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Case Report

One-side facial granulomatous rosacea: atypical manifestation of Demodex infection

Yang Luo, Jian-Hong Zhang, Lan-Xi Wu, Nan Zhou, Xiu-Li Luan, Yu-Jiao Sun, Li Zhang

Department of Dermatology, The 940th Hospital of Joint Logistics Support Force of The Chinese People's Liberation Army, Lanzhou, Gansu Province, China

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Abstract: Rosacea is a common chronic inflammatory dermatosis affecting the central area of the face or the eyes. It is divided into four categories and one variant, granulomatous rosacea (GR). GR is very rare and always presents with facial erythema, multiple papules, pustules and nodules in both sides of the face. The diagnosis of GR depends on the histopathologic finding of a granulomatous infiltrate. We report a case of a 26-year-old male with localized GR on the right half of the face. A skin biopsy showed a granuloma structure in old lesions. Microscopic examination revealed Demodex mites in the secretion from lesions. Similar manifestations were observed on the skin of the back of a Japanese rabbit when it was injected with Demodex mites extracted from the lesions in the patient. A diagnosis of Demodex-induced GR was established. The patient was successfully treated with oral ornidazole tablets against Demodex and topical recombinant bovine basic fbroblast growth factor gel to repair skin lesions for 8 weeks, with no recurrence during 6 months of follow-up. This case suggests that Demodex play an important role in the pathogenesis of GR.

Keywords: Ornidazole, recombinant bovine basic fbroblast growth factor gel, granulomatous rosacea, Demodex

Introduction

Rosacea is a chronic inflammatory skin disease and usually affects the central area of the face or the eyes. In 2017 the National Rosacea Society Expert Committee (NRSEC) classified rosacea into four subtypes (erythematotelangiectatic, papulopustular, phymatous and ocular) and the granulomatous variant [1]. Granulomatous rosacea (GR) is very rare and is categorized as a separate variant because of its unique histopathologic findings [2]. We report a case of a 26-year-old male with GR localized to the right half of the face who was successfully treated with oral ornidazole tablets and topical recombinant bovine basic fbroblast growth factor gel, with no recurrence during 6 months of follow-up.

Case report

A 26-year-old Chinese male with one-side facial erythema, papules, and nodules with itching for 8 months, was admitted to the Dermatology Department of our hospital in April 2018. The patient reported mild itching without obvious joint swelling and deformity, night sweats, coughing or other systemic symptoms. He reported no animal-breeding history. In August 2017, the patient was diagnosed with discoid lupus erythematosus (DLE) at another hospital and received oral hydroxychloroquine sulfate tablets (0.2 g×2/day) for 8 months, which did not improve the lesions but increased his liver burden.

Physical examination showed lesions mainly on the right forehead and auricula, presenting as scattered nodules about 0.3-1 cm in diameter with multiple papules and invasive erythema, covered with fine scales. No other obvious lesions were observed on the skin, mucosa or nails (**Figure 1A1**, **1A2**). Tuberculin skin test and antinuclear antibodies (ANA) tests were both negative.

Histopathological examination of a biopsy sample from the old skin lesions was performed. Hematoxylin-eosin (HE) staining of the old skin lesions showed a dermal granuloma structure (**Figure 2A**, **2B**), which was consistent with a previous study [3, 4]. The acid-fast staining was negative (**Figure 2C**). The secretion from hair

