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Chapter 5

Drug-Induced Acneiform Eruptions

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Abstract

Acne vulgaris is a chronic skin disease that develops as a result of inflammation of the pilosebaceous unit and its clinical course is accompanied by comedones, papules, pustules, and nodules. A different group of disease, which is clinically similar to acne vulgaris but with a different etiopathogenesis, is called “acneiform eruptions.” In clinical practice, acneiform eruptions are generally the answer of the question “What is it if it is not an acne?” Although there are many subgroups of acneiform eruptions, drugs are common cause of acneiform eruptions, and this clinical picture is called “drug-induced acneiform eruptions.” There are many drugs related to drug-induced acneiform eruptions. Discontinuation of the responsible drug is generally sufficient in treatment.

Keywords: acne, cutaneous toxicities, drug-induced acneiform eruptions, papule, pustule

1. Introduction

Acne vulgaris (AV) is a common skin disorder, which affects almost 85% of individuals at least once during life time. Although AV pathogenesis is not clearly understood yet, increased sebum production, androgenic hormones, ductal hypercornification, abnormal follicular keratinization, colonization of Propionibacterium acnes (P. acnes), inflammation, and genetic predisposition have been suggested to enhance acne development [1]. Hormone-dependent juvenile acne is a more frequent subgroup, whereas mechanical and drug-induced acne, which are particularly encountered during adulthood, are associated with the drug use with specific underlying etiologies [2]. Acneiform drug eruptions represent a sudden-onset clinical presentation, where the comedones are not observed [3]. In addition, several drugs are known to be associated with drug-induced acneiform eruptions [2]. In particular, the development of new target-specific molecules in the field of oncology, such as epidermal growth factor receptor inhibitors (EGFRIs), has caused a significant increase in the incidence of drug-induced acneiform eruptions [2, 3] (Table 1).
**Hormones**
- Oral, inhaled and topical corticosteroids
- Corticotropin (ACTH)
- Androgens and anabolic steroids
- Hormonal contraceptives
- Other hormones
  - thyroid-stimulating hormone, danazol

**Neuropsychotherapeutic drugs**
- Tricyclic antidepressants
  - amineptine, maprotiline, imipramine
- Lithium
- Antiepileptic drugs
  - hydantoin, lamotrigine, valproate
- Antipsychotics
  - aripiprazole
- Selective serotonin reuptake inhibitors

**Vitamins**
- Vitamins B1, B6, B12

**Cytostatic drugs**
- Dactinomycin (actinomycin D)
- Azathioprine, thiourea, thiouracil

**Immunomodulating molecules**
- Cyclosporine
- Sirolimus
- Others
  - topical tacrolimus, topical pimecrolimus

**Antituberculosis drugs**
- Isoniazid
- Rifampin (rifampicin)
- Ethionamide

**Halogens**
- Iodine
- Bromine
- Chlorine
- Others: halothane gas, lithium

**Miscellaneous**
- Dantrolene
- Quinidine
- Antiretroviral therapy

**Targeted therapies**
- Epidermal growth factor receptor inhibitors (EGFR inhibitors)
  - erlotinib, gefitinib, imatinib
- Epidermal growth factor receptor monoclonal antibodies
  - cetuximab, panitumumab
- TNFa inhibitors
  - lenalidomide
  - infliximab
  - adalimumab
- G-CSF
  - vemurafenib
- VEGF inhibitor
  - bevacizumab
This section focuses on the clinical and differential characteristics of drug-induced acneiform eruptions, drugs which may lead to this clinical presentation, and available treatment options in the light of the current literature data.

2. Clinical characteristics

Drug-induced acneiform eruptions may occur during childhood, adolescence, and adulthood. Lesions typically appear as monomorphic inflammatory papules and pustules without comedones or cysts. Papulopustular lesions usually involve on face, neck, chest, and upper back and can be extended beyond the seborrheic regions. Although its clinical course varies between patients, it often has a rapid onset without a previous history of AV. Papulopustular lesions may develop weeks, months, or even years after the exposure of the causative drug, and lesions may continue developing after the discontinuation of the drug [1].

