

# Drug-Induced Acneform Eruptions: Definitions and Causes

Saira Momin, DO; Aaron Peterson, DO; James Q. Del Rosso, DO

Several drugs are capable of producing eruptions that may simulate acne vulgaris, clinically, histologically, or both. These include corticosteroids, epidermal growth factor receptor inhibitors, cyclosporine, anabolic steroids, danazol, anticonvulsants, amineptine, lithium, isotretinoin, antituberculosis drugs, quinidine, azathioprine, infliximab, and testosterone. In some cases, the eruption is clinically and histologically similar to acne vulgaris; in other cases, the eruption is clinically suggestive of acne vulgaris without histologic information, and in still others, despite some clinical resemblance, histology is not consistent with acne vulgaris.

Drugs are a relatively common cause of eruptions that may resemble acne clinically, histologically, or both. With acne vulgaris, the primary lesion is comedonal, secondary to ductal hypercornification, with inflammation leading to formation of papules and pustules. In drug-induced acne eruptions, the initial lesion has been reported to be inflammatory with comedones occurring secondarily. In some cases where biopsies were obtained, the earliest histologic observation is spongiosis, followed by lymphocytic and neutrophilic infiltrate. Important clues to drug-induced acne are unusual lesion distribution; monomorphic lesions; occurrence beyond the usual age distribution of acne vulgaris; sudden onset within days; widespread

involvement; and clearing of lesions when the drug is discontinued.<sup>1</sup>

## CORTICOSTEROIDS

It has been well documented that high levels of systemic corticosteroid exposure may induce or exacerbate acne, as evidenced by common occurrence in patients with Cushing disease.<sup>2</sup> Systemic corticosteroid therapy, and, in some cases, exposure to inhaled or topical corticosteroids are recognized to induce monomorphic acneform lesions.<sup>2-4</sup> Corticosteroid-induced acne consists predominantly of inflammatory papules and pustules that are small and uniform in size (monomorphic), with few or no comedones. Anti-inflammatory effects of topical corticosteroids may initially suppress inflammatory papules and pustules and decrease erythema; however, patients may experience dramatic flare-ups when the topical agent is discontinued.<sup>5,6</sup>

Percutaneous absorption of corticosteroid after topical application varies among individuals, vehicle formulations, and anatomic locations. The groin, neck, and face absorb increased amounts of topical corticosteroids and are more likely to develop local side effects.<sup>5</sup> Variable percutaneous absorption is caused by the thickness of the stratum corneum and its lipid composition.<sup>5,7</sup> Facial skin is more permeable, has a thin stratum corneum, and has

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*Dr. Momin is Dermatology Resident and Dr. Peterson is Traditional Rotating Intern, Valley Hospital Medical Center, Touro University College of Osteopathic Medicine, Las Vegas. Dr. Del Rosso is Dermatology Residency Director, Valley Hospital Medical Center, and Clinical Associate Professor, Dermatology, Touro University College of Osteopathic Medicine, Henderson, Nevada, and University of Nevada School of Medicine, Las Vegas.*

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*Correspondence not available.*

natural distribution shunts because of numerous sebaceous follicles, which allow more of the drug to penetrate to subepidermal structures.<sup>8</sup> There is a defective epidermal barrier in atopic dermatitis, and the penetration of topical corticosteroids is 2 to 10 times greater than that through healthy skin.<sup>5</sup>

Lesions of corticosteroid-induced acne and acne vulgaris appear to evolve differently based on histologic evaluation. In acne vulgaris, an observed early pathologic change is abnormal keratinization of the follicular epithelium. In acneform eruptions associated with corticosteroid use, early histologic changes are necrosis and rupture of a segment of the follicular epithelium, leading to perifollicular abscess that presents clinically as monomorphic inflammatory papules and pustules.<sup>9,10</sup> In acne vulgaris, the primary lesion is the comedone; however, comedones may also be present in corticosteroid-induced acne. It has been suggested that topical corticosteroids induce comedone formation by rendering the follicular epithelium more responsive to the comedogenesis.<sup>9,12</sup> Comedone formation occurs during a period of months and may evolve into the dominant lesion in the late stages of corticosteroid-induced acne.<sup>10,12</sup> Topical application of corticosteroids leads to increased concentration of free fatty acids in skin surface lipids and increased numbers of bacteria in the pilosebaceous duct.<sup>13,14</sup> Free fatty acids, formed in pilosebaceous ducts by breakdown of triglycerides in the sebaceous secretion, may contribute to comedogenesis.<sup>13</sup>

Tagami<sup>15</sup> reported a case of an acneform eruption that appeared unilaterally on the face of a middle-aged woman approximately one month after the start of oral corticosteroid therapy for facial paralysis. It was proposed that the resultant lack of facial muscle movement due to Bell palsy played a role in the pathogenesis of acneform lesions. Normal facial movement, which would promote a constant outflow of sebum from the lumen of the sebaceous follicles, was lacking on the paralyzed side.

## EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Epidermal growth factor receptor inhibitors (EGF-RIs) are a group of medications used for therapy of advanced stages of several forms of cancer. Epidermal growth factor receptors (EGF-Rs), also known as HER1 or ErbB1, are overexpressed in many tumors and play a role in the development and progression of cancer, especially solid tumors of the head and neck, lung, breast, ovary, prostate, and colon. In cutaneous locations, including epidermal keratinocytes, sebocytes, and the outer root sheath of hair follicles, EGF-Rs are expressed normally and are involved in normal cell growth and differentiation.<sup>16</sup> Gefitinib and erlotinib are small-molecule EGF-RIs that selectively inhibit the tyrosine kinase activity of the intracellular domain,

preventing autophosphorylation and subsequent activation of signaling cascades. Cetuximab, trastuzumab, and panitumumab (ABX-EGF) are monoclonal antibodies that bind to the extracellular domain of the EGF-R, blocking activation and signal transduction of the receptor.<sup>16,17</sup>

Cases have been reported of acneform eruptions in patients receiving EGF-RIs. During trials, acneform eruptions were seen in 66% of patients with use of gefitinib, 75% of patients with erlotinib, and 86% of patients with cetuximab. These reactions generally appeared after 7 to 14 days of treatment, with acneform eruptions occurring on seborrheic areas such as the face, neck, retroauricular area, shoulders, upper trunk, and scalp.<sup>16,17</sup> The skin lesions consist of erythematous follicular papules and pustules that may coalesce to form lakes of pus that evolve to form yellow crusts. The skin lesions are not preceded by visible comedones, and, in contrast to acneform eruptions caused by other drugs, EGF-R-induced skin lesions may be accompanied by pruritus. Sometimes, spontaneous improvement can be seen even when treatment with the EGF-Ri is continued, but the patient may exhibit a flare-up following each subsequent administration.<sup>17</sup> Some studies have reported that there is a positive correlation between the presence and grade of cutaneous eruption and survival time.<sup>16</sup> Patients who presented with this type of acneform eruption had a significant increase in survival time than did those with no cutaneous reaction. Also, increase in the severity of the acneform eruption seemed to correlate with an increase in survival time.<sup>16,17</sup> Acneform eruptions have not been reported with inhibitors of other EGF-R family members such as trastuzumab, a monoclonal antibody against the HER2 receptor.<sup>17</sup>

Histopathologic evaluation of the acneform eruption seen with EGF-RIs is not consistent with that seen in acne vulgaris, demonstrating suppurative neutrophilic folliculitis and perifolliculitis preceded by early infiltration with T lymphocytes that surround the follicular infundibulum. Intraepidermal acantholysis is sometimes present. No comedone formation is seen.<sup>16,17</sup>

The pathogenic mechanism of acneform eruptions associated with EGF-RIs has not been firmly established. The cell-cycle inhibitor p27 may play a role because p27 is unregulated by the use of EGF-RIs.<sup>16</sup> Cell-cycle inhibitor p27 is a regulator that inhibits the actions of cyclin-dependent kinase CDK2, preventing progression from G<sub>1</sub> phase to S phase in the cell cycle. Increased expression of p27 results in alterations in cell growth and differentiation, leading to changes in the stratum corneum of the follicular infundibulum and resulting in hyperkeratosis, abnormal desquamation, follicular plugging with bacterial overgrowth, and development of acnelike lesions.<sup>16</sup> Although *Propionibacterium acnes*

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has not been found in the follicles of the patients with EGF-R $\alpha$ -induced eruptions, other microorganisms have been found in the plugged infundibulum, which may possibly induce an inflammatory response.<sup>16</sup> It is also possible that monoclonal antibody inhibitors themselves may induce an inflammatory reaction by the activation of neutrophils and complement through the binding of its Fc domain.<sup>16</sup>

Yalçin et al<sup>18</sup> reported a patient with non-small-cell lung carcinoma who developed an acneform eruption on the face, trunk, and upper extremities, sparing the region exposed to previous radiotherapy while on erlotinib treatment. Skin biopsies were performed from the spared previously irradiated skin and from neighboring affected nonirradiated skin. Histologic examination revealed suppurative folliculitis destroying follicular epithelium and adnexal structures in the nonirradiated skin specimens. Although eccrine glands and piloerector muscles were normal, there were no follicular structures identified in the previously irradiated skin specimens. No differences were noted between irradiated and nonirradiated skin in EGF-R expression with staining for EGF-Rs.