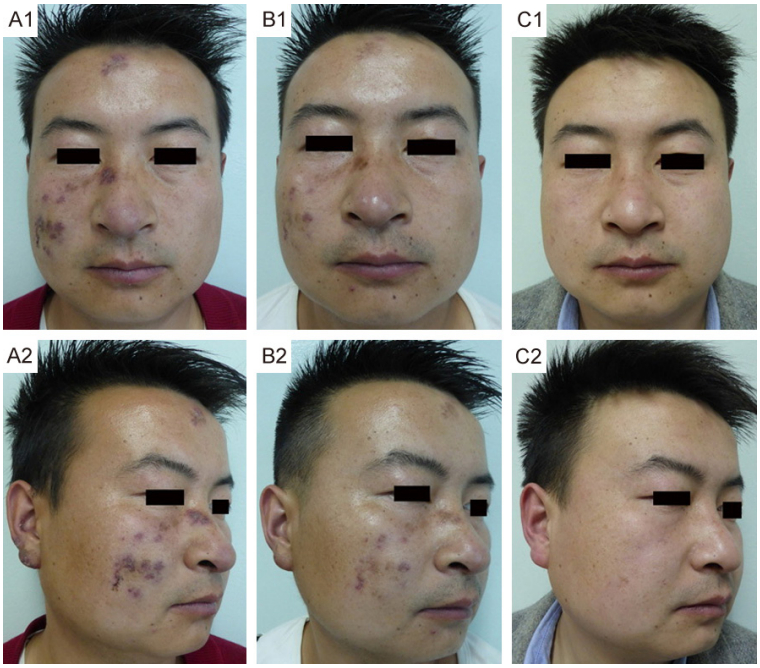

Figure 1. Photographs show (A1, A2) lesions before treatment: mainly on the right forehead and auricular area, presenting as scattered nodules, papules and erythema covered with fine scales; (B1, B2) appearance after 8 weeks of treatment with oral ornidazole tablets and topical recombinant bovine basic fbroblast growth factor gel: nodules and papules had subsided, and the erythema had partially improved with local residual pigmentation; and (C1, C2) appearance at 6-month follow-up: facial skin lesions were cured and no new and recurrent lesions were observed.

follicle sebaceous glands was collected from the patient's lesions, treated with 16% potassium hydroxide and observed under the optical microscopy at ×40 magnification. Demodex parasites were observed (**Figure 2D**). Based on Koch's postulates [5], similar manifestations were observed on the skin of the back of a Japanese rabbit after it was injected with Demodex mites extracted from the lesions of the patient (**Figure 3**). No signs of discoid lupus erythematosus were observed. On the basis of clinical manifestations, laboratory tests, animal experiments, and pathological features, GR caused by Demodex infection was diagnosed. Oral ornidazole tablets (500 mg, twice per day) were administered for an anti-Demodex effect, and recombinant bovine basic fibroblast growth factor gel (0.2 g/cm^2, twice per day) was topically used for 8 weeks to repair skin lesions by promoting skin healing as well as avoiding scar formation [3, 4]. The skin lesions gradually improved after 8 weeks of treatment; the nodules and papules were dissipated and erythema partially faded leaving a mild pigmentation (**Figure 1B1**, **1B2**). No Demodex parasites were observed in the pilosebaceous exudates from the same site under light microscopy. After 6 months of follow up, facial skin lesions had subsided, and there were no new or recurrent lesions (**Figure 1C1**, **1C2**).

Discussion

Rosacea is a common chronic inflammatory dermatosis affecting 1-10% of the global population [6]. It is divided into four categories and one granulomatous variant [1]. The clinical manifestations of rosacea are diverse, and its diagnosis mainly depends on its clinical manifestations [7]. The pathogenesis of rosacea is complicated, and the exact pathogenesis and pathophysiology are poorly understood. However, Demodex mites are reported to play an important role in rosacea [8-10].

GR is a variant subtype of rosacea. GR always presents with erythema, multiple papules, pustules and nodules on the face, and typically affects middle-age women and occasionally children [11-14]. The lesions in the present case differed from the classic clinical presentation and only involved the right forehead and auricular area. At present, the diagnosis of GR is dependent on the histopathologic finding of a granulomatous infiltrate [2]. It is characterized by papules, occasional granulomatous lesions and a histopathological presentation of epithelial-like cell granulomas [15]. The histopathological findings in this patient were consistent with the characteristics of GR. The lesions were scattered as one-side facial nodules, papules and erythema, accompanied by suspected paresthesia, which led to initial misdiagnosis at another hospital.

There are several possible causes of GR. One study reported that GR is associated with changes in the innate immune response [13]. Another study reported that GR is related to