3. Diagnosis and differential diagnosis

Diagnosis of drug-induced acneiform eruptions is not based on any specific criteria. There are some clue signs that may be helpful to differentiate this clinical presentation from other common skin disorders. The sudden onset and monomorphic character of the lesions, absence of comedones in general, the presence of lesions in regions where acne vulgaris is not commonly present, the development of lesions at any age, and the presence of a history of drug use were

<table>
<thead>
<tr>
<th>Drug-induced acneiform eruption</th>
<th>Acne vulgaris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomorphic lesions, lacking comedones, and cysts</td>
<td>Polymorphic lesions (mixture of comedones, papules, pustules, and nodules)</td>
</tr>
<tr>
<td>Extension beyond seborrheic areas to include arms, trunk, lower back, and genitalia</td>
<td>Localized primarily on seborrheic areas such as the face and neck and, less commonly, on the upper back, chest, and arms</td>
</tr>
<tr>
<td>Unusual age of onset (&gt;30 years)</td>
<td>Commonly affects adolescents and young adults</td>
</tr>
<tr>
<td>Resistant to conventional acne therapy</td>
<td>Improves with conventional acne therapy</td>
</tr>
<tr>
<td>Onset after drug initiation, improvement after drug withdrawal, or reoccurrence after drug reintroduction</td>
<td>No causative relationship to drug therapy</td>
</tr>
</tbody>
</table>

Table 2. Drug-induced eruption versus acne vulgaris [1, 3].

Proteasome inhibitor
- bortezomib
Histone deacetylase inhibitor
- vorinostat

EGF, epidermal growth factor; TNFa, tumor necrosis factor-a; VEGF, vascular endothelial growth factor; G-CSF, granulocyte colony-stimulating factor.

Table 1. Drugs involved with acneiform eruptions [2, 3].
the supportive findings and clues in the diagnosis. Clues, which may be helpful to differentiate drug-induced acneiform eruptions from idiopathic AV, are summarized in [1, 3] (Table 2). Cases that represent a diagnostic challenge should be extensively questioned with respect to medication history. Temporal relationship between the medication use and symptom development is very important [1].

4. Causative drugs

4.1. Hormones

4.1.1. Corticosteroids and corticotropin (ACTH)
Acneiform eruptions induced by the use of systemic corticosteroid therapy were first reported in 1950s [4]. Exposure to oral [5], intravenous [6], topical [7], or inhaled steroids [8] may result in or exacerbate acne. Development of acneiform eruptions was also reported during corticotropin therapy [4]. Perioral dermatitis is a form of acneiform eruption which may develop due to the use of highly potent corticosteroids [9]. During topical corticosteroid therapy, lesions may not become erythematous due to anti-inflammatory effects [10]. Although lesions usually begin to develop within 2–4 weeks after the administration of oral or topical therapy, they can also occur months after therapy. Dose, treatment duration, and individual factors may significantly affect the clinical presentation [2].

4.1.2. Androgens and anabolic steroids
Androgens are known to cause adolescent acne by increasing sebum production. In addition, anabolic steroids and synthetic hormones, which have androgenic activities, also show similar effects on the sebaceous glands [11]. In a prospective study, Fyrand et al. reported an increase in acne incidence among puberty-aged men who were administered injectable testosterones [12]. Moreover, acne incidence was also found to be higher among young athletes who used anabolic-androgenic steroids to increase their muscle mass [13].

4.1.3. Hormonal contraceptives
Hormonal contraceptive agents may induce or exacerbate acne [2]. A previous study demonstrated that 26.8% of women who used contraceptive etonogestrel implants developed acne [14]. Additionally, women who were placed a levonorgestrel-releasing intrauterine device developed inflammatory papular lesions 1–3 months after the procedure [15].

4.1.4. Other hormones
Danazole is an antigonadotropic agent used for the treatment of hereditary angioedema and endometriosis. Development of nodulocystic acneiform eruptions was previously reported in a woman receiving danazole therapy for endometriosis [16]. Thyroid hormones may also rarely result in acneiform eruptions [17].
4.2. Neuropsychotherapeutic drugs

4.2.1. Tricyclic antidepressants

Amineptine is one of the non-halogenated tricyclic antidepressants [3]. Amineptine may result in fast-onset acneiform eruptions consisting of macrocysts, microcysts, and comedones, months or even years after the initiation of therapy. Severity of the disease is associated with the dose and duration of therapy [1]. Amineptine and its products were found in serum, urine, and skin lesions, and histological examinations showed that this drug may result in keratinizing syringometaplasia in neutrophilic eccrine hidradenitis and eccrine glands [18]. Tricyclic antidepressants such as maprotiline [19] and imipramine [20] are also known to cause acneiform eruptions.

