

## Follicular contact dermatitis revisited: A review emphasizing neomycin-associated follicular contact dermatitis

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Received: June 9, 2014 Revised: September 19, 2014

Accepted: September 23, 2014

Published online: December 16, 2014

### Abstract

Follicular contact dermatitis clinically presents as individual papules that include a central hair follicle. Pathologic features involve the follicle and the surrounding dermis: spongiosis and vesicle formation of the follicular epithelium associated with perifollicular and perivascular lymphocytic inflammation. Using the PubMed database, an extensive literature search was performed on follicular contact dermatitis and neomycin. Relevant papers were reviewed and the clinical and pathologic features, the associated chemicals (including a more detailed description of neomycin), the hypothesized pathogenesis, and the management of follicular contact dermatitis were described. Several agents—either as allergens or irritants—have been reported to elicit follicular contact dermatitis. Several hypotheses have been suggested for the selective involvement of the follicles in follicular contact dermatitis: patient allergenicity, characteristics of the agent, vehicle containing the agent, application of the agent, and external factors. The differential diagnosis of follicular contact dermatitis includes not only recurrent infundibulofolliculitis, but also drug eruption, mite infestation, viral infection, and dermatoses that affect hair follicles. The primary therapeutic intervention for follicular contact dermatitis is withdrawal of the causative agent; treatment with a topical corticosteroid preparation may also

promote resolution of the dermatitis. In conclusion, follicular contact dermatitis may be secondary to allergens or irritants; topical antibiotics, including neomycin, may cause this condition. Several factors may account for the selective involvement of the hair follicle in this condition. Treatment of the dermatitis requires withdrawal of the associated topical agent; in addition, topical corticosteroids may be helpful to promote resolution of lesions.

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**Key words:** Allergic; Contact; Dermatitis; Follicular; Irritant; Neomycin; Papular

**Core tip:** Follicular contact dermatitis can be elicited by several agents and clinically presents as individual papules that include a central hair follicle. Pathologic features involve the follicle and the surrounding dermis. Hypotheses for the selective involvement of the follicles include patient allergenicity, characteristics of the agent, vehicle containing the agent, application of the agent, and external factors. The differential diagnosis includes dermatoses that affect hair follicles, drug eruption, infundibulofolliculitis, mite infestation and viral infection. Treatment with a topical corticosteroid preparation and/or withdrawal of the causative agent are therapeutic interventions for follicular contact dermatitis.

Cohen PR. Follicular contact dermatitis revisited: A review emphasizing neomycin-associated follicular contact dermatitis. *World J Clin Cases* 2014; 2(12): 815-821 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v2/i12/815.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v2.i12.815>

### INTRODUCTION

Contact dermatitis can be either allergic or irritant in eti-

ology. Follicular contact dermatitis is a variant of contact dermatitis that has been observed in individuals secondary to incidental exposure or patch testing to the eliciting agent. The allergens and irritants that have previously been reported to cause follicular contact dermatitis are summarized and neomycin-associated follicular contact dermatitis is emphasized.

## CLINICAL MORPHOLOGY AND SYMPTOMS OF FOLLICULAR CONTACT DERMATITIS

Follicular contact dermatitis is usually characterized by individual papules that include a central hair follicle. However, prominent hairs within the papules may not be readily visible when the lesions surround vellus hairs<sup>[1]</sup>. The papular lesions are frequently pruritic and occasionally painful or burning. The individual lesions have also been described as poral<sup>[2,3]</sup> or acneiform<sup>[1]</sup>. In addition, the clinical spectrum of follicular contact dermatitis also includes follicular-based pustules<sup>[3]</sup>.

## PATHOLOGY OF FOLLICULAR CONTACT DERMATITIS

Microscopic examination of the perifollicular papule is similar, regardless of the eliciting contactant. The pathologic changes involve the follicle and the surrounding dermis. There is often spongiosis and vesicle formation of the follicular epithelium or the eccrine sweat ducts or both. In the dermis, predominantly lymphocytic inflammation is noted around the periadnexal vessels, the follicle and/or the eccrine pore. Importantly, the epithelium adjacent to the follicle or pore is normal in appearance<sup>[1-12]</sup>.

## ALLERGIC CONTACT DERMATITIS AND TOPICAL ANTIBIOTICS

Allergic contact dermatitis to topical antibiotics is a relatively common phenomenon. The North American Contact Dermatitis Group reported that among patients referred for patch testing, during 1985 to 2004, the prevalence of allergic contact dermatitis to neomycin ranged from 7.2 to 13.1 percent<sup>[13]</sup>.

