

The Role of *Chlamydia pneumoniae* in the Etiology of Acne Rosacea: Response to the Use of Oral Azithromycin

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Acne rosacea is a chronic skin disorder that requires long-term therapy. Oral azithromycin has been used successfully to treat acne vulgaris, an observation that suggested an infectious agent may play an active role in the etiology of this disorder. Ten adults (not previously reported) with acne rosacea were selected to be treated with oral azithromycin. Nine of the 10 subjects received 250 mg 3 times weekly for periods ranging from 5 to 19 weeks, at which time follow-up examinations were performed on 8 of the 9 treated subjects; 1 subject was lost to follow-up. Prior to therapy, C pneumoniae antigen was detected in malar biopsy specimens in 4 of 10 subjects by immunoperoxidase technique (using monoclonal antibody to C pneumoniae). Serum antibodies against C pneumoniae were detected in 8 of 10 intent-to-treat subjects. Using polymerase chain reaction, C pneumoniae was not detected in peripheral blood mononuclear cells. The inflammatory response in tissues was characterized by a widespread infiltration of polymorphonuclear neutrophil cells, lymphocytes, and plasma cells, which support the clinical diagnosis of acne rosacea. Nine of 10 subjects treated with azithromycin showed moderate to marked improvement of their acne rosacea. No adverse reactions to azithromycin occurred,

and the drug appeared to be safe and effective. These preliminary data suggest the need for further investigation with clinical trials to study long-term tolerability and efficacy and also strongly implicate C pneumoniae in the pathogenesis of acne rosacea.

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Acne rosacea is a chronic skin disorder that presents with symmetrical facial flushing and edema, leading to telangiectases that can later develop into papules, pustules, and persistent erythema. Tissue overgrowth of the nose (rhinophyma) also may occur. Conjunctival areas of involvement are known to occur, especially in the severest forms of acne rosacea. The prevalence of acne rosacea has been estimated to be about 10%,^{1,2} with women affected more often than men.

Although the cause of this disorder was originally thought to be a vascular phenomenon aggravated by degenerative changes in pilosebaceous units,¹⁻³ infectious causes also have been theorized¹ (eg, *Helicobacter pylori* infection in association with other gastrointestinal disorders,⁴ *Demodex folliculorum* infestation⁵). Hormonal influences, emotional stress, increased humoral vasoactive mediators such as substance P, food intolerance, and the degenerative effect of the sun constitute other postulated causes.⁶⁻⁸

Effective treatment (improvement in 80%–90% of cases) of acne rosacea has been achieved with oral tetracyclines or topical metronidazole. Combining these 2 modalities achieves a more rapid response and is a widely used method of modern day therapy.^{3,4,9,10} Oral use of azithromycin 3 times weekly also has been successfully used to treat acne vulgaris,^{11,12} an observation that suggested an infectious agent may play an active role in the etiology

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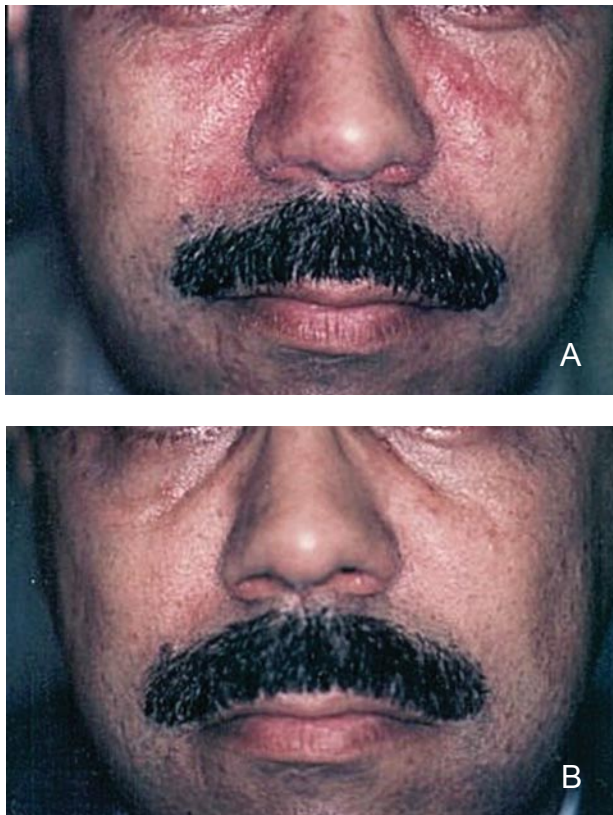


Figure 1. Subject with acne rosacea before (A) and after 10 weeks of treatment with 250 mg of oral azithromycin 3 times weekly (B).

of acne rosacea. We were the first to report that *C pneumoniae* may be involved in the pathogenesis of acne rosacea, based on a case of an elderly patient with persistent acne rosacea who responded to azithromycin therapy. Results of a skin biopsy taken of an active lesion prior to therapy tested positive for *C pneumoniae* antigen using species-specific monoclonal antibodies, which prompted us to conduct a more thorough investigation of the role *C pneumoniae* may play in the etiology of acne rosacea.

