists, chlorpromazine, indomethacin, and ibuprofen [55], are useless or poorly tolerated.

There is no treatment that grants good results in erythrosis. Conventional local vasoconstrictors have no effect. Sunscreens should be prescribed, and any exposure to heat sources should be thoroughly avoided.

Three facts should be taken into consideration while treating patients with papulo-pustular rosacea. First, their facial skin is extremely sensitive to topical agents, which are seldom tolerated. Second, as mentioned before, many patients have been on topical corticosteroids for a long time and should be warned that, after steroid withdrawal, any treatment may initially worsen the disease. Worsening is actually due to a rebound effect, but it may induce the patient to abandon the treatment (and his doctor). Third, the success of placebos is usually great, accounting for as many as 45% of successes [56].

Oral treatment consists of tetracyclines, metronidazole, cyproterone acetate [57], and 13-*cis*-retinoic acid [58].

In my experience, metronidazole is by far the most effective treatment. I use 500 mg/day for 20 days, and it is rare that the patients are not cured after that time.

Tetracyclines are a second choice treatment because they are less active [59] and relapses are more frequent [60].

Cyproterone acetate (10 mg) in an oral contraceptive has been found effective in a very small sample of patients [57].

Inflammatory changes and even telangiectases should disappear within 8 weeks of treatment with 0.05–1.0 mg/kg body weight 13-*cis*-retinoic acid [58].

Side effects of metronidazole include gastrointestinal disturbances that resolve spontaneously and, much more rarely, a cutaneous erythematous rash. Peripheral neuropathies mainly occur after patients have received a cumulative dose of >30 g [61]. The disulfiram-like effect requires abstinence from alcohol. Long-term problems may arise from its effect on the genetic material of somatic cells. The frequency of chromosome aberrations in cultured lymphocytes from patients on high-dose and long-term metronidazole was found to be higher than in control subjects [62]. Metronidazole treatment in schedules longer than 30 days [60] should therefore be avoided or confined to the cases that did not respond to other treatments [63] and, obviously, excluded in pregnancy.

Phototoxicity of tetracyclines may be a serious inconvenience, rosacea being prevalent in spring. Due to its teratogenic properties 13-*cis*-retinoic acid cannot be given in fertile women.

The mechanism by which metronidazole acts is unknown. Its possible direct activity on *Demodex folliculorum* seems unlikely. The mite has been shown to survive in as much as 1 mg/ml metronidazole [64]. It may be that one or more of its metabolites are the actual effective agents. Metronidazole's major urinary product, the 2-hydroxymethyl derivative, is up to 10 times more

active as an antibacterial agent than metronidazole itself [65] and its possible antiparasitic activity should be studied.

Besides the suppression of the cell-mediated immunity, metronidazole may act against anaerobes, including *Propionibacterium acnes*, modifying the intestinal flora from which active metabolites might be produced.

Understanding the mechanism of action of tetracyclines and other antibiotics such as chloramphenicol, ampicillin, and erythromycin could provide an important etiologic clue. They may act by suppressing skin flora, but bacteria do not seem to play any role in rosacea; they may reduce the number of mites [66], possibly through a reduction of bacteria the mites live upon; some of the antibiotics reduce leukocyte migration and phagocytosis [67].

Cyproterone acetate and 13-*cis*-retinoic acid presumably work by suppressing sebum production [68]. Since sebaceous activity has long ago proved not to play any role in rosacea [69], the decreased sebum production may affect the bacterial or parasitic survival in the skin. It is to be noted, however, that *Demodex folliculorum* derives its diet from the proteins rather than from the lipids of sebum [70].

Local treatment should be cautiously tried, 10% sulfur cream [71], 2% erythromycin in ethanol solution [72], and 1% metronidazole cream [73] have been found to be as effective as oral antibiotics.

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