Allergic contact dermatitis to topical antibiotics is most commonly observed in certain at-risk populations. These include patients with chronic eczematous dermatoses (such as atopy and stasis dermatitis), chronic otitis externa, chronic venous insufficiency, and post operative or post traumatic wounds. In addition, an occupational risk to develop allergic contact dermatitis to antibiotics occurs more frequently in those individuals who handle them regularly, such as farmers, health care workers, pharmaceutical employees, and veterinary surgeons<sup>[13]</sup>.

## CHEMICALS CAPABLE OF ELICITING FOLLICULAR CONTACT DERMATITIS

Several chemicals, including topical antibiotics, have been described in either individual reports or larger studies to elicit follicular contact dermatitis. The agents associated with the development of follicular contact dermatitis can be allergens (Table 1)<sup>[1-10,14-21]</sup> or irritants (Table 2)<sup>[4,5,11,22-28]</sup>. Several metals have been associated with follicular patch test reactions: chromium, cobalt, copper, fluoride, and nickel<sup>[3,29]</sup>. Allergic and non-allergic development of follicular contact dermatitis has also been observed following exposure to tocopheryl linoleate, a vitamin E derivative<sup>[4,5]</sup>.

### Neomycin-associated follicular contact dermatitis

**Neomycin-drug characteristics:** Neomycin is produced by the growth of *Streptomyces fradiae*. It is an aminoglycoside antibiotic. Its efficacy as an antimicrobial is based upon the drug's ability to irreversibly bind to the 30S ribosomal RNA subunits and inhibit bacterial protein synthesis<sup>[13,30-32]</sup>.

Neomycin can be used as a topical antibiotic and has activity against many aerobic Gram-negative organisms (except *Pseudomonas aeruginosa*). It is also effective against some aerobic Gram-positive bacteria including *Staphylococci*. However it is not effective against *Streptococci*<sup>[13,30-32]</sup>.

Neomycin is usually formulated commercially as 20% neomycin sulfate in a petrolatum vehicle. However, it is often combined with other topical antibiotics such as bacitracin zinc and polymyxin B sulfate. This is done to expand the antimicrobial coverage<sup>[13,30-32]</sup>.

**Neomycin-clinical presentation:** The woman in Figures 1-4 developed follicular contact dermatitis to an antibiotic ointment that contained neomycin sulfate in combination with bacitracin zinc and polymyxin B sulfate. Indeed, individual hair follicles were observed in the center of the papular lesions (Figure 4). Allergic contact dermatitis has been reported to all three components of this antibiotic<sup>[33-35]</sup>. However, follicular contact dermatitis has only been described in association with neomycin.

**Neomycin-prior observations:** Allergic contact dermatitis to neomycin was initially reported in 1952<sup>[36]</sup>. Six years later, in 1958, Epstein<sup>[9]</sup> described contact dermatitis to neomycin as "...an aggravation or "irritation" of a pre-existing dermatitis..." and not the obvious picture of an acute contact dermatitis. He considered it to represent a dermal contact sensitivity reaction<sup>[9]</sup>. The lesions elicited by patch testing clinically presented as papules and histologically demonstrated an intact epidermis with pathologic changes in the dermis<sup>[9]</sup>.

Subsequently, Jillson *et al*<sup>[7]</sup> reported contact dermatitis to neomycin in 10 patients with atopic dermatitis. One of the patients, a 50-year-old woman had an eczematous dermatitis of her left flexor arm for which prior treatment with neomycin ointment had irritated the dermati-