Imatinib (ST1571), a tyrosine kinase inhibitor, is well tolerated and has a significant antileukemic activity in patients with chronic myelogenous leukemia. Martin et al<sup>19</sup> reported a similar cutaneous eruption with imatinib treatment to those associated with other EGF-R $\alpha$ s.

### GRANULOCYTE COLONY-STIMULATING FACTOR

Granulocyte colony-stimulating factor (G-CSF), a potent stimulator of neutrophils, is an important treatment for significant neutropenia, especially in patients with cancer who are receiving chemotherapy. It has been reported that both G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) cause localized and generalized cutaneous eruptions mediated by neutrophils, and GM-CSF has been reported to cause widespread erythematous macules and papules.<sup>20</sup> Horn et al<sup>21</sup> showed that a perivascular infiltrate developed in skin from a patient undergoing chemotherapy that was incubated with GM-CSF. Lee and Dover<sup>20</sup> reported a case of a teenage boy who had a mixed germ cell tumor of the testis with metastasis, who underwent radical orchiectomy and was given chemotherapy and G-CSF. The patient experienced exacerbation of preexisting acne vulgaris correlating with the administration of G-CSF.<sup>20</sup>

### ANTI-TUMOR NECROSIS FACTOR- $\alpha$

Infliximab is a chimeric (mouse-human) monoclonal antibody targeting tumor necrosis factor (TNF)- $\alpha$ . Bassi et al<sup>22</sup> reported 2 cases where the patients receiving infliximab for Crohn disease and ankylosing spondylitis developed papules, pustules, nodules, and open and

closed comedones. Both patients had a predominance of noninflammatory acne lesions, and one patient also exhibited inflammatory lesions. The clinical appearance differed from that of monomorphic papules of corticosteroid-induced acneform lesions.<sup>22</sup> One case of a teenage boy with Crohn disease who developed severe nodulocystic acne after 3 perfusions of infliximab has been reported.<sup>22,23</sup> There was only one case of acneform eruption reported in a retrospective review of side effects in 73 infliximab-treated patients with psoriasis.<sup>22,24</sup> The mechanism of induced anti-TNF- $\alpha$  acneform eruption is unknown. Interleukin-1 $\alpha$ , TNF- $\alpha$ , and interferon- $\gamma$  may play a role in hypercornification of the infundibulum and/or innate immune response leading to inflammatory acne lesions, and, therefore, anti-TNF- $\alpha$  effects would be expected to improve rather than promote development of acneform lesions.<sup>22</sup>

### SIROLIMUS

Sirolimus is an immunosuppressive drug used after organ transplantation. The most common dermatologic side effects of sirolimus are pathologies of the pilosebaceous apparatus, chronic edema, angioedema, and mucous membrane disorders.<sup>25,26</sup> Mahé et al<sup>25</sup> described acneform eruptions in 45% of 80 patients soon after starting sirolimus, predominantly in men. In sirolimus-induced acneform eruptions, only inflammatory lesions that primarily involved the sebaceous regions were observed; however, lesions also frequently extended to the forearms, inner surface of the arms, cervical area, and scalp. A few patients were observed to have severely painful, nodular, edematous lesions on the neck and face.<sup>25,26</sup> Histologic examinations suggested nonspecific folliculitis.<sup>25</sup>

The role of sirolimus in the cause of acne may be due to direct toxic effects on follicles or its chemical toxic modification of sebum. The mechanism of acneform lesion development secondary to use of sirolimus is not known; however, it may be due to its effects on EGF and testosterone synthesis. Sirolimus inhibits EGF action by inhibiting the mTOR pathway. Testosterone upregulates EGF receptor synthesis, and sirolimus downregulates testosterone synthesis. Therefore, sirolimus might induce acneform lesions because of its direct inhibition of EGF action and may do so predominantly in men because of the downregulation of the EGF-R by testosterone suppression.<sup>25</sup>

### CYCLOSPORINE

The development of acneform lesions in organ-transplant recipients is common and has usually been attributed to the use of corticosteroids. Cyclosporine (CsA) is a potent immunosuppressive agent used after organ transplantation. There have been reports of cyclosporine-induced acneform eruptions. Highly lipophilic, one of CsA's

possible routes of elimination may be via the sebaceous gland, which is the major cutaneous site for the elimination of lipids through sebum, and the drug may modify the pilosebaceous follicles.<sup>27</sup>

El-Shahawy et al<sup>28</sup> reported a case of severe nodulocystic acne that rapidly and significantly improved after complete withdrawal of CsA. Azurdia et al<sup>29</sup> reported 3 white male patients who were treated with cyclosporine following organ transplantation, who developed acne keloidalis nuchae of the occipital scalp and nuchal neck.

