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CHRONIC INFLAMMATORY DERMATOSIS: ROSACEA, OVERVIEW, DESCRIPTION, PRESENTATION, EPIDEMIOLOGY, PATHOPHYSIOLOGY, TYPES, DIFFERENTIAL DIAGNOSIS, TREATMENT OF THE DISEASE AND ITS ROLE IN PREGNANCY

Bryam Esteban Coello García[1], María Belén Gutama Baculima[2], Barbara Tatiana Reyes Moscoso[3], Adriana Elizabeth Avilés Torres[4], Tamara Alejandra Salamea Montenegro[5], Karina Noemí Contreras García[6], Karen Leonela Bravo Vinces[7], Fátima Viviana Benalcázar Chiluisa[8], Gloria Fernanda Erazo Guerra[9], Carla Thaylee Pinos Cabrera[10]

[1]Postgraduate Doctor in Orthopedics and Traumatology at Faculdade de Ciências Médicas Minas Gerais. Belo Horizonte - Brasil. ORCID https://orcid.org/0000-0003-2497-0274
[2]General Practitioner in Independent Practice, Faculty of Medical Sciences, Universidad de Cuenca. Azuay- Ecuador ORCID https://orcid.org/0009-0000-4174-4928
[3]General Practitioner in Independent Practice, Faculty of Medical Sciences, Universidad de Cuenca. Azuay- Ecuador ORCID https://orcid.org/0009-0002-6952-3347
[4]General Practitioner in Independent Practice,Faculty of Medical Sciences, Universidad Católica de Cuenca. Azuay- Ecuador ORCID https://orcid.org/0009-0002-7805-524X
[5]General Practitioner in "Hospital Jose Félix Valdivieso",faculty of Medical Sciences, Universidad del Azuay. Cuenca- Ecuador ORCID https://orcid.org/0009-0005-6161-1395
[6]General Practitioner at "Hospital Básico de Gualaquiza - Misereor". Morona Santiago - Ecuador ORCID: https://orcid.org/0000-0001-5899-1618
[7]General Practitioner at "Hospital Misereor" Morona Santiago-Ecuador. ORCID https://orcid.org/0009-0005-2921-690X
[8]General Practitioner in Orthopedics and Traumatology in "Hospital General Latacunga". Latacunga - Ecuador. ORCID:https://orcid.org/0009-0007-0618-1753
[9]General Practitioner in Independent Practice, faculty of Medical Sciences, Universidad Tecnológica Equinoccial. Ecuador. ORCID https://orcid.org/0009-0000-3858-3801
[10]General Practitioner in "Hospital Misereor Gualaquiza",faculty of Medical Sciences, Universidad Católica de Cuenca. Azuay- Ecuador ORCID https://orcid.org/0000-0003-2752-4667
Corresponding Author : *Bryam Esteban Coello García* ***Address:*** *Rua Tiradentes 266.Campo Belo. Minas Gerais. Brasil* ***Postal Code:*** *37270-000*

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SUMMARY

Introduction: *Rosacea is a chronic inflammatory dermatosis involving especially the cheeks, nose, chin and forehead, characterized by repetitive episodes of transient flushing or erythema, persistent erythema, in addition to phymatous changes, papules, pustules and telangiectasias.*

Objective: *to detail the current information related to rosacea, description, presentation, epidemiology, pathophysiology, types, differential diagnosis, treatment of the disease and its role in pregnancy.*

Methodology: *a total of 50 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 39 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed,*

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Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: rosacea, treatment, chronic inflammatory dermatosis.

Results: *Phymatous changes are not frequent, however they occur primarily in the nose (rhinophyma) and more commonly in men. Rosacea usually begins between 30 and 50 years of age, however it can occur at any age. The approximate population prevalence is between less than 1 to 22%. The neurocutaneous mechanisms in rosacea, reflecting reactivity to temperature change, alcohol, sports, UV rays and spicy foods, may be mediated by the ankyrin and vanilloid subfamilies of the transient receptor potential (TRP). Increased rosacea can occur in pregnancy and multiple cases linked to rosacea fulminans (RF) are reported in the literature.*

Conclusions: *Rosacea is characterized by repetitive episodes of redness, persistent erythema, inflammatory papules-pustules and telangiectasias. Previously rosacea was divided into ocular, phymatous, fulminant and granulomatous types, however there is now a new classification of rosacea. In the treatment the first thing is to identify the trigger, then make some general recommendations on the skin such as the use of sunscreen and finally give treatment that can be both topical and systemic or even to use laser or other procedures. The differential diagnosis of rosacea is broad and should be carefully analyzed. Treatment in pregnant women is a huge challenge, because several of the treatments for rosacea are contraindicated or have limited evidence of probable side effects to the fetus.*