**Table 1 Agents associated with allergic follicular contact dermatitis**

Agent	Comment	Ref.
Ammonium fluoride	A farm helper who sprayed trees with chemical and had an exudative dermatitis and a postal employee with right foot and bilateral popliteal dermatitis; patch test showed folliculoporal reaction	[2]
Chromium trioxide	A shoe-shiner with severe hand dermatitis, a plasterer who worked with cement (after a cast had been applied to his hand to treat a fracture), and an electrician with chronic dermatitis flared when he drilled through aluminum coated with zinc chromate primer; all had a folliculoporal patch testing reaction	[2]
Cobalt chloride	103 follicular patch test reactions in 853 heavy metal workers that were tested	[3]
Colored permanent pressing sheets chemical	Sheets were 50% cotton and 50% polyester; widely disseminated erythematous follicular keratotic papules; primarily on hairy areas with a predominance on legs and forearms. Several washings of sheets did not prevent dermatitis; it persisted up to 8 wk after sheets removed	[10]
Copper sulfate	110 patients patch tested; 8 of 69 who reacted had follicular or poral (folliculoporal) reactions	[2]
Cosmetic creams	5 young women in a 3 mo period; at sites where cream applied following bathing or before sun exposure: extensor limbs (with well developed vellus hairs) were greatly affected	[1]
Dander (human)	Patch test reactions to dander histologically showed eczematous changes in the upper parts of hair follicles and clinically consisted of erythema and papules; they were positive in 120 of 181 atopic patients, 2 of 28 allergic contact dermatitis patients, and 1 of 31 normal controls	[14]
Formaldehyde	A postal employee with right foot and bilateral popliteal dermatitis; patch test showed folliculoporal reaction 2 women developed textile contact dermatitis to a new long sleeved shirt and new pajamas; a hair usually pierced the center of the papular lesions Positive patch test reactions frequently showed a follicular pattern; in some patients, only bright red follicular papules set in a background of normal appearing skin	[2,8,15]
Homomenthyl salicylate	Sunscreening chemical in a suntan lotion; 2 women with follicular dermatitis. One of the woman developed consort allergic contact dermatitis from contact with her boy friend who used the lotion; she was originally misdiagnosed as having recurrent disseminated infundibulofolliculitis	[6]
Methyl glucose sesquistearate	Follicular dermatitis developed to both a lotion and facial cream that contained this chemical	[16]
Neomycin	Repeat topical application on abdomen (current report) and patch test reaction (woman with atopy and left arm dermatitis that flared after applying neomycin ointment	[7,9]
Nickel sulfate	A farm helper who sprayed trees with chemical and had an exudative dermatitis; patch test showed folliculoporal reaction 29 follicular patch test reactions in 853 heavy metal workers that were tested Female production line worker with dermatitis of hands, chest and face after exposed to metals and cutting fluids and patch test positive to nickel; she developed follicular contact dermatitis in her pubic area 2 d after shaving with a metal razor blade	[2,17,18]
Paraphenylenediamine	An atopic woman with recurrent episodes of follicular-based pruritic papules on her face, chest and back beginning 3 wk after starting daily oral hydrochlorothiazide; she had a similar dermatitis after contact with "black hair dye" and positive patch test reaction to paraphenylenediamine (which cross reacts with her new oral antihypertensive)	[19]
Polyoxyethylene laurylether	An emulsifier (and an addition of lauryl alcohol and ethylene oxide) used in cosmetics. A woman developed pruritic follicular facial papules after starting to use new cosmetics; both a use test and a patch test for polyoxyethylene laurylether showed a follicular papular reaction	[20]
Potassium dichromate	61 follicular patch test reactions in 853 heavy metal workers that were tested	[3]
Selenium salts	In glass industry, 4 employees exposed to barium and sodium selenite suffered from dermatitis and/or conjunctivitis; 2 of the patients developed follicular allergic contact dermatitis with papulo-follicular lesions. Patch testing with sodium selenite confirmed the diagnosis	[21]
Sodium tungstate	3 follicular patch test reactions in 853 heavy metal workers that were tested; heavy metal contains about 90% tungsten carbide	[3,18]
Tocopheryl linoleate	Vitamin E derivative added to base formulation of a cosmetic line in Switzerland; 905 patients with papular and follicular dermatitis. Positive patch test reactions to cosmetics and vitamin E linoleate	[4,5]

tis<sup>[7]</sup>. Patch testing to neomycin ointment "...was characterized by multiple small (papules of) eczematous areas rather than a confluent eczematous plaque<sup>[7]</sup>".

The patient in Figures 1-4 developed allergic contact dermatitis to neomycin. Her initial lesions were perifollicular papules. Some of these subsequently developed into confluent plaques.

## PATHOGENESIS OF FOLLICULAR CONTACT DERMATITIS

Several hypotheses have been suggested for the selective involvement of the follicles in follicular contact dermatitis in contrast to the diffuse clinical changes more fre-

quently observed in allergic or irritant contact dermatitis. These include direct penetration of the stratum corneum by the agent *via* the pilosebaceous apparatus, hapten conjugation of the agent to a substance only present in the infundibular region, or both<sup>[6]</sup>. Other factors may also influence the development of follicular contact dermatitis.

