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

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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 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.

INTRODUCTION

Contact dermatitis can be either allergic or irritant in etiology.
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. The papular lesions are frequently pruritic and occasionally painful or burning. The individual lesions have also been described as poral or acneiform. In addition, the clinical spectrum of follicular contact dermatitis also includes follicular-based pustules.

**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 perifollicular vessels, the follicle, and/or the eccrine pore. Importantly, the epithelium adjacent to the follicle or pore is normal in appearance.

**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.

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.

**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) or irritants (Table 2). Several metals have been associated with follicular patch test reactions: chromium, cobalt, copper, fluoride, and nickel. Allergic and non-allergic development of follicular contact dermatitis has also been observed following exposure to tocopherol linoleate, a vitamin E derivative.

**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.

**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 Strep- tooccci.**

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.

**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. 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. Six years later, in 1958, Epstein 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. The lesions elicited by patch testing clinically presented as papules and histologically demonstrated an intact epidermis with pathologic changes in the dermis.

Subsequently, Jillson et al. 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 dermatitis.
A postal employee with right foot and bilateral popliteal dermatitis; patch test showed folliculoporal reaction

Ref. 103 follicular patch test reactions in 853 heavy metal workers that were tested

Comment A farm helper who sprayed trees with chemical and had an exudative dermatitis; patch test showed folliculoporal reaction

61 follicular patch test reactions in 853 heavy metal workers that were tested

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 | [2,8,15] |
| 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 | [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 lauryl ether       | 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 lauryl ether 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 selenium suffered from dermatitis and/or conjunctivitis; 2 of the patients developed follicular allergic contact dermatitis with papulo-follicular lesions. Patch testing with sodium selenium 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] |

Table 1 Agents associated with allergic follicular contact dermatitis

Tocopheryl linoleate

Table 1 Agents associated with allergic 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[17], but also more commonly develop follicular contact dermatitis[18,19]. Hence, the patient’s diathesis to allergens may influence whether they develop follicular contact dermatitis.

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 frequently observed in allergic or irritant contact dermatitis. These include direct penetration of the stratum corneum by the agent into the pilosebaceous apparatus, hapten conjugation of the agent to a substance only present in the infundibular region, or both[18]. Other factors may also influence the development of follicular contact dermatitis.
Cohen PR. Follicular contact dermatitis

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, precipitated coal tar, and pitch                                                                 | [25]        |
| Croton oil                | Occupational source for irritant pustular and follicular irritant contact hand dermatitis                                                                                                                                                                       | [25]        |
| Debrisoquin               | Occurs after swimming in water contaminated by sea algae (Lyngbya majuscule 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                  | Antitrust 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]        |
| Naphthalones              | 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 1, T2N0M0 adenocarcinoma of the sigmoid colon. Her tumor was successfully managed by a laparoscopic anterior resection of the sigmoid colon.

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[19]. 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[14, 18].

Vehicle containing the agent

Lipophilic irritant agents absorb through the pilosebaceous apparatus[19]. However, water-soluble substances penetrate more easily into and around hair follicles[19]. Yet, in patch test reactions to metals, follicular contact dermatitis is more common when the testing vehicle is petrolatum as compared to water[19].

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[41, 42]. 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;
however, it was not associated with either the presence of acne or sweating. 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. These external factors enhanced the penetration of the allergen into the follicles of the patients who developed dermatitis.

**DIFFERENTIAL DIAGNOSIS OF FOLLICULAR CONTACT DERMATITIS**

Conditions to be considered in the differential diagnosis of follicular contact dermatitis are listed in Table 3. Some of the patients with follicular contact dermatitis were initially considered to have disseminated recurrent...
CONTACT DERMATITIS

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, is 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.

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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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 Cauca-
sian. 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.

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.

The other patients had been exposed to a chemical used in colored permanent-pressed sheets. 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).

*Table 3  Clinical differential diagnosis of follicular contact dermatitis*