KEYWORDS: *rosacea,treatment,dermatosis,inflammatory.*

INTRODUCTION

Rosacea is a chronic inflammatory dermatosis involving especially the cheeks, nose, chin and forehead, characterized by repetitive episodes of transient flushing or erythema, persistent erythema, in addition to phymatous changes, papules, pustules and telangiectasias. The eyeball may also be altered. Because rosacea affects the face, it has a great negative impact on the quality of life, as well as on well-being and self-esteem. Current scientific literature refers to alterations in the functions of the innate and adaptive immune systems, as well as neurovascular dysregulation under the spectrum of clinical manifestations of rosacea. In 2002, rosacea was classified into 4 subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. In 2017, a phenotype-based approach was suggested for better diagnosis and classification. Fixed centrofacial erythema and phymatous changes are particularly considered as diagnostic criteria for rosacea. Rosacea in most cases is not a life-threatening disease, with a very good overall prognosis(1-8).

METHODOLOGY

A total of 50 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 39 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: rosacea, treatment, chronic inflammatory dermatosis.

The choice of the bibliography exposes elements related to a panoramic review of rosacea; in addition to this factor, a description, presentation, epidemiology, pathophysiology, types, differential diagnosis, treatment of the disease and its role in pregnancy are presented.

DEVELOPMENT

Description, Presentation and Epidemiology.

Rosacea is a chronic inflammatory dermatosis of multifactorial cause that produces episodes of erythema, papulopustular lesions and telangiectasias mainly in the central area of the face comprising the cheeks, nose, forehead, as well as the chin, periorbuccal and periocular region. Rosacea is characterized by repetitive episodes of redness, persistent erythema, inflammatory papules-pustules and telangiectasias. Phymatous changes are not frequent, however they occur primarily in the nose (rhinophyma) and more commonly in men. Slightly more than 50% of individuals with rosacea present with ocular features including:

- Photophobia.
- Dryness.
- Conjunctivitis.
- Foreign body sensation.
- Blepharitis
- Infrequently keratitis.

Rosacea usually begins between 30 and 50 years of age, however it can occur at any age. The approximate population prevalence is between less than 1 to 22%, however these values are possibly related to differences in study design and methodology, type of population, geographic location, and social and cultural variations(1,5,7,9-16).

Pathophysiology

Currently, the dysregulation of innate, adaptive and inflammasome immune mechanisms, as well as neurocutaneous mechanisms, have been shown to be important in the pathogenesis of rosacea. Genetic susceptibility with modified immune reactivity is suggested by the relationship of rosacea with single nucleotide polymorphisms in genes linked to the major histocompatibility complex(17,18).

Innate and adaptive immune activation can be triggered by microbes, such as Demodex species and different bacteria like Bacillus oleronius and Staphylococcus epidermidis. Innate immune activation leads to up-regulation of toll-like receptor 2 from keratinocytes (TLR2) and proteinase-activated receptor 2 (PAR2). These previously named receptors promote the expression of the antimicrobial peptide cathelicidin, which shortly thereafter will activate the bioactive LL-37 by kallikrein protease 5 (KLK-5), leading to erythema and angiogenesis. TLR2 simplifies the activation of the NLRP3 inflammasome leading to

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the creation of pustules, pain and vascular response via interleukin-1β and tumor necrosis factor-alpha (TNF-α); in addition to prostaglandin E2 release. TLR2 can also generate telangiectasia, erythema, and inflammation through the expression of chemokines, proteases, cytokines, and angiogenic factors. Activation of PAR2 leads to inflammation, pain and pruritus combined with recruitment of neutrophils and T lymphocytes, mast cell degranulation and increased release of inflammatory cytokines, prostaglandins and chemokines. The activation of the adaptive immune system, conferred by the presence of T-helper T lymphocytes type I (TH1) and T-helper T 17 (TH17) with their important immune mediators generates an increase in inflammation and further immune activation(1,7,19). Neurocutaneous mechanisms in rosacea, reflecting reactivity to temperature change, alcohol, sports, UV rays and spicy foods, may be mediated by the transient receptor potential (TRP) subfamilies ankyrin and vanilloid. Particular subfamily receptors can elicit a response to various external triggers leading to the release of vasoactive neuropeptides such as substance P, pituitary adenylate cyclase-activating peptide and calcitonin gene-related peptide. Sensory nerves also express TLR2 and PAR2 and can maintain the activation of inflammatory mechanisms(1,20).

Table 1. Novel classification of rosacea on the basis of diagnostic, major, and secondary features of rosacea.