## ANDROGENS AND ANABOLIC-ANDROGENIC DRUGS

The use of anabolic-androgenic steroids in the United States has increased markedly among athletes and those who want to rapidly build muscle. These agents initially produce a sense of euphoria, diminish fatigue, increase protein synthesis in skeletal muscle cells causing hypertrophy of striated muscle, and increase lean body mass.<sup>30,31</sup> Androgens stimulate the sebaceous glands, which leads to increased follicular keratinization resulting in comedone formation. High dosages of testosterone and anabolic-androgenic steroids can increase skin surface lipids, including cholesterol and free fatty acid levels, and increase the *P. acnes* organism population. Skin biopsy specimens after anabolic-androgenic steroid use show significant enlargement of sebaceous glands, especially with intramuscular anabolic-androgenic steroids.<sup>30,31</sup> The amount of free androgen in serum may have an important association with development of acne lesions, suggested by stronger enzymatic conversion to the more active dihydrotestosterone or increased receptor sensitivity toward androgens in the skin.<sup>32</sup> Administration of testosterone induced synthesis of androgen receptors in the sebaceous glands of the Syrian hamster and resulted in an increase in sebum production.<sup>33,34</sup>

Cutaneous signs are often the first clinical manifestations of anabolic-androgenic steroid use or abuse. Induction and worsening of acne is a commonly observed complication.<sup>35</sup> Anabolic-androgenic steroids can induce cystic acne, with onset sometimes months following cessation of drug intake.<sup>30</sup> Heydenreich<sup>35</sup> reported a case of acne fulminans caused by misuse of testosterone, anabolic steroids, or both. Traupe et al,<sup>33</sup> reported 3 cases of acne fulminans in tall boys following testosterone therapy.<sup>33</sup>

Oral preparations include methandrostenolone, ethylestrenol, stanozolol, fluoxymesterone, oxymetholone, and oxandrolone. Parenteral steroids include nandrolone phenylpropionate, nandrolone deconoate, testosterone enanthate, testosterone propionate, and testosterone propionate.<sup>30,31</sup>

## DANAZOL

An antigonadotropic agent with mild androgenic properties, danazol is useful in the treatment of pelvic and

ovarian endometriosis, sexual precocity, and hereditary angioedema. Danazol is a derivative of 17 $\alpha$ -ethinyl testosterone (ethisterone). It suppresses the pituitary-gonadal axis by diminishing the output of both follicle-stimulating hormones and luteinizing hormones from the pituitary gland. It does not seem to influence the secretion of other trophic pituitary hormones.<sup>36</sup>

Greenberg<sup>36</sup> reported a young woman who developed nodulocystic acne while being treated for endometriosis with danazol. There have been other reported cases of acneform eruptions induced by danazol.<sup>36</sup>

## LEVONORGESTREL IMPLANTS AND INTRAUTERINE DEVICES

Studies show increased acne development in women using levonorgestrel implants and in women using intrauterine devices. The tendency to notice increased acne eruptions was more pronounced for women who had previous problems with acne. The results of androgen determinations in women complaining or not complaining of increased acne during treatment with levonorgestrel implants is not a result of increased plasma levels of androgens, but rather a reflection of a different skin metabolism of and/or sensitivity to androgens among the susceptible women.<sup>37</sup>

## VALPROATE

Valproate is an antiepileptic drug used to treat epilepsy, bipolar disorder, and migraine cephalgia in reproductive-aged women. In women, many valproate users are reported to have isolated polycystic ovarian syndrome, such as elevated serum testosterone or luteinizing hormone concentrations.<sup>38</sup> Joffe et al<sup>38</sup> reported that new-onset oligomenorrhea with hyperandrogenism developed in 10.5% of women with bipolar disorder who were treated with valproate. The clinical features of hyperandrogenism are hirsutism, acne, male pattern alopecia, and elevated androgen concentrations.<sup>38</sup>

## AMINEPTINE

Cases of acneform eruption have been reported in association with use of amineptine, a tricyclic antidepressant.<sup>39,40</sup> Amineptine may induce a florid, retentional acnelike eruption with multiple comedones, microcystic lesions, and macrocystic lesions involving the face, ears, neck, trunk, and pubic area. Many reported cases involve adult women, and the severity of the cutaneous lesions is usually related to accumulated amineptine after chronic intake. Inflammatory lesions are usually absent or scarce, occasionally presenting as apparent secondary infection or inflammation associated with cystic lesions.<sup>39</sup>

Histologically, there is cystic dilatation in the ducts of the sebaceous glands with formation of keratin-filled

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comedones. Other changes observed with acneform eruption associated with amineptine occur in eccrine sweat glands, showing keratinizing syringometaplasia with areas of neutrophilic eccrine hidradenitis.<sup>39</sup>