### Patient allergenicity

Previously individuals with atopy were considered less likely to be susceptible to allergic contact dermatitis. However, several subsequent studies have demonstrated that atopic patients not only develop contact dermatitis to metals<sup>[37]</sup>, but also more commonly develop follicular contact dermatitis<sup>[38,39]</sup>. Hence, the patient's diathesis to allergens may influence whether they develop follicular

**Table 2 Agents associated with irritant follicular contact dermatitis**

Agent	Comment	Ref.
Beetle toxin	Pederin toxin released as a defensive mechanism from the rove (staphylinid) beetle in hot tropical and moderate climate regions typically limited to uncovered body areas	[22,23]
Bis-hydroxyethyl-tallow amine	Antistatic agent used to impregnate plastic tote boxes; outbreak of the hand or arms of 48.3% (14 of 29) of employees of the incoming inspections department of a microelectronic plant. The chemical provoked both follicular and nonfollicular irritant dermatitis; it was also a potential skin sensitizer	[24]
Coal-tar products	Hand dermatitis presenting with follicular papules and pustules at the site of exposure to coal-tar oils, creosote, pitch	[25]
Croton oil	Occupational source for irritant pustular and follicular irritant contact hand dermatitis	[25]
Debromoaplysiatoxin	Occurs after swimming in water contaminated by sea algae ( <i>Lyngbya majuscula</i> Gomont); the alga cause a seaweed dermatitis in persons swimming off the coast of Oahu, Hawaii. Topical application of the toxin produces an irritant pustular folliculitis	[26]
Fluorine	Antirust solution containing 20% ammonium bifluoride diluted in water; acute irritant contact dermatitis in an atopic child. Rusted buckles of the right shoe cleaned with solution; 12 h later, the 19-mo-old boy developed an erythematous pustular dermatitis on the areas of the treated buckles	[27]
Greases	Occupational source for irritant pustular and follicular irritant contact hand dermatitis	[25]
Naphthalenes	Occupational source for irritant pustular and follicular irritant contact hand dermatitis	[25]
Petroleum	Hand dermatitis presenting with follicular papules and pustules at the site of exposure to petroleum derivatives: crude oil and fractions, cutting oils; lesions develop at the contact site to oil-soaked and tar-soaked clothes	[25]
Propylene glycol	It is used as a solvent, a plasticizer, a component of household products, a food additive and an ingredient in cosmetics and pharmaceutical preparations. 45138 patients patch tested; only 1044 (2.4%) patients with actual allergic contact dermatitis and 43 (0.10%) patients with non-allergic follicular reactions	[28]
Tri-phenyl-tin-fluoride	It is a bioactive organo-tin compound used as agricultural fungicides, general biocides, bactericides, herbicides, insecticides and antifoulant in boat paints (ship bottom coatings); it is moderately toxic to the skin. The patient's forearm accidentally contacted an empty drum that was still contaminated with the chemical; within 2 d he developed multiple follicular keratosis-like red papules evenly distributed over the affected area	[11]
Tocopheryl linoleate	Vitamin E derivative added to base formulation of a cosmetic line in Switzerland; 905 patients with papular and follicular dermatitis. In a few patients, the skin reaction appeared after a few applications on discontinuous days or more rarely after a single application suggesting an irritation reaction	[4,5]



**Figure 1** Neomycin-associated follicular contact dermatitis presenting as follicular papules on the right abdomen, in and around the umbilicus, and the suprapubic region. The patient is a 59-year-old Asian woman who presented with itchy lesions at the sites of prior incisions on her lower abdomen. Her past medical history was significant for stage I, T2N0M0 adenocarcinoma of the sigmoid colon. Her tumor was successfully managed by a laparoscopic anterior resection of the sigmoid colon.

contact dermatitis<sup>[17]</sup>.

### Characteristics of the agent

Heavier molecules are less easily capable of penetrating the epidermis as compared to lighter molecules. Hence, it can be hypothesized that the heavier molecules exhibit a preference for entering the dermis through the pilosebaceous units of hair follicles. For example, cobalt demonstrates an increased number and severity of contact dermatitis reactions at follicles<sup>[3]</sup>. Neomycin, is a larger

molecule than cobalt; therefore, the size of neomycin may account for the observed follicular contact dermatitis to this agent (Figures 1-4).

The concentration of the agent can also influence a predilection for follicular contact dermatitis. Not only cobalt, but also tungstate shows an increase in follicular reactions at higher concentrations<sup>[3,18]</sup>.

### Vehicle containing the agent

Lipophilic irritant agents absorb through the pilosebaceous apparatus<sup>[40]</sup>. However, water-soluble substances penetrate more easily into and around hair follicles<sup>[3]</sup>. Yet, in patch test reactions to metals, follicular contact dermatitis is more common when the testing vehicle is petrolatum as compared to water<sup>[3]</sup>.