4.2.2. Lithium

Lithium may cause fast-onset inflammatory lesions on face, axilla, groin, arms, and buttocks. Lithium-induced acneiform eruptions are more frequent among men and those who are allergic to lithium [21]. No direct relation was shown between dose and severity of acne [2].

4.2.3. Antiepileptic drugs

Several antiepileptic agents were associated with drug-induced acneiform eruptions [22]. Phenytoin [23], phenobarbital [22], lamotrigine [24], and valproate [25] are among the most common culprits. Phenytoin is known to cross the placenta and cause acneiform eruptions, hypertrichosis, and gingival hyperplasia [26].

4.2.4. Aripiprazole

Aripiprazole is a quinolone-derivative antipsychotic drug reported to induce papulopustular acneiform eruptions in a patient 10 days after the initiation of therapy [27].

4.2.5. Selective serotonin reuptake inhibitors

All selective serotonin reuptake inhibitors may cause acneiform eruptions on the face, chest, and back regions [28].

4.3. Vitamins B1, B6 and B12

Acneiform eruptions characterized by monomorphic inflammatory papulopustular lesions localized on the face, neck, upper back, and chest may develop after the B12 injection therapy (Figure 1). The reason underlying this is not clearly known; however, the lesions rapidly disappear after discontinuation of therapy [29]. Several pharmaceutical preparations also involve B1 (thiamine) and B6 (pyridoxine) vitamins in addition to B12; however, the role of these vitamins in acne development is still controversial [30].
4.4. Cytostatic drugs

4.4.1. Dactinomycin (actinomycin D)

Dactinomycin, which is a cytostatic agent used for the treatment of solid tumors, is associated with acneiform eruptions. It has been suggested that dactinomycin induces acneiform eruptions through its androgenic characteristics and due to its tricyclic chemical structure [1].

4.4.2. Other cytostatic drugs

Although rare, the development of acneiform eruptions has been reported upon the use of azathioprine, thiourea, and thiouracil; however, the evidences are still limited [17, 31].

4.5. Immunomodulating molecules

4.5.1. Cyclosporine

Cyclosporine is an agent with immunosuppressive activity and it is used after organ transplantations and for the treatment of psoriasis and atopic dermatitis. As it is a highly lipophilic

Figure 1. Inflammatory papules and pustules on the chest after B12 injection treatment.
compound, it can potentially be eliminated through the sebaceous glands. Therefore, cyclosporine may induce acneiform eruptions by affecting the pilosebaceous follicle structures and functions [31].

4.5.2. Sirolimus

Sirolimus, which is an immunosuppressive agent used after organ transplantation, can result in acneiform eruptions [32]. Sirolimus is believed to exert toxic effects on the follicles and alter the sebum production and synthesis of epidermal growth factor (EGF) and testosterone [33]. In a prospective French study, acneiform eruptions were reported to develop in 46% of 80 patients who received sirolimus therapy after renal transplantation [34].

4.5.3. Other immunosuppressants

Tacrolimus is a macrolide-derivative agent with T-cell-specific immunosuppressive activity which blocks calcineurin-dependent-signaling pathway [3]. There are case reports indicating that topical tacrolimus [33] and pimecrolimus [35] may result in facial acne.

4.6. Antituberculosis drugs

4.6.1. Isoniazid

Isoniazid (INH) is a drug used for the treatment and prophylaxis of tuberculosis. It has been suggested that INH more easily results in acneiform eruptions in patients with slow acetylatoring phenotypes [3]. Previously, it was reported that acneiform eruptions might develop even 18 months after the initiation of INH therapy and disappear after the discontinuation of therapy [36].

4.6.2. Rifampin

Rifampin was associated with chronic papular acneiform eruption on face, neck, and shoulders, developing 5 weeks after the treatment onset [37].

4.6.3. Ethionamide

Ethionamide is an agent used for the treatment of tuberculosis and is associated with the development of acneiform eruptions [38].

4.7. Halogens

Iodide, bromide, and chloride are salt-containing drugs which result in iododerma, bromoderma, and chloracne, respectively. It has been suggested that these drugs induce acneiform eruptions, as they are eliminated via the sebaceous glands [1].

4.7.1. Iodine

Iododerma refers to the skin eruptions with different clinical presentations caused by oral, parenteral, or topical iodine administration. Lesions may be papular, pustular, or vesicular;
however, lesions in erythematous, urticarial, froncular, carbuncular, bullous, vegetating, or ulcerating pattern can also develop. Lesions beginning at the seborrheic region may extend to the whole body [2]. Although its pathogenesis is unclear, a suggested hypothesis includes cell-mediated immune reaction, inflammatory mechanism, and idiosyncratic reactions [39]. Discontinuation of iodine therapy is usually sufficient for symptom recovery, whoever the use of topical or systemic steroids may become necessary in severe cases [1].