The mechanism of action of amineptine-induced acneform eruption is unknown but likely the result of drug accumulation in the cutaneous glands.<sup>39,40</sup> Fazio et al<sup>41</sup> extensively studied skin lipids in a case of amineptine-induced acneform eruptions and demonstrated an elevated reduction of sebaceous lipid fractions in both cysts and skin surface lipids. Amineptine and its metabolites have been found in sebaceous and eccrine sweat glands.<sup>40,42</sup>

Because of the amphetaminelike properties of amineptine, it is abused by some patients, including the elderly. The abuse is facilitated by rapid tolerance to the drug and to the onset of withdrawal symptoms (eg, moodiness, agitation, insomnia) in the days immediately following discontinuation. Usually, the acneform eruption disappears when the drug is discontinued.<sup>43</sup>

Although apparently rare, other tricyclic antidepressants, such as maprotiline and imipramine, occasionally have been known to trigger acneform eruptions.<sup>40,43</sup>

### DACTINOMYCIN

Dactinomycin, used in the treatment of solid tumors, has been associated with occasional development of an acneform eruption. Blatt and Lee<sup>44</sup> reported a case of a prepubertal girl who received dactinomycin in combination with other chemotherapeutic agents that have not been implicated in the development of acne lesions. They noted a rise and fall of serum androstenedione, dehydroepiandrosterone, and testosterone levels over the period of time, defined by 2 courses of therapy inclusive of dactinomycin. A gradual improvement of the acneform eruption was noted as hormone levels diminished, which supports a relationship between drug exposure, the presence of the eruption, and hormone levels.<sup>44</sup>

Interestingly, dactinomycin shares a similar tricyclic structure with amineptine.<sup>44</sup> It is not clear whether dactinomycin directly stimulates androgen production or leads to an increase in adrenocorticotrophic hormone production by inhibiting activity of an enzyme along the cortisol synthesis pathway.<sup>44</sup>

### HYDANTOIN

A case of facial neonatal acne was reported in an infant with fetal hydantoin syndrome.<sup>45</sup> Hydantoin, which crosses the placenta, is reported to cause numerous skin reactions including hypertrichosis of extensor surfaces of the limbs and worsening of acne, which improves when the treatment is stopped. Treatment of pregnant women with systemic halogens and corticosteroids may result in neonatal acne vulgaris.<sup>45</sup>

A young white male was reported to develop acne keloidalis–like lesions on the central scalp while on treatment with diphenylhydantoin (phenytoin) and carbamazepine.<sup>46</sup> Firm, red papules, 0.5 cm in diameter, some coalescing into longitudinal plaques with scattered sterile pustular foci, were present clinically. Initial biopsy taken from a papule showed dense inflammatory infiltration composed of polymorphonuclear cells, lymphocytes, histiocytes, and plasma cells in the dermis. A subsequent biopsy showed marked fibrotic changes in the dermis. Withdrawal of carbamazepine with continuation of diphenylhydantoin for one year resulted in slowly progressive worsening of the skin disorder, despite treatment with topical corticosteroids. Progressive improvement was noticed only when diphenylhydantoin was also discontinued. Reinstitution of treatment with carbamazepine alone did not induce exacerbation.<sup>46</sup>

### LITHIUM CARBONATE

Lithium has been associated with various cutaneous side effects including acneform eruptions. It has been reported that nearly one half of male patients who were on lithium complained of acne as a secondary cutaneous reaction.<sup>47</sup> It appears that lithium may aggravate some cutaneous conditions that are associated with a prominence of neutrophilic infiltration and predisposes particularly to the development of acne vulgaris. Lithium may act as a triggering or aggravating factor.<sup>47</sup>

Two cases of acne papules and pustules on the face, neck, chest, groin, and axillae after treatment with lithium were reported.<sup>48</sup> In another report, 18 patients developed lithium-induced folliculitis located on the arms and legs.<sup>49</sup> In 4 female patients, exacerbation of acne on the face and neck was noted after lithium treatment.<sup>50</sup> A young female patient was reported to develop a severe acneform eruption on her face, chest, and back soon after she started taking lithium; however, comedone formation was not observed. Histopathologic examination revealed neutrophilic folliculitis, which was more consistent with folliculitis than with acne vulgaris.<sup>51</sup>

### DANTROLENE

Two cases of an acneform eruption, comprising primarily of open comedones, were reported in middle-aged women being treated with dantrolene for spasticity.<sup>52</sup> Histology of the skin showed keratin-filled cysts communicating with the epidermal surface. Besides the face, acne in both cases favored sites of chronic trauma and friction. Acneform eruptions in patients receiving dantrolene have been reported to exhibit a predilection for areas subject to pressure, such as the back and extensor aspect of the forearms.<sup>52,53</sup>