A study of 10 different patients, not reported previously, found azithromycin to be safe and effective for the treatment of acne rosacea.¹³ The aim of this study was 2-fold: first, to examine the effects of oral azithromycin in subjects with acne rosacea; second, to investigate whether *C pneumoniae*, an infectious agent, played a role in the etiology of acne rosacea in those subjects treated with oral azithromycin. We used direct-antigen detection methods on tissue biopsy specimens to document the presence of *C pneumoniae* antigen, and we used serology tests to detect antibody to *C pneumoniae*.

Materials and Methods

Study Design—A series of 10 adults (6 men) were selected in an office setting to receive oral

azithromycin monotherapy for the treatment of acne rosacea (age range, 34–72 years). The subjects agreed to take 250 mg of oral azithromycin 3 times weekly (Mondays, Wednesdays, and Fridays), a dosage regimen shown to be effective for the treatment of acne vulgaris.^{11,12} An academic institutional review board approved the study protocol, and all subjects signed an informed consent form. Subjects were encouraged to regularly wash involved skin with a commercially available soap substitute, the sole topical agent allowed. The subjects were not receiving treatment for acne rosacea before starting azithromycin nor were they taking any medication that could either exacerbate or improve clinical signs and symptoms of acne rosacea. The subjects reported no history of using azithromycin for this indication. Subject demographics, clinical stage, evidence of eye involvement, biopsy site, clinical response, and duration of treatment (signaled by time until follow-up), appear in the Table, along with the definitions of clinical stage and clinical response.

Histologic Studies—Routine histologic studies were assessed from formalin-fixed paraffin-embedded sections that were stained with hematoxylin and eosin. Immunocytochemistry analysis for detection of *Chlamydia* was performed on deparaffinized sections, using the avidin-biotin-peroxidase complex immunostaining system with the genus-specific monoclonal antibody CF2, species-specific anti-*Chlamydia trachomatis* monoclonal antibody KK-12, and species-specific anti-*C pneumoniae* clone 161.

Serologic Studies—Serum samples were obtained at the time of the initial office visit. Sera were tested for immunoglobulin (Ig) G and IgM antibodies against *C pneumoniae* and *C trachomatis* by microimmunofluorescence assay.¹⁴ Subjects with a serovar-specific IgM antibody titer of 1:8 or higher or an IgG titer of 1:8 or higher were considered to have a positive response to *C pneumoniae* or *C trachomatis* in this study.

Results

Clinical Outcome Posttreatment—Prior to initiation of therapy, the possible side effects of azithromycin were explained to the subjects, including nausea, gastric discomfort, vaginitis, and possible rash. No subjects complained of any symptoms associated with the medication use. In 8 of 9 treated subjects, evaluation of azithromycin treatment occurred after 5 to 19 weeks of treatment (Table). Subject 7 was lost to follow-up, and subject 3 did not begin treatment due to pregnancy. The initial severity of disease was defined as severe in subjects 2, 5, 8, 9, and 10 (Figure 1). Their clinical response was rated as marked.

Histologic Studies—Before therapy began, *C pneumoniae* antigen was detected in biopsy

