Stomatitis Medicamentosa—A Case Report

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Abstract

Mucosal allergies represent a growing problem and often go undiagnosed by health professionals. The prevalence of mucosal allergies due to drugs routinely prescribed in dental practice appears to be increasing. Ingestion of certain drugs by individuals with idiosyncratic reactions or intolerance may result in allergic manifestations referred to as stomatitis medicamentosa. The clinical features may vary from a burning sensation to ulcerative lesions in the oral cavity. These lesions resolve with discontinuation of the causative agent. However, antihistamines and steroids are the drugs of choice in severe cases. We describe herein the case of a 45-year-old woman with an allergic reaction to an Over-the-Counter drug, treated in the Department of Oral Medicine & Radiology at D.A. Pandu Memorial R.V. Dental College, Bangalore, India. The pathogenesis, clinical features, diagnosis and treatment are discussed.

Introduction

Drug allergy covers a variety of sensitivity reactions following exposure to drugs and chemicals, but is unrelated to any inherent pharmacological activity or toxicity of the material. Practically every known drug has been recognized at one time or another as capable of producing an allergic reaction in a sensitive individual (1)). Certain drugs, however, have a far greater propensity for producing reactions than others. It is impossible to list even a small portion of the overwhelming number of drugs that have been known to produce an allergic reaction (2). Several categories of allergic reactions have significant oral and facial involvements. These clinical entities are well defined and frequently described in the medical and dental literature (1, 2). The oral mucous membrane may be the sole site of involvement or may be part of a more generalized skin reaction to the offending drug. Mucosal allergies represent a growing problem and often go undiagnosed by health professionals(3). A mucosal allergic reaction caused by systemic administration of drugs is known as stomatitis medicamentosa. We present herein the case of a 45-year-old woman with acute allergic reaction in the oral cavity due to a Over-the-Counter drug.

Case report

A 45-year-old woman reported to the Department of Oral Medicine & Radiology at D.A. Pandu Memorial R.V. Dental College, Bangalore, India, with a 2-day history of a severe burning sensation in the oral cavity. Initially the patient experienced burning sensation within half an hour after administration of an Over-the-Counter drug (ibuprofen) she had obtained from the pharmacist for tooth pain. The burning sensation became suddenly and severely aggravated after administration of a second dose. There was no history of fever following administration of this drug. A history of disturbed sleep and difficulty swallowing due to the burning sensation was elicited. Her medical, dental and family histories were non-contributory. The patient was poorly nourished and of slight build, with no signs of anemia or icterus. No cutaneous or ocular lesions were apparent. Intraoral examination revealed multiple (10–12) ulcers at the vermilion border of the lower lip and angle of the mouth (Fig. 1). The ulcers were encrusted and showed varying

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sizes of 1-2mm. The dorsal surface of the tongue was coated with yellowish slough and movements of the tongue were restricted due to presence of ulcers on the tongue (Fig. 2). Similar ulcerative lesions measuring 1 × 2mm were seen bilaterally over the entire buccal mucosa. Mouth opening was restricted due to the presence of ulcers in the retromolar area. Based on the chief complaint and drug history, a provisional diagnosis of stomatitis medicamentosa was made. Differential diagnoses for the lesions included erythema multiforme (EM). Skin testing was performed on the inner surface of the patient’s forearm by intradermal inoculation of the suspected allergen (ibuprofen). Skin erythema was apparent at the site of inoculation within 20 min after inoculation. The patient was referred for further investigations, and peripheral blood smears showed an increase in relative eosinophil count to 15% (normal, 1-4%) using Wright’s stain to count the eosinophils. The erythrocyte sedimentation rate was higher than normal, at 57 mm/h (normal, 0-20 mm/h). Periodic acid Schiff staining of scrapings from lesions was non contributory. An increase in serum immunoglobulin (Ig) E levels to 1,120 IU/ml suggested a type I hypersensitivity reaction. Based on these investigations, skin test results and the elicited history, we reached a conclusive diagnosis of stomatitis medicamentosa. The patient was instructed to discontinue usage of the drug after diagnosing the condition and was later prescribed systemic steroids (prednisolone, 60mg/day) for 1 week along with topical antihistamines (benzydamine hydrochloride) and germicidal (chlorhexidine) mouthwash. To overcome complications associated with steroid use, the dosage was tapered to 30 mg/day after the first week. After 3 weeks of therapy, all lesions had completely resolved (Figs. 3, 4) and the patient was referred to an endodontist for evaluation of the tooth pain.

Discussion

The list of offending medications and their resultant side effects appears endless. In a short and highly beneficial article, Matthews listed more than 150 frequently prescribed medications and related them to 46 oral and perioral side effects (4). The oral mucosa is exposed to a wide range of ingested medications (5). However, immediate and severe reactions have been reported in the literature (4, 5).

Pathogenesis

The term "allergy" is used to define a specific immune reaction to one or more exogenous substances, termed "allergens". The immune system is made up of two functional components: an adaptive component; and an innate component (6). The innate immune system is situated in organs such as the skin and mucosa. When an antigen enters the body, specialized helper T-cells (Th cells) respond to foreign materials in two ways: Th1 responses; and Th2 responses. IgE is associated with Th2 responses,
which generally occur immediately after exposure. The clinical symptoms of IgE reactions are due to inflammatory Th2 cytokines (7). IgE antibodies also initiate a series of reactions that result in the release of inflammatory mediators, such as histamine, C-reactive protein and other chemicals from specialized cells called mast cells. The role of mast cells in allergic tissue inflammation is well recognized. Interleukin (IL)-4 in the presence of stem cell factor (SCF) regulates the functional status of mast cells and increases the release of IgE-dependent mediators (8, 9).