Novel classification of rosacea on the basis of diagnostic, major, and secondary features of rosacea.

Diagnostic features	Major features	Secondary features
Persistent centro-facial erythema associated with aggravation by trigger factors	Flushing/transient erythema	Burning sensation
Phymatous changes	Inflammatory papules and pustules	Stinging sensation
	Telangiectasia	Edema
	Ocular manifestations	Dry sensation of the skin
	Lid margin telangiectasia	
	Blepharitis, keratitis, conjunctivitis, and sclerokeratitis	

Source: Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea(2,5,21).

Types

Ocular Rosacea

Ocular involvement may be seen in more than half of individuals with rosacea. Eyelid hygiene and systemic management with tetracyclines should be used as treatment for this type of rosacea. Oral omega-3 fatty acids, cyclosporine ophthalmic emulsion and doxycycline are indicated for management. Some investigators noted that IPL may also improve dry eye symptoms in individuals with rosacea following periocular facial skin treatment; note that eye shields must be properly applied for ocular protection. In other trials, individuals with severe ocular rosacea benefited from an enhanced metronidazole water-soluble silver(I) complex, with good results in uncorrected visual acuity tests, as well as more convenient objective and subjective assessment of tear film parameters. Other authors recommend a flexible treatment with eyelid wash, preservative-free artificial tears, warm compresses, topical antibiotics, topical steroids, topical cyclosporine, oral doxycycline, azithromycin suspension and erythromycin suspension. We have to emphasize early identification and management in cases of children with ocular irritation, recurrent chalazion, peripheral corneal infiltrates that are of long duration and Meibomian gland disease(6,22-24).

Phymatous Rosacea

The Rosacea Classification and Staging Expert Committee of the National Rosacea Society classified rosacea fymatosa as a specific subtype of rosacea in 2002. Phymatous rosacea occurs mostly on the nose, also called rhinophyma. In 2017, fymatous changes were designated as one of the characteristic and diagnostic phenotypes of rosacea. The rosacea treatment update in the ROSacea COnsensus (ROSCO) indicates that management for phyma is going to depend on whether it is inflamed or not. For inflamed phyma or active phyma, oral doxycycline and oral isotretinoin were indicated, whereas for non-inflamed phyma or fibrotic phyma, physical modalities were indicated. Some authors used CO 2 laser ablation due to its efficacy, reliability, practicality and predictability. Studies recommended using a porcine extracellular matrix after shaving excision of rhinophyma: this treatment reduces the number of dressing removals and the re-epithelialization time (2,4-6,10,25,26).

Rosacea Fulminans

Rosacea fulminans, also called pyoderma facialis or rosacea conglobata, is a rare disease characterized by inflammatory papules, pustules, nodules and cysts on the face. Rosacea fulminans may be associated with pregnancy and inflammatory

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bowel disease. Some research suggests systemic treatment with corticosteroids and/or isotretinoin to improve symptoms and decrease scarring rates(6,27,28).

Granulomatous Rosacea

The National Rosacea Society Expert Committee on the Classification and Staging of Rosacea recognized it as a variant of rosacea in 2002; however, in the current classification system, granulomatous rosacea was not named. This disease often presents a chronic course, which is complex to manage. Trials show successful treatment with chromophore gel-assisted phototherapy, oral doxycycline, oral metronidazole, topical ivermectin, topical brimonidine, oral steroids and oral dapsone(2,5,29-33).

Treatment

The first thing in the management of rosacea is to advise the affected individual to identify and then avoid triggers such as:

- Ultraviolet light.
- Alcoholic beverages
- Spices.
- Changes in climate.

General dermal care advice for all individuals with rosacea includes:

- Broad-spectrum sunscreen with SPF 30 or higher.
- pH-balanced skin cleansers.
- Regular use of moisturizers.

Rosacea often causes the skin to become sensitive and irritable, so avoid products that cause irritation. Cosmetics containing green pigment are best suited to cover persistent erythema. Almost all therapies are aimed at decreasing inflammation. Topical steroids should be avoided in rosacea because of their association with rebound flare-up or induction of perioral dermatitis. Persistent erythema and telangiectasias are not entirely secondary to inflammation and often need treatment directed at the skin vasculature, such as brimonidine, oxymetazoline, or vascular lasers. Phymatous changes in rosacea result in irreversible skin changes that require surgical intervention if necessary(8,34,35).

Topical Treatment

Erythema

- Brimonidine tartrate is an alpha-2 agonist in gel at 0.33%, applied daily on the face.
- Oxymetazoline hydrochloride is an alpha-1 agonist in a 1% cream applied daily on the face.

