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Carbamazepine-Induced Erythema Multiforme Major with Mucosal Involvement: A Case Report

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Abstract:
Erythema multiforme major is an acute immune mediated mucocutaneous disorder that is typified by high involvement of mucosal and targetoid skin lesions. The most frequent etiological agents are infections, though there are also some known medications that can cause an infection.
Carbamazepine, a widely used antiepileptic drug was found as a known but uncommon cause of EMM. Drug-induced EMM is a type of hypersensitivity reaction, which is characterized by cytotoxic immune reaction and causes keratinocyte damage. Early detection is vital, and timely removal of the causing agent greatly affects the prognosis and minimizes the chances of developing a higher level of cutaneous adverse reactions.
We describe a case of 21-year-old female who reported seizure disorder history and developed fever, pruritic skin lesions, and mucosal involvement soon after the start of carbamazepines treatment. Physical diagnosis showed several targetoid lesions with central hyperpigmentation as well as oral and ocular erosions. Laboratory results were mostly normal. A diagnosis of carbamazepine-induced EMM was made based on the typical clinical features. The offending drug was immediately discontinued and started on symptomatic therapy along with supportive care.
This report undelines the clinical importance of considering carbamazepine as a possible etiological agent in EMM as well as the importance of alertness in patients who present with acute mucocutaneous symptoms following recent drug exposure.

INTRODUCTION:

Erythema multiforme (EM) is an acute, immune-mediated hypersensitivity reaction, which mainly affects the skin and in more severe manifestations, the mucous membranes, characterized by the formation of bullous, papular, or macular lesions, often with characteristic target lesions, especially in the extremities [1]. It is widely divided into erythema multiforme minor and erythema multiforme major, the latter exhibiting a wider mucocutaneous involvement [2]. Although infections, particularly Herpes simplex virus, are most often the primary trigger, autoimmune, as well as drug-induced infections, though less common, are all clinically significant [2,3].
Antiepileptic drugs like carbamazepine are also identified as highly causative drugs and are linked to an extensive variety of cutaneous side effects, ranging between mild and eruptions to severe and potentially fatal diseases [5,7]. Carbamazepine is an anticonvulsant frequently prescribed in the treatment of epilepsy

and other nervous disorders [10]. It is thought to be mediated by a cell-mediated immune response in which cytotoxic T lymphocytes attack keratinocytes that have drug-relevant antigens on them, leading to epidermal damage and the formations of typical lesions [3,6]. These lesions are usually target-like (targetoid) in nature and can spread to mucosal surfaces in more severe cases [2]. Even though EM is considered to be self-limiting, erythema multiforme major may be linked with systemic manifestations and should be promptly diagnosed and treated [1]. It is important to differentiate prudently Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) since the conditions vary greatly in their severity, prognosis, and skin area involvement [2,7].
This report is an example of a case of carbamazepine-induced Erythema multiforme major in a young female, with special focus on clinical presentation, diagnosis and management of drug-induced hypersensitivity reactions.

CASE PRESENTATION:
A 21-year-old woman reported 7 days of having a headache and fever. She had a history of 10 years of epilepsy which was previously treated with levetiracetam (500 mg).
The patient had a breakthrough seizure ten days before presentation, and her antiepileptic therapy was changed to carbamazepine (200 mg). She experienced lesions of the oral caviy, lips, upper and lower limbs two days after carbamazepine was initiated. The lesions were first seen as erythematous macules and slowly evolved to fluid filled lesions especially around the lips and oral mucosa. They were linked to pruritic, erythematous papules all over the body, cracked lips, and excessive lacrimation.

Cutaneous examination showed several, well-defined, hyperpigmented plaques with surrounding erythema on bilateral upper and lower limbs, as well as foci of ulceration and crusting. Involvement was in both oral and conjunctival mucosa. Ophthalmological examination revealed eyelash matting with discharge and membrane peeling was carried out.