**Clinical Features**

Type I allergic reactions are characterized by Quincke’s edema (angioedema), which can become life threatening for patients if the upper respiratory tract becomes involved (10). Type I also cause urticarial reactions on the skin, in the form of erythematous papules accompanied by pruritus or a tingling sensation. However, none of these findings were observed in the present case. The affected mucosa exhibits a diffuse distribution of lesions varying in appearance from multiple areas of erythema, to extensive areas of erosion or ulceration (11). Patients will complain of a burning sensation with altered taste sensation and difficulty swallowing. Although the lesions of the oral cavity resembled EM clinically, this possibility was excluded as a diagnosis due to absence of target lesions. Biopsy was not performed in this patient, as the patient reported a severe burning sensation and because the majority of severe cases of toxic epidermal necrolysis are caused by drug reactions that usually result in sloughing of the skin and mucosa in large sheets (12). EM has been classified according to the degree of mucosal involvement and the nature and distribution of skin lesions. As the most common form, EM minor typically affects a single mucous membrane and may be associated with target lesions on the extremities (13). EM major is more severe, typically involving two or more mucous membranes with more variable skin involvement. This feature is used to distinguish EM major from Stevens-Johnson syndrome, which shows extensive skin involvement (13). The microscopic appearance of EM is not diagnostic. Although considerable variation occurs, corresponding to the variation in clinical appearance, cutaneous or mucosal lesions generally exhibit intracellular edema of the stratum spinosum of the epithelium and edema of the superficial connective tissue, which may actually produce subepidermal vesicles with varying degrees of inflammatory cell infiltration (chiefly by lymphocytes, but often including neutrophils and eosinophils) (14). Anaphylactic stomatitis arises after the drug enters the circulatory system and binds to IgE-mast cell complexes (15). Oral lesions may occur alone or in association with urticarial skin lesions or other signs and symptoms of anaphylaxis (such as...
hoarseness, respiratory distress and vomiting). The affected mucosa exhibits diffuse distribution of lesions, varying in appearance from multiple areas of erythema to extensive areas of erosion or ulceration. The histopathological features of anaphylactic stomatitis typically reveal a non-specific pattern of subacute mucositis that contains lymphocytes intermixed with eosinophils and neutrophils (15). Such reactions in the oral mucosa are considerably less common than cutaneous reactions, and present in various patterns. Common reactions produced in the oral cavity are stomatitis, ulceration, gingival hyperplasia, pigmentation, altered salivary function and altered taste sensation (15, 16). However, some authors believe that separation of these entities leads to unnecessary confusion and that terms like stomatitis medicamentosa should be discarded (16). The final diagnosis in this case was confirmed based on skin testing, increased eosinophil counts and an increased IgE level suggestive of anaphylactic reaction. Various tests can help in diagnosing type I hypersensitivity reaction, such as radioallergosorbent tests (RASTs) to detect the amount of IgE antibody reacting with the suspected or known allergen (17), leukocyte histamine release assays, surface markers for basophil activation and leukotriene release tests (18).

Mechanism of ulcer healing
Ulcer healing is a complex process that involves cell migration, proliferation, re-epithelialization, angiogenesis and matrix deposition leading to scar formation (19). All these processes are controlled by growth factors, transcription factors and cytokines. Granulation tissue develops at the ulcer base within 48–72 h after ulceration. Epithelial cells at the ulcer margin undergo dedifferentiation, express epidermal growth factors and start to actively proliferate. These cells migrate from the ulcer margin on to the granulation tissue to re-epithelialize the ulcer base. Granulation tissue consists of macrophages, fibroblasts and proliferating endothelial cells that form microvessels throughout the process of angiogenesis (20). The growth of these structures is stimulated by cytokines, IL-1 and tumor necrosis factor α. As the granulation tissue matures, it becomes more fibrous through condensation of collagen bundles and the surface of the lesion becomes epithelialized and leads to scar formation.

Diagnostic Testing
Diagnosis of an allergic reaction is typically based on the medical history, clinical findings and the results of patch testing. Some practitioners use patch tests to confirm the diagnosis of type IV allergic reaction. Limits exist to the utility of patch tests, due to their poor sensitivity and relatively high rate of false-negative results (21). The skin test (prick test) helps in diagnosis of type I allergic reaction. This test involves intradermal inoculation of suspected antigens. The results are then read within 15–30 min. If the result is positive, red, papular or vesicular reactions will be apparent on the skin. These tests are used in the diagnosis of drug and food allergies, which may manifest as ulcerative lesions of the oral mucosa (22).

Management
The causative agent should be discontinued and, if necessary, replaced with another drug that provides a similar therapeutic result. Mild localized lesions can be relieved by administration of topical cortisone or antihistamines, while secondary infection can be prevented by use of germicidal drugs. Generalized and severe lesions warrant the use of adrenaline or systemic steroids.

Conclusion
Almost all over-the-counter drugs are capable of causing adverse reactions. The oral manifestations of pharmacotherapy are often non-specific and vary in significance. These undesirable effects can mimic many disease processes. To avoid unnecessary diagnostic procedures and treatments, clinicians need to recognize the disorder to allow quick and accurate diagnosis.

References