Inflammatory Papules and Pustules

- Ivermectin 1% cream is applied daily.
- Azelaic acid 15% gel, foam or cream 20% is applied daily 1 or 2 times.
- Metronidazole 0.75% and 1% gel or cream is applied daily 1 or 2 times.
- Topical or systemic tranexamic acid may help with symptoms in individuals with rosacea by stabilizing the immune response and angiogenesis.

Ocular Involvement

- Artificial tears.
- Fusidic acid gel is placed daily 1 to 2 times on the eyelids.
- Metronidazole gel 0.75% is placed daily 1 to 2 times on the eyelids.
- Cyclosporine eye drops 0.05% are placed daily 1 to 2 times on the eyelids.

Systemic Treatment

Redness

- Propranolol 20 to 40 mg 2 to 3 times a day.
- Carvedilol 6.25 mg 2 to 3 times per day.
- Clonidine 50 mcg 2 times a day.

Inflammatory papules and pustules.

- Doxycycline in sub antimicrobial dose, in modified release presentation 40 mg per day, 30 mg immediate release and 10 mg delayed release beads, for 8 to 12 weeks.
- Minocycline 50 to 100 mg twice daily for 8 to 12 weeks.
- Tetracycline 250 to 500 mg twice daily for 8 to 12 weeks.
- Azithromycin 250-500 mg 3 times a week for 4 to 8 weeks.
- Isotretinoin 0.25 to 0.3 mg/kg/day for 12 to 16 weeks.

Phyma-Inflamed.

- Doxycycline 100 mg 1 to 2 times a day for 8 to 12 weeks.
- Tetracycline 250 to 500 mg twice a day for 8 to 12 weeks.
- Isotretinoin 0.25-0.3 mg/kg/day for 3 to 4 months.

Ocular Involvement

- Doxycycline in sub antimicrobial dose, modified release presentation 40 to 100 mg per day.

Procedures/Interventions

Erythema-Telangiectasia

- Intense pulsed light therapy.
- NdYAG laser.
- PDL 585 to 595 nm pulsed dye laser.

Phyma-Non-Inflamed

- CO2 laser 10,600nm.
- Surgical resection.
- Electrosurgery.

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Referral to an ophthalmologist is indicated if the individual shows any eye involvement, significant symptoms or visual disturbance. Topical treatment is indicated in pregnant women. Azithromycin, erythromycin and clarithromycin are considered safe in pregnancy with mild to severe inflammatory rosacea. Systemic management is usually used for flare-ups with no response to individual topical therapy. It is preferable to maintain topical management so that remission remains after flare-up control(1,8,23,36-38).

Differential Diagnosis

- Acne: having comedones is exclusive of acne.
- Redness: in rosacea limited to the face.
- Acute cutaneous lupus erythematosus: with very similar malar eruption, however it respects the nasolabial folds and does not present papulopustules.
- Seborrheic dermatitis shows erythema and greasy desquamation on the scalp and face. It is mostly distributed in the nasolabial folds and hair-bearing surfaces of the face. Because the 2 entities are common, several individuals will show both seborrheic dermatitis and rosacea. Treatment of one may eventually unmask the other.
- Keratosis pilaris rubra usually occurs in adolescent individuals with small follicular papules on the lateral cheeks and neck over erythematous patches.
- Drug-induced acneiform eruption: with abrupt onset and related to drug intake, the skin changes are usually monomorphic, bony at the same stage and also involve the trunk(8).

Rosacea During Pregnancy

Increased rosacea can occur in pregnancy and multiple cases linked to rosacea fulminans (RF) have been reported in the literature. Treatment in the pregnant woman is a huge challenge because several of the treatments for rosacea are contraindicated or have limited evidence regarding the likely side effects to the fetus. Some studies show topical ivermectin to be more effective than metronidazole, however it presents a more alarming pregnancy category. Azithromycin is the only oral therapy for rosacea that is considered safe for pregnant women, being used to treat RF(39).

CONCLUSIONS

Rosacea is characterized by repetitive episodes of redness, persistent erythema, inflammatory papules-pustules and telangiectasias. Previously rosacea was divided into ocular, phymatous, fulminant and granulomatous types, however there is now a new classification of rosacea. In the treatment the first thing is to identify the trigger, then make some general recommendations on the skin such as the use of sunscreen and finally give treatment that can be both topical and systemic or even to use laser or other procedures. The differential diagnosis of rosacea is broad and should be carefully analyzed. Treatment in pregnant women is a huge challenge because several of the treatments for rosacea are contraindicated or have limited evidence of probable side effects to the fetus.

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