## ORAL ISOTRETINOIN

Tretinoin is known to be effective for the topical treatment of acne probably by decreasing retention hyperkeratosis and comedone formation and through downregulation of receptor-2, which is toll-like.<sup>54</sup> Isotretinoin (13-*cis*-retinoic acid) is a vitamin A analogue that has been shown to be remarkably effective in treating cystic acne and acne conglobata and has a profound suppressive effect on sebum secretion.<sup>54,55</sup>

Adverse cutaneous reactions to isotretinoin have been reported, including ulceration, hemorrhagic crusting, and tenderness of preexisting acne lesions.<sup>55</sup> The appearance of excess granulation tissue may resemble pyogenic granulomas underlying many of the crusts. The ulceration and crusting that occurred in these patients are similar to those seen in acne fulminans, but none of the patients experienced fever or arthralgias. Histologic evaluation showed foci of epidermal ulceration and a dense inflammatory cell infiltrate in the middle and upper dermis, consisting of numerous lymphocytes, plasma cells, and moderate numbers of neutrophils and eosinophils. In the middle and lower dermis, the connective tissue became denser and less infiltrated with inflammatory cells, but numerous fibroblasts were seen. The underlying pathophysiologic mechanism of the reaction is unknown. Skin fragility may occur in patients during treatment with isotretinoin and is associated with the loss of desmosomes and desmosomal attachments and with the accumulation of an amorphous material within the epidermis.<sup>55</sup> At sites of inflammation, this fragility may result in frank ulceration with subsequent crust formation.<sup>55</sup> A case of acne fulminans with severe myalgia believed to be precipitated by isotretinoin therapy has been reported.<sup>56</sup> Acne fulminans and bilateral seronegative sacroiliitis reported to be triggered by isotretinoin has also been described.<sup>57</sup>

Cystic acne and comedonal acne as side effects of etretinate therapy for psoriasis have also been reported.<sup>58,59</sup> Etretinate alters keratinization and cellular differentiation but appears to have little effect on sebum production.<sup>58,59</sup>

## ANTITUBERCULOSIS DRUGS

In 1959, isoniazid-induced acneform eruptions were reported to occur in 16% of 2600 patients receiving a combination of isoniazid and aminosalicylic acid; 11% of these acne patients were slow inactivators of the isoniazid.<sup>60</sup> In another report, 7 patients were noted to develop acneform eruptions associated with isoniazid therapy.<sup>61</sup> Five of these patients who had extensive eruptions were slow inactivators of isoniazid. Histologically, one case showed open and closed comedones and an absence of inflammatory infiltrate, which is reported to be characteristic of the early phase of isoniazid-induced

acne. A second biopsy specimen showed spiny follicular plugs consisting of *Demodex folliculorum* organisms, colonies of *Corynebacterium acnes* (*P acnes*), and an absence of inflammatory infiltrate. The third biopsy from a later phase of the eruption exhibited prominent inflammatory infiltrate, no comedones, and hyperplastic follicular epithelium, which are features compatible with those seen in the resolving phase of acne vulgaris.<sup>61</sup> The following factors should be considered in the diagnosis of isoniazid-induced acne: occurrence in older persons, absence of recent or remote history of acne vulgaris, and sudden, extensive efflorescence of lesions.<sup>61</sup>

Chronic papular acneform lesions of the face, neck, and shoulders have been observed in 8 of 24 men with genitourinary tuberculosis who were receiving rifampicin. Withdrawal of the medication led to disappearance of the skin lesions within 3 weeks. Ethionamide, thiacetazone, and prothionamide have also been reported to cause acneform eruption.<sup>62</sup>

## QUINIDINE

A case of numerous papules and pustules was reported to occur on the chest and back of a 57-year-old man who had a history of premature ventricular contractions soon after the initiation of quinidine therapy.<sup>63</sup> Quinidine therapy was continued, and excellent resolution of the eruptions occurred within 4 weeks of topical treatment with erythromycin solution and benzoyl peroxide. The lesions reappeared when his acne therapy was discontinued.<sup>63</sup>

## TACROLIMUS

Tacrolimus is a macrolide derivative that acts by blocking the calcineurin-dependent signal transduction pathway with strong T-cell-specific immunosuppressive activity.<sup>64,65</sup> Primarily used for treatment of atopic dermatitis, it has been used to treat other inflammatory and immunologic skin disorders, including vitiligo. A case of focal acne was reported during topical tacrolimus therapy for vitiligo.<sup>64</sup> Rosaceaform dermatitis has also been reported during treatment of facial inflammatory dermatoses with tacrolimus ointment.<sup>65</sup>

## BETA-BLOCKER

Dermatologic side effects from beta-blockers are reported to be extremely rare.<sup>66</sup> Facial acne was reported in a young adult with no history of dermatologic disease after starting propranolol for migraine prophylaxis.<sup>66</sup> The acne did not improve with treatment but resolved completely after discontinuing the propranolol. Facial acne reappeared a few weeks after starting nadolol for migraine prophylaxis and again resolved completely on discontinuation of the beta-blocker. The mechanism of acne of the beta-blocker-associated acneform eruption is not clear.<sup>66</sup>