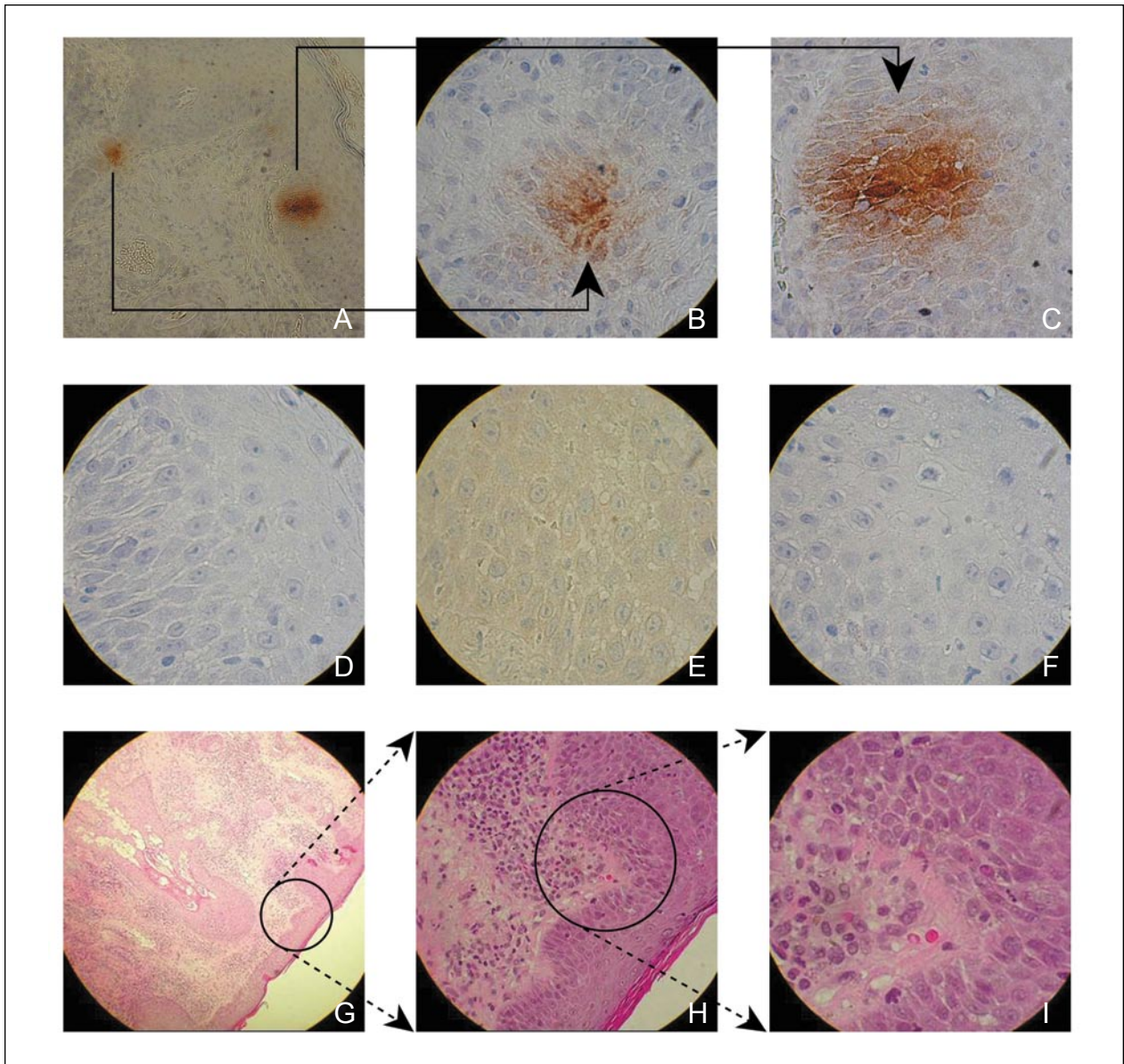


Figure 2. Detection of *Chlamydia pneumoniae* in subjects with acne rosacea using the avidin-biotin-peroxidase complex immunostaining system. Monoclonal antibody species-specific for *C pneumoniae* (A, original magnification $\times 40$; B and C, original magnifications $\times 100$). No primary antibody (control) (D, original magnification $\times 100$), species-specific *Chlamydia trachomatis* monoclonal antibody KK-12 (E, original magnification $\times 100$), and genus-specific monoclonal antibody CF-2 (F, original magnification $\times 100$). Typical inflammatory infiltrates of subjects with acne rosacea with hematoxylin and eosin staining (G–I; original magnifications $\times 10$, 40, and 100, respectively).

specimens from active lesions, mostly malar specimens, in subjects by immunoperoxidase technique in 4 of 10 tissues tested (Figure 2). These same 4 subjects also were positive for *C pneumoniae* by serology.

All subjects with *C pneumoniae* antigen by immunoperoxidase technique also were positive for *C pneumoniae* serology, which strongly suggests that *C pneumoniae* may indeed play a role in the inflammatory responses observed in the histology, and thus, its presence may correlate clinically with active rosacea.

Subjects 1 and 3 had a mild inflammatory infiltration; all others had moderate to heavy polymorphonuclear neutrophils, lymphocytes, and plasma cells throughout the biopsy.^{15,16} A favorable clinical response following the systemic use of azithromycin was noted in all 9 subjects treated.

Serologic Studies—No IgM antibodies for *C pneumoniae* were detected in any of the 10 subjects. However, IgG was elevated (titer $\geq 1:16$) in 8 of 10 subjects. One subject (subject 9) also

Subject Demographics, Clinical Response, Duration of Treatment, and Detection of *Chlamydia* Species*