4.7.2. Bromine

Although bromoderma is defined as skin eruption induced by bromide intoxication, it is not frequent at the present. Currently, several drugs with sedative, anti-epileptic, spasmolytic, and expectorant activities contain bromide [40]. Bromoderma clinically resembles iododerma and its diagnosis can be confirmed by increased serum and urine levels of bromide [41].

4.7.3. Chlorine

Acneiform eruptions may develop due to skin exposure to various industrial chemicals such as chlorine and its products. These chlorinated hydrocarbons result in the presentation of chloracne, characterized by cysts, pustule, folliculitis, and comedones [42]. Lesions usually develop at malar, postauricular, axillary, and genital regions, but may extend further [43]. Chloracne treatment is challenging and the lesions may continue developing for a long time, despite avoiding exposure to chloracnegens [44].

4.7.4. Other agents

Halothane is a halogenated anesthetic gas which may result in the development of acneiform eruptions hours after the exposure of the administering health-care personnel [45]. Lithium was reported to cause halogenoderma-like eruptions in two cases in the literature [46].

4.8. Miscellaneous drugs

Dantrolene is a muscle relaxant used for the treatment of spasticity. Dantrolene-induced acne consists of blackheads, comedones, cysts, pustules, and abscesses, and the lesions particularly localize at the regions exposed to chronic trauma, friction, and pressure. Lesions may develop 6 months to 4 years after the treatment onset [1].

Quinidine [47] and antiretroviral therapy [48] were also reported to cause acneiform eruptions.

4.9. Targeted therapies

Targeted therapies refer to a special group of medicines interacting with specific key molecules that play roles in the pathophysiology of inflammatory and tumoral diseases. This group of therapeutic agents includes tyrosine kinase inhibitors such as gefitinib, erlotinib, and imatinib, monoclonal antibodies such as cetuximab, panitumumab, and infliximab, soluble
antibodies such as etanercept, transcription modulators such as vorinostat, and proteosome inhibitors such as bortezomib [2].

Epidermal growth factor receptor (EGFR) inhibitors are chemotherapeutic agents used for the treatment of specific cancer types. Rapidly developing acneiform eruption has been a hallmark of EGFR inhibitor therapy [49]. Based on previously published series, 60–100% of patients receiving EGFR inhibitor therapy develop acneiform eruptions [49–52]. Monoclonal antibodies targeting EGFR, such as panitumumab, may also cause acneiform eruptions (Figure 2). Patients with a previous history of adolescent acne or folliculitis are more prone to acneiform eruptions and lesions commonly develop after the first cycle of therapy. Inflamed papules and pustules, accompanied by itching in seborrheic regions, are characteristic findings [3]. The development of acneiform eruptions after the EGFR inhibitor therapy was suggested to be a prognostic factor indicating good treatment response [53]. Incidence and severity of acneiform eruption are dose-dependent. Tetracycline derivatives may be used to control severe lesions [3].

Tumor necrosis factor (TNF) inhibitors are particularly used for the treatment of autoimmune disorders and they may also induce acneiform eruptions. Among this class of drugs, infliximab was the agent most frequently associated with acneiform eruptions [54]. The development of acneiform eruptions was also reported in a male patient receiving adalimumab therapy due to Crohn’s disease [55]. In addition, lenalidomide, a thalidomide derivative, was demonstrated to be associated with acneiform eruptions due to its anti-TNF activity [56].

5. Treatment

Drug-induced acneiform eruptions are usually well tolerated. The most important step of treatment is identification of the causative drug and discontinuation of treatment, whenever possible. Conventional acne therapy may be used, if the treatment cannot be discontinued; however, treatment resistance is a common concern. Oral antibiotics such as doxycycline can be used in moderate and severe cases. In more severe cases, oral isotretinoin may also be used under close monitoring and by avoiding potential drug interactions [1].

Figure 2. Severe acneiform eruption on the chest during therapy with panitumumab for metastatic colon cancer.
6. Conclusion

Drug-induced acneiform eruptions are frequently seen side effects, and it is difficult to prevent them. It should be kept in mind that many drugs could cause drug-induced acneiform eruptions in clinical practice, and it is important to obtain a detailed history of drug use in suspected cases for appropriate follow-up and treatment approach.

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