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### ORAL DAPSONE

Acne fulminans and hemolysis were reported in a young female patient treated with oral dapsone.<sup>67</sup> This patient had preexisting mild acne vulgaris of the face and was given dapsone after poor response to oral tetracyclines. One week after starting oral dapsone, she had worsening of the lesions and developed facial pain and a low-grade fever. Some of the lesions had excoriated to form ulcers, others were crusted, and some were hemorrhagic. Comedones were not observed. Additionally, the patient was later diagnosed with dapsone-induced hemolysis. Dapsone was immediately stopped, and high doses of vitamin C and intravenous methylene blue were given, along with oral prednisone, and dramatic improvement of the facial acneform lesions was noted.<sup>67</sup>

### AZATHIOPRINE

One case of azathioprine-induced acneform drug eruption during treatment of multiple sclerosis was reported.<sup>68</sup>

### LAMOTRIGINE

Lamotrigine is used for the treatment of some forms of seizure disorder and bipolar disorder.<sup>69</sup> Two cases of lamotrigine-induced acneform eruption have been reported.<sup>69</sup> Acneform lesions developed on the back in both cases within a few months after the target dose of lamotrigine had been reached and while the patients received no other drugs. Resolution was noted without therapy when lamotrigine was discontinued. The 2 patients had prior treatment with lithium, but the eruptions did not develop until 1 to 2 months after lithium was discontinued. The possibility that the preceding treatment with lithium may be a related causative factor cannot be ruled out.<sup>69</sup>

### GOLD

A patient with rheumatoid arthritis first developed an eruption consistent with lichen planus and, subsequently, acneform lesions on the face and trunk after gold sodium thiomalate treatment.<sup>70</sup> Gold is retained in the body for a prolonged duration and is especially bound in the kidneys, liver, and skin.<sup>70</sup> Excretion of gold can be demonstrated in the urine for up to 12 months after discontinuing the treatment.<sup>70</sup> The patient had not taken any other drugs and did not come into contact with acneform materials; therefore, his acne was most likely provoked by gold.<sup>70</sup>

### PSORALEN-UV-A

Oral and topical methoxsalen (8-methoxypsoralen) with long-wave UVA is commonly used to treat psoriasis. A case of acne believed to be induced by psoralen-UV-A (PUVA) treatment has been reported.<sup>71</sup> The patient, with extensive psoriasis on PUVA treatment, had developed an

acneform eruption on the chest and back that consisted mainly of small, red, dome-shaped papules and a few comedones and pustules. A biopsy specimen of a papular lesion showed a dilated pilosebaceous follicle filled with inflammatory debris and keratin.<sup>71</sup> Perioral dermatitis was reported in 4 of 80 patients treated with PUVA, and 2 of these cases also had acneform eruptions localized to the forehead.<sup>72</sup>

Acnelike eruptions on the face, induced by light, were first described using the term *light-sensitive seborrhoid*.<sup>72,73</sup> The designation acne aestivalis (Mallorca acne) is used for a papular eruption occurring after intense sun exposure in an anatomic distribution characteristic of acne vulgaris.<sup>72,74</sup>

Acne usually improves during the summer with exposure to sunshine, although it may be aggravated in some patients, particularly in a hot and humid climate, possibly related to marked eccrine sweating. Patients undergoing PUVA treatment are usually irradiated in enclosed cabinets and cubicles in rather confined areas. Despite powerful extractor fans and fans incorporated in the cabinets and modules used, the temperature and humidity in these units are often high, and some patients sweat profusely. Other factors including the UVA light itself may contribute to the development of acneform eruption.<sup>71</sup>

### VITAMINS B<sub>6</sub> AND B<sub>12</sub>

A case of facial acneform eruption due to a megadose of vitamins B<sub>6</sub> and B<sub>12</sub> has been reported.<sup>75</sup> Histologic evaluation of a facial lesion was reported to show parakeratosis overlying a focally spongiotic epidermis. There was a mononuclear inflammatory infiltrate in the papillary dermis and in a perivascular location. When the patient was instructed to discontinue use of the nutritional supplement, there was dramatic improvement in the eruption.<sup>75</sup>

Exacerbation or onset of inflammatory acne related to vitamins B<sub>2</sub> (riboflavin), B<sub>6</sub> (pyridoxine), and B<sub>12</sub> (cyanocobalamin) have been reported in European literature.<sup>75</sup> The lesions of vitamin B-induced acne may occur as exacerbations of preexisting acne vulgaris, as new onset of multiple papules and papulopustules, or as an explosive pustular eruption involving the face. The pathogenesis is unknown, although it has been postulated that the origin of B<sub>6</sub>/B<sub>12</sub>-induced acne may be similar to that of isoniazid-induced acne.<sup>75,76</sup>