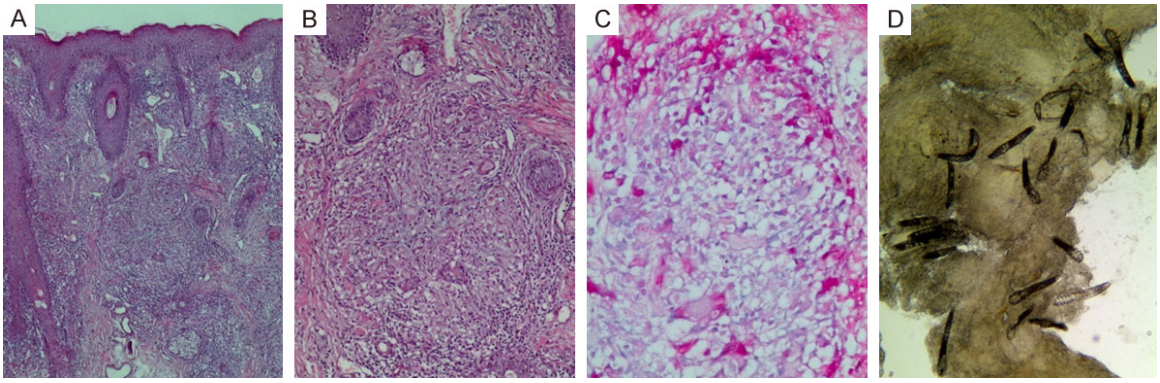

Figure 2. (A, B) Hematoxylin-eosin staining of the skin biopsy. (A) Angiotelectasis and vascular proliferation in the dermis. A granuloma structure was seen above the sebaceous gland (×40 magnification); (B) The magnified view of (A). The granuloma structure consisted of lymphocytes, epithelioid cells and multinucleated giant cells (×100 magnification). (C) The granuloma structure was negative for acid-fast staining (×200 magnification). (D) Demodex observed in the sebaceous gland secretion of hair follicle from the lesion of the patient (×40 magnification).

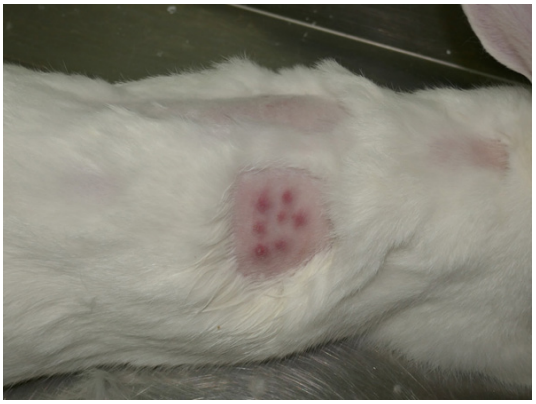

Figure 3. Lesions on the skin of the back of a Japanese rabbit after injection with Demodex mites extracted from the lesions of the patient. The lesions were scattered erythematous papules with a diameter of 0.5-1 cm on the skin of the back of the Japanese rabbit.

immunosuppression [16, 17]. Recently, Demodex was found to be associated with GR [11]. In the present case, the lesions in the current patient manifested as one-side facial erythematous papules, which can be caused by several diseases, such as autoimmune disease (DLE) and cutaneous tuberculosis. Negative results from ANA tests and skin biopsy of mature lesions as well as the ineffectiveness of treatment against DLE ruled out the possibility of DLE. The patient had neither a history of tuberculosis nor symptoms of tuberculosis, and acid-fast staining was negative. Taking all these findings together, cutaneous tuberculosis was ruled out. Skin biopsy of mature facial lesions showed the granuloma structure in the dermis. Based on Koch's postulates [5], similar manifestations were observed in the skin of a Japanese rabbit after it was intradermally injected with Demodex mites extracted from lesions of the patient, on the basis of our previous report [3, 4], and the patient was given treatment against Demodex, which had clear efficacy. A diagnosis of GR caused by Demodex was made.

There is no standard treatment for GR [18]. One pediatric patient was successfully treated with topical azelaic acid, suggesting that topical azelaic acid may be used to treat childhood GR and prevent recurrence [13]. Oral minocycline also has been reported to improve lesions [14]. In another case, oral thalidomide and topical pimecrolimus were used to successfully cure refractory GR [19].