Subject No.	Age, y (Sex)	Clinical Stage [†]	Eye Involvement	Biopsy Site	Clinical Response [‡]	Follow-up, wk	IP Technique	CP		CT		Serotype [§]
								Micro-IF IgM	Micro-IF IgG	Micro-IF IgM	Micro-IF IgG	
1	67 (M)	Moderate	Y	Right malar	++	19	Pos	<1:8	1:16	<1:8	<1:8	TWAR
2	58 (F)	Severe	Y	Left cheek	+++	15	Neg	<1:8	<1:8	<1:8	1:16	CJFG
3	34 (F)	Moderate	Y	Right malar			Neg	<1:8	1:16	<1:8	1:16	BDEL1L2, TWAR
4	53 (F)	Moderate	Y	Left malar	+++	13	Neg	<1:8	<1:8	<1:8	<1:8	Not detected
5	42 (M)	Severe	Y	Left side nose	+++	5	Neg	<1:8	1:32	<1:8	<1:8	TWAR
6	72 (M)	Moderate	Y	Left maxilla	+++	8	Pos	<1:8	1:16	<1:8	<1:8	TWAR
7	35 (F)	Moderate	N	Right malar	++	2	Neg	ND	1:32	ND	1:16	ACJ, TWAR
8	42 (M)	Severe	N	Left side nose	+++	10	Pos	<1:8	1:64	<1:8	1:32	BDEL12, TWAR
9	56 (M)	Severe	Y	Right side nose	+++	13	Neg	<1:8	1:16	1:16	<1:8	TWAR, H
10	50 (M)	Severe	Y	Right infraorbital	+++	12	Pos	<1:8	1:32	<1:8	<1:8	TWAR

*IP indicates immunoperoxidase; CP, *Chlamydia pneumoniae*; IF, immunofluorescence; IgM, immunoglobulin M; IgG, immunoglobulin G; CT, *Chlamydia trachomatis*; M, male; Y, yes; Pos, positive; F, female; Neg, negative; N, no; ND, not done.

[†]Clinical stage defined as mild (facial erythema with absence of papules or pustules), moderate (facial erythema with 1–12 papules or pustules), severe (facial erythema with >12 papules or pustules).

[‡]Clinical response defined as slight (+) (diminution in facial erythema with no essential change in the number of papules or pustules), moderate (++) (marked reduction in facial erythema and substantial reduction in the number of papules or pustules), or marked (++++) (faint residual erythema with elimination of papules and pustules).

[§]*C pneumoniae* has the serotype TWAR; *C trachomatis* has the serotypes A, B, C, D, E, F, G, H, I, J, K, L1, L2, and L3.

^{||}Did not start therapy because of pregnancy.

[¶]Lost to follow-up.

had evidence of antibody to *C trachomatis* by detectable IgM antibody (titer=1:16) but not of IgG. Four other subjects (subjects 2, 3, 7, and 8) had elevated levels of IgG (titer \geq 1:16) for *C trachomatis* (Table).

Comment

Acne rosacea, a chronic disorder, poses a challenge to physicians. There is a need to search for new and effective therapies. When our subjects initially presented with the first symptoms of disease, there was no noted association of any recent respiratory illness. However, subsequent questioning gave possible indications that some of the subjects had a prolonged respiratory ailment before their presentation with acne rosacea. It was hard to determine if this information was clinically reliable because it is possible that the information was offered to please the interviewer.

C pneumoniae is associated with asthma, chronic lung disease, and many other conditions. The organism's presence also has been found in atherosclerotic plaques.¹⁵ Our interest was in determining whether *C pneumoniae* plays an etiologic role in promoting chronic infection and inflammation in acne rosacea. Subjects were immediately treated with an oral course of azithromycin following the skin biopsy procedure (except subject 3). Azithromycin was chosen because it has been previously shown to be safe and effective in the treatment of acne vulgaris.

Of the 10 subjects in our study with acne rosacea, eight had at least one positive *C pneumoniae* test, suggesting a major role of *C pneumoniae* in acne rosacea. Serologic tests showed, as expected, no IgM for *C pneumoniae*, but an elevated IgG was demonstrated in 8 of 10 subjects. The subjects in which *C pneumoniae* antigen was detected by immunoperoxidase technique also were positive by serology. *C pneumoniae* was not detected in peripheral blood mononuclear cells (data not shown) using polymerase chain reaction. All samples contained DNA (β -globulin) as the internal control. Negative polymerase chain reaction findings were most likely caused by relatively high levels of red blood cells (known to be an inhibitory factor) in the samples. Subjects 1, 6, 8, and 10 had antigen-positive tissues. Subjects 1, 6, and 10 also had eye involvement, as well as *C pneumoniae* antibody by serology. Conjunctival disease often is associated with the more severe forms of the disease.

The favorable clinical response with azithromycin use in our study suggests the need for further investigation with clinical trials to study

long-term efficacy and tolerability. The precise role of *C pneumoniae*, which currently remains unknown, needs to be elucidated. The organism's presence in the skin lesions of some subjects with acne rosacea deserves larger scale investigation. Further studies will investigate eye secretions for local antibody production. Cultures and the use of nucleic acid amplification tests as diagnostic tests to detect the presence of organisms in the eye and other involved tissues will be employed. These approaches will provide crucial evidence to support that *C pneumoniae* plays a significant role in the clinical manifestation of acne rosacea.

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