### TETRACYCLINE

A tetracycline-induced acneform eruption was first described in 1969.<sup>77,78</sup> A 30-year-old male patient was reported to develop an acneform eruption from tetracycline.<sup>78</sup> The patient was on tetracycline for infected

seborrheic dermatitis of the face and scalp and on prednisone for an unknown disease of the central nervous system. Multiple red, superficial follicular pustules of the neck, chest, back, and upper arms were noted. The eruption slowly resolved when both prednisone and tetracycline were discontinued. Although corticosteroid-induced acne may have been considered, one month later the patient was again started on tetracycline, and a similar eruption appeared on the same areas and slowly subsided after tetracycline was discontinued. Subsequent readministration of tetracycline one month later also provoked a similar eruption.<sup>78</sup>

### TETRAETHYLTHIURAM DISULFIDE

Tetraethylthiuram disulfide has been used extensively in the treatment of alcoholism. A repeated cystic acneform eruption of the face, anterior chest, and back, coincident with the ingestion of tetraethylthiuramdisulfide has been reported.<sup>79</sup> With each recurrent episode of acneform lesions, withdrawal of the drug repeatedly resulted in subsiding of the eruption.<sup>79</sup>

### HALOGENS

Iodides and bromides have been reported to induce a flare of inflammatory acne.<sup>80</sup> The mechanism is unknown but may relate to stimulation of neutrophil function. The most common sources of halogens are some thyroid medications, expectorants containing potassium iodide, contrast medium, iodized salt, vitamin and mineral preparations, and some sedatives.<sup>80,81</sup> The inflammatory eruption occurs in the typical acne areas (face and upper trunk), as well as elsewhere, commonly in an asymmetrical distribution pattern. Initial lesions are often follicular pustules, and later, comedonal lesions can emerge as a hyperkeratotic reaction to chronic inflammation.<sup>81</sup>

Chloracne is an acneform eruption resulting from marked exposure to halogenated aromatic compounds. The condition is a symptomatic marker for systemic poisoning.<sup>82</sup> It is difficult to treat and can last for long periods without known additional exposure to chloracnogens. The most sensitive areas of the human skin to chloracnogens are inferior to and lateral to the eye (malar crescent) and behind the ear. The genitalia, both penis and scrotum, are also sensitive regions. If sufficient exposure and toxic reaction have occurred, lesions may appear on the shoulders, chest, back, and, eventually, the buttocks and abdomen. The axillary regions have been commonly involved only in those patients who have ingested or inhaled the chloracnogens as the sole or major route of exposure. The primary lesion of chloracne is the comedone. In the most severe cases, the patients also manifest inflammatory lesions. Dioxins are also included on the list of halogenated compounds.<sup>82</sup>

### WHITE PETROLATUM

White petrolatum–induced unilateral acne developed in a young woman attempting to relieve the effects of Bell palsy by massaging her face nightly.<sup>83</sup> White petrolatum is thought to be noncomedogenic and safe to use in acne-prone skin. However, it may be occlusive and could cause a pustular reaction.<sup>83</sup>

### SUNSCREENS

Fourteen of 29 sunscreen formulations, including sun-tan promoters, were found to be comedogenic when applied to the external ear canal of albino rabbits.<sup>84</sup> It was reported that UV exposure enhanced the comedogenic effect. The vehicles, rather than the UV-absorbing compounds, seemed to be responsible.<sup>84</sup>

### COW UDDER OINTMENT

Two cases of widespread and atypical acneform eruptions were reported to be associated with use of cow udder ointment.<sup>85</sup> Cow udder ointment contains boric acid and starch in a wax and oil base. The patients were using the cow udder ointment for treatment of atopic eczema and psoriasis.<sup>85</sup>

### CONCLUSION

It is important to consider drug-induced acneform eruptions whenever a patient is being treated pharmacologically and recent onset or worsening of acne is apparent. Several medications have a proven causal relationship, with the percentage of patients affected exceeding 80%,<sup>16,17</sup> whereas other medications may have only a few reported cases. It can be concluded that nearly any medication used to treat almost any disease is a possible culprit, and with new medications being developed and implemented constantly, it is vital to recognize acneform eruptions and be able to differentiate them from other possibly unrelated eruptions. Although the mechanisms may vary considerably, the responsibility of dermatologists and the practitioners prescribing the medications is to familiarize themselves with the common offenders, recognize the common presentation and appearance of such an eruption, and determine if the side effect is acceptable in the overall success of the treatment desired. To better educate the medical community, every practitioner should assume the responsibility to report future cases with medications previously unknown to cause such eruptions.

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