A total of three cases of Demodex-related GR have been reported. As summarized in the **Table 1**, all three cases had no immunodeficiency diseases or other special comorbidities such as tuberculosis and systemic lupus erythematosus. Clinical manifestations included symmetrically distributed facial erythema and papules, which were similar to the skin lesions in the present case, except that they were unilaterally distributed in the present case, which increased the difficulty of diagnosis based on clinical manifestations alone. Skin biopsy was the main diagnosis method used. Using dermoscopy, Kelati et al. [11] found Demodex mites. The pathological findings in the present case were similar, with a granuloma structure

Table 1. Summary of the literature related to granulomatous rosacea associated with Demodex infestations

Author, Year	Patient basic information	Clinical manifestation	Complications	Diagnosis method	Pathological manifestation	Diagnosis	Drug, dose and time	Outcome
Present case	26-year-old Chinese male	Skin lesions mainly on right forehead and auricular area, presenting as scattered nodules, papules and erythema covered with fine scales.	None	Skin biopsy and microscopic examination of sebaceous secretion	Granuloma structure consisted of lymphocytes, epithelioid cells and multinucleated giant cells	Granulomatous rosacea	Oral ornidazole tablets 500 mg, twice per day and recombinant bovine basic fibroblast growth factor gel 0.2 g/cm^2, twice per day was topically used for 8 weeks	After 6 months of follow-up, facial skin lesions had subsided, and no new or recurrent lesions were observed.
Kelati et al. (2017)	54-year-old Moroccan man	Erythematous, telangiectatic, confluent papules of the lateral side around the eyes without any scales, crusts, or pustules.	Psoriasis	Dermoscopy and skin biopsy	Granulomatous dermatitis with the presence of Demodex folliculorum in biopsied tissue	Granulomatous rosacea	Topical metronidazole for a total of 10 weeks	Significant improvement.
Lee et al. (2007)	48-year-old woman	Numerous erythematous, dome-shaped papules distributed on the face and neck.	None	Skin biopsy	Dense inflammatory infiltrate around a hair follicle with two mites present in the infiltrate	Granulomatous rosacea-like demodicidosis	Systemic and topical metronidazole for 3 weeks, and low-dose oral prednisolone	Facial papules resolved.
Amichai et al. (1992)	25-year-old Israeli woman	Skin lesions symmetrically distributed on both cheeks, lower eyelids, and nose. The lesions were composed of erythematous papules 2 mm in diameter, which coalesced on the cheeks to form plaques 2-3 cm in diameter. A few pustules were also present.	Mild asthma	Skin biopsy	Enlarged hair follicles containing structures of Domodex folliculorum. Dense infiltrate composed of histiocytes with a few giant cells surrounded by lymphocytes, forming noncaseating foreign body granuloma in the dermis	Granulomatous rosacea	Minocycline HCl 100 mg/day and topical clindamycin phosphate for a total of 8 weeks	Cessation of medications was not followed by recurrence of skin lesions.

and observation of Demodex mites. The case reported by Lee et al. [21] was diagnosed with GR-like demodicidosis with pathological manifestations of Demodex wrapped in inflammation cells. Skin biopsy was also applied for assistance in the present case. Moreover, Demodex mites were found in the sebum secretion from skin lesions regarding treatment, Kelati et al. [11] and Lee et al. [21] used a metronidazole-based anti-Demodex regimen to relieve facial lesions. Amichai et al. [20] used minocycline HCl and topical clindamycin phosphate as anti-inflammation treatment, and skin lesions subsided without recurrence after the drug the stopped. We previously found that anti-Demodex mite treatment can cure rosacea in patients with Demodex infection [3, 4]. In the present case, the facial erythema, papules and nodules gradually improved upon anti-Demodex treatment with ornidazole. Then the patient was treated with recombinant bovine basic fibroblast growth factor gel for topical use to repair the lesions, and no scars were observed during follow-up. Because anti-Demodex treatment cured GR in this case and microscopic examination and similar manifestations were observed in animal experiments in the present case, we propose that Demodex mites play an important role in the pathogenesis of GR. However, further investigation is needed to uncover why this particular patient presented with a one-sided facial distribution of lesions.

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The patient provided written informed consent for publication of the case report. The animal experiments were approved by the ethics committee of The 940th Hospital of Joint Logistics Support Force of the Chinese People's Liberation Army (2019KYLL006).

Disclosure of conflict of interest

None.

Abbreviations

GR, granulomatous rosacea; NRSEC, National Rosacea Society Expert Committee; DLE, discoid lupus erythematosus; ANA, antinuclear antibodies test; HE, hematoxylin-eosin.

Address correspondence to: Dr. Yang Luo, Department of Dermatology, The 940th Hospital of Joint Logistics Support Force of The Chinese People's Liberation Army, 333 Binhenan Road, Lanzhou 730050, Gansu, China. Tel: +86-13919764779; Fax: +86-931-8994003; E-mail: lytmmu@163.com

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