Laboratory tests showed an increase in the Erythrocyte sedimentation rate (35 mm/hr) which is an indication of an inflammatory process. Later reports revealed leukocytosis (15,600 cells/mm^3), which was indicative of a hypersensitivity reaction. The Absolute eosinophil count (AEC) and Antinuclear antibody (ANA) were within normal range and this helped to rule out other immune-mediated diseases. Abdominal Ultrasonography was normal.

A diagnosis of erythema multiforme major attributed to carbamazepine was established on the basis of clinical manifestations along with the temporal relationship between drug exposure and the onset of symptoms. Carbamazepine therapy was discontinued promptly, and symptomatic management was initiated with intravenous hydrocortisone in combination with oral cetirizine. Supportive care measures comprised the application of topical corticosteroids to skin lesions, administration of prednisolone acetate eye drops for ocular involvement, and the use of saline compresses supplemented with antiseptic treatment.
The patient had a considerable positive response to treatment and the pruritis and progressive application of lesions were managed. She was discharged with advice for follow-up after one week.

DISCUSSION:

Erythema multiforme major (EMM) is the more severe variant of the erythema multiforme spectrum, characterized by severe mucosal involvement and sometimes systemic manifestations [1]. The high rate of developing symptoms in less than two days with the initiation of carbamazepine, in this case, is a strong indicator of a drug-induced cause, which is consistent with what has been reported previously [4,8].

Carbamazepine is an aromatic antiepileptic medication commonly known to induce severe cutaneous adverse reactions (SCARs), such as Erythema multiforme, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [5,10]. The genetic factors that contribute to susceptibility to these reactions include possession of the HLA-B*15:02 allele, which has been linked with the increased risk in some groups of people [7].

The pathophysiology is a cytotoxic T cell-mediated delayed type IV hypersensitivity reaction-mediated reaction. These immunocytes attack keratinocytes that express the drug-related antigens and this causes apoptosis and further epidermal damage [3]. This process clinically leads to the development of typical target-like lesions, with involvement of mucosa observed in more severe cases [2,6]. The presence of oral and conjunctival mucosa in the current patient aids in the diagnosis of erythema multiforme major and demonstrates a greater level of severity [2,9]. The presence of leukocytosis and increased inflammatory markers as laboratory findings further suggest that there is an ongoing inflammatory reaction [3].

One should note the difference between erythema multiforme and SJS and TEN because they differ significantly in regard to their severity, prognosis, and treatment options. In comparison to SJS/TEN, erythema multiforme is usually characterized by focal epidermal detachment and target lesions [2,7]. The immediate withdrawal of the suspected drug forms the foundation of management. The inflammation is usually managed with supportive care (systemic corticosteroids, antihistamines, and topical therapies) and helps in recovery [2,4]. A multidisciplinary approach is necessary in instances where the eyes are involved so as to reduce the chances of long-term complications [9].

The case emphasizes the importance of early detection of carbamazepine-induced cutaneous reactions. Early diagnosis and early intervention are important in minimizing morbidity and preventiong further development to a more serious and potentially fatal illness like SJS and TEN [10].

CONCLUSION:

Erythema multiforme major is a clinically important mucocutaneous hypersensitivity reaction potentially causing by Autoimmune disorders, Infections and commonly prescribed drugs . The case also highlights the need to ensure early diagnosis of drug-induced etiology, especially in cases where targetoid lesions and mucosal involvement occurs after drug initiation. The mainstay of management is to withdraw the offending agent immediately to avoid progression to severe cutaneous adverse reactions. Systemic and topical corticosteroids and multidisciplinary management are supportive care that is significant in recovery. Increased clinical attention is necessary when administrating high-risk drugs like aromatic anticonvulsants. Early detection and intervention can have a considerable impact on the morbidity, and patient outcomes.

ABBREVIATIONS:

EMM: Erythema Multiforme Major
SJS: Stevens Johnsons Syndrome
SCAR: Severe Cutaneous Adverse Reactions

TEN: Toxic Epidermal Necrolysis
ANA: Antinuclear Antibody
AEC: Absolute Eosinophil Count

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