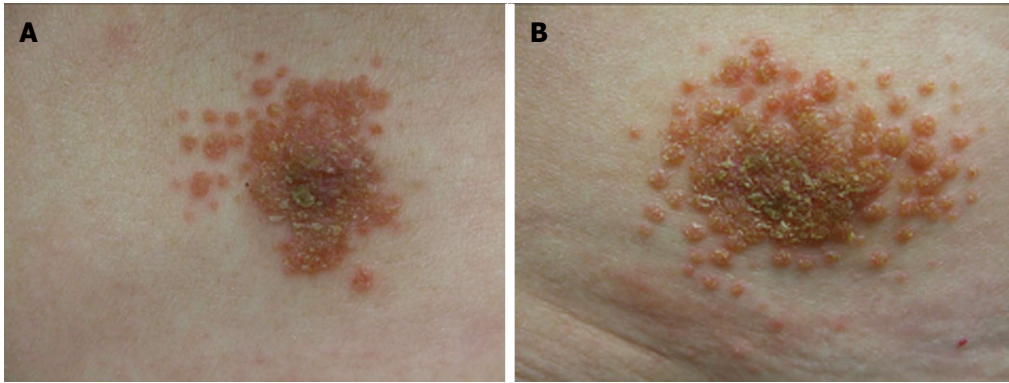
### Application of the agent

Not only in patch testing, but also in clinical use features regarding the application of the agent can potentially influence the occurrence and severity of follicular contact dermatitis<sup>[41,42]</sup>. It is reasonable to hypothesize that repeated application and occlusion of the agent may allow for greater contact with larger areas of epithelium instead of only the follicles, resulting in a more confluent dermatitis. Therefore, follicular reactions are less likely to occur when the agent is applied more frequently or is occluded.

### External factors

Follicular contact dermatitis to heavy metals was increased in individuals with hyperkeratosis of their hair follicles;

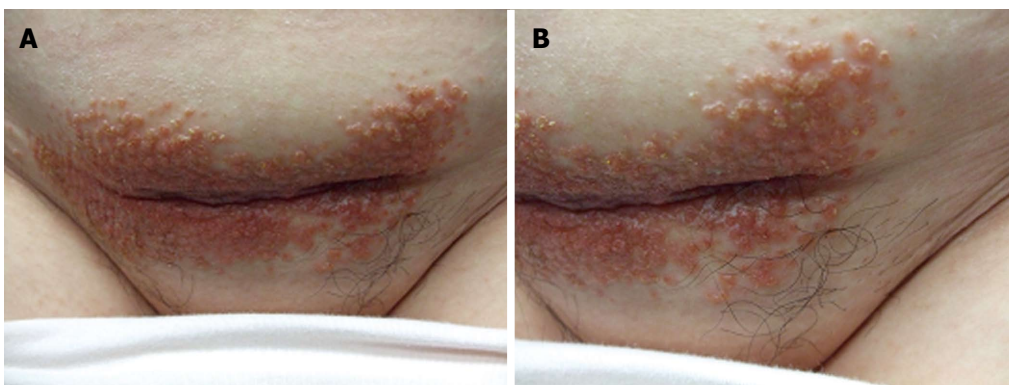




**Figure 2** Closer view of neomycin-associated follicular contact dermatitis on the right mid abdomen (A) and right lower abdomen (B). The woman noted, one month postoperatively, that there was still some drainage from her surgical wounds. She was instructed to daily clean the sites and apply an antibiotic ointment that contained neomycin sulfate, polymyxin B zinc, and bacitracin zinc (Neosporin ointment). She began to develop small individual lesions at the sites of antibiotic ointment application after 6 wk of daily topical treatment; however, she continued to treat the incision sites for another 4 wk as the individual lesions enlarged and some become confluent-before seeking medical attention.



**Figure 3** Cutaneous examination of her abdomen and suprapubic region (A) showed individual and confluent red-brown pruritic papules where she had been applying the antibiotic ointment to prior incision sites: right mid abdomen, right lower abdomen, umbilicus and periumbilical area (B, distant view and C, closer view) and suprapubic region.



**Figure 4** Distant (A) and closer (B) inspection, particularly of the lesion in her suprapubic area, showed individual hair follicles in the center of the papules. The topical antibiotic was discontinued and flucanide 0.05% cream was applied twice daily; all of the lesions resolved within 2 wk with residual post inflammatory hyperpigmentation at the sites.

however, it was not associated with either the presence of acne or sweating<sup>[3]</sup>. In contrast, not only sweating, but also pressure and friction contributed to the development of follicular contact dermatitis caused by a chemical in colored permanent pressing sheets<sup>[10]</sup>. These external factors enhanced the penetration of the allergen into the follicles of the patients who developed dermatitis<sup>[10]</sup>.

## DIFFERENTIAL DIAGNOSIS OF FOLLICULAR CONTACT DERMATITIS

Conditions to be considered in the differential diagnosis of follicular contact dermatitis are listed in Table 3<sup>[6,10]</sup>. Some of the patients with follicular contact dermatitis were initially considered to have disseminated recurrent

**Table 3 Clinical differential diagnosis of follicular contact dermatitis**

Drug eruption
Fiberglass dermatitis
Food allergy
Hyperkeratosis follicularis et follicularis in cutem penetrans (Kyle's disease)
Infundibulofolliculitis
Keratosis follicularis (Darier's disease)
Keratosis pilaris
Perforating folliculitis
Pityriasis rubra pilaris
Scabies
Viral exanthema

infundibular folliculitis—even though they were Caucasian<sup>[6,10]</sup>. In contrast to follicular contact dermatitis which was characterized by severe itching or areas of erythema and oozing or both in some of the patients, infundibular folliculitis is typically observed in black patients as mild to moderately pruritic or burning, flesh colored, widely distributed, non-inflammatory follicular papules; the papules are typically refractory to treatment and the recurrent episodes persist for weeks to months before spontaneously resolving<sup>[43,44]</sup>.

An individual in whom infundibulofolliculitis was suspected presented with recurrent 2-mm erythematous follicular papules. She was a 24-year-old nurse whose skin eruption partially improved with topical corticosteroids and resolved when her boyfriend moved to another city. However, it recurred when he returned and they went to the beach. Subsequently, the diagnosis of consort follicular contact dermatitis to the homomenthyl salicylate in her boy friend's Coppertone sunscreen lotion was considered and confirmed by positive patch testing to the lotion; additional patch testing to each component of the lotion was only positive for homomenthyl salicylate<sup>[6]</sup>.

The other patients had been exposed to a chemical used in colored permanent-pressed sheets<sup>[10]</sup>. Not only the distribution and duration of the follicular contact dermatitis, but also the histopathology of the chemical-associated lesions were similar to those observed in individuals with infundibulofolliculitis. However several features permitted the patients with follicular contact dermatitis to be differentiated from those with infundibulofolliculitis: severe itching (as compared to mild or moderate pruritus), the presence of erythematous and even oozing areas (as compared to noninflammatory lesions) and a white patient population (as compared to occurring in African American individuals)<sup>[10]</sup>.

## MANAGEMENT OF FOLLICULAR CONTACT DERMATITIS

The primary management of follicular contact dermatitis is withdrawal of the causative agent. The skin lesions for many of the affected individuals either resolved spontaneously or following treatment with a topical corticosteroid preparation. However, in some of the patients

lesions either persisted or recurred even after elimination of the inducing chemical or repetitive washing of the eliciting item from the source of exposure; specifically, follicular contact dermatitis persisted up to 8 wk after exposure to chemical in colored permanent-pressed sheets had been eliminated and new lesions would appear even after the sheets had been washed 3 or 4 times<sup>[10]</sup>.

## CONCLUSION

Follicular contact dermatitis clinically presents as individual papules that include a central hair follicle. Pathologic features involve the follicle and the surrounding dermis: spongiosis and vesicle formation of the follicular epithelium associated with perifollicular and perivascular lymphocytic inflammation. Several chemicals, including topical antibiotics, can elicit follicular contact dermatitis—either as allergens or irritants. Neomycin-associated follicular contact dermatitis was initially reported in 1952. Subsequently, follicular contact dermatitis in additional patients treated with neomycin was observed and the diagnosis was confirmed by patch testing with the agent. Several hypotheses have been suggested for the selective involvement of the follicles in follicular contact dermatitis: patient allergenicity, characteristics of the agent, vehicle containing the agent, application of the agent, and external factors. The differential diagnosis of follicular contact dermatitis includes not only recurrent infundibulofolliculitis, but also drug eruption, mite infestation, viral infection, and dermatoses that affect hair follicles. Withdrawal of the causative agent is the primary therapeutic intervention for follicular contact dermatitis. In addition, treatment with a topical corticosteroid preparation may promote resolution of the dermatitis.

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