Case Report

Ocular Manifestations in Paediatric Erythema Multiforme: A Case Report

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ABSTRACT

Erythema multiforme (EM) is a type IV cytotoxic hypersensitivity reaction characterized by classic target lesions on the skin and mucosa, typically affecting the oral, genital, and rarely, ocular mucosa. We describe a 9-year-old girl with widespread rashes, blisters and target lesions on her trunk for three days. She had eye redness, discomfort, a week-long fever, and a dry cough, without any medication. Ophthalmological examination revealed localized conjunctival injection in her right eye, with no visual impairment or corneal lesions. The diagnosis of EM major (EMM) was based on prior infection, characteristic skin lesions, and mucosal involvement, including ocular manifestation of conjunctival injection. Treatment requires addressing the underlying cause and ophthalmologic consultation for systemic or topical corticosteroids, antibiotics, lubricants, and antihistamines. This case highlights the diagnostic challenges of atypical EM presentations, emphasizing the need for comprehensive evaluation, early recognition, and interdisciplinary collaboration to prevent severe ocular complications and preserve vision.

Key Words: Erythema Multiforme, Conjunctival injection, Hypersensitivity reaction.

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INTRODUCTION

Erythema multiforme (EM) is a condition that manifests as a type IV cytotoxic reaction predominantly targeting keratinocytes, elicited by a hypersensitivity response. Various etiological factors including infections such as herpes simplex virus (HSV), Mycoplasma pneumoniae, fungal pathogens, as well as pharmaceutical agents such as Penicillin, Sulphonamides and Non-steroidal anti-inflammatory drugs (NSAIDs) are described.[1] EM manifests globally across diverse age demographics, with a notable incidence among young adults under the age of 40 years. Despite its clinical significance, the precise prevalence of EM remains elusive, estimated to be less than 1% annually.[1–3]

This condition can be classified into two groups that are EM minor (EMm) if it only involves the skin with no mucosal involvement and EM major (EMM) if it involves both the skin and the mucous membrane and is characterized by cutaneous lesions affecting less than 10% of the body's surface area.[1,3,4] In earlier times, EMM was thought to be in the same class as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), although clinical evidence

over the past decade has firmly established EMM as a distinct entity.[4] Histopathological features in SJS/TEN show necrotic tissue found by dendritic cells and macrophages, in contrast to EM, which shows lymphocytic infiltration of T cells.[1]

EM predominantly affects the oral mucosa (70%) but may also involve other areas such as the genitalia, upper respiratory tract, pharyngeal and ocular mucosa.[1,3] Ocular involvement, including conjunctival scarring, keratitis and uveitis, has been documented either independently or concurrently with other mucosal surfaces.[4] EM typically manifests as concentric lesions known as target lesions on the skin.[3] Mucocutaneous signs such as blistering and ulceration often follow prodromal symptoms including fever, lymphadenopathy, cough, headaches and malaise.[1]

Patients with EM usually seek dermatological treatment initially, with ophthalmological consultation occurring later in cases of significant ocular involvement, which is indicated by symptoms including chemosis, conjunctival scarring, keratitis, uveitis, and pseudomembrane formation.[5] This case emphasizes the intricacy of EM and its related ocular involvement, since EM may present with a range of atypical symptoms that could delay identification and impair outcome.

Case Presentation

A 9-year-old girl came to the emergency room complaining of rashes and blisters on several areas of her body for the past three days. Complaints of rashes were accompanied by crusting lips, oral mucosal lesions, ocular discomfort, and sores on the external genitalia. She has had a fluctuating fever between 37.5-38.5°C for the past week, accompanied by dry cough. History of taking antibiotics, vitamins, herbs, or other medications for the past 8 weeks was denied. The previous history of drug allergy was negative. History of similar complaints in the patient or family is absent.

Vital signs revealed pulse 123x/min, respiratory rate 20 x/min, SpO2 97%, and temperature 37.5°C. The face, left ear, chest, abdomen, back, both palms, and both lower limbs showed multiple erythematous-violaceous vesicles that were lenticular-nummular, discrete, and circumscribed, with an erythematous base **(Figure 1a-f)**. These were accompanied by erosions, yellow-black crusts, and coarse scales covering approximately 2.5% of the body surface area (BSA). Some lesions showed target lesions with three zones (purplish vesicles, pale concentric circles, and peripheral red circles) **(Figure 1c)**.

Ophthalmological examination revealed both eyes had visual acuity of 20/20. The right eye (RE) revealed localized conjunctival injection on the temporal side of the eye **(Figure 2)** with no corneal lesions. The left eye (LE) was normal. Ocular motility examination showed unrestricted movement in all directions. Intraocular pressure (IOP) appeared normal on palpation. Anterior chambers were deep and clear, without any signs of hyphaemia or hypopyon. Both pupils were symmetrical, with normal direct and consensual responses. Slit-lamp and funduscopic examinations were not conducted.

Following an assessment of the patient's medical history and physical examination (localized efflorescence), a diagnosis of EMM was established. The treatment consists of administration of methylprednisolone, cetirizine, ranitidine, and betadine mouthwash. Additionally, a regimen consisting of betamethasone cream and gentamicin ointment was prescribed for body lesions, while lesions on the lips were treated with bufacomb in orabase ointment.

DISCUSSION

EM generally occurs as a result of complication of a local or systemic disease (infections) and/or hypersensitivity reaction to medications. Among the infections that can cause EM, 90% are herpes simplex virus (HSV) type 1, followed by HSV type 2, Influenza virus, Epstein-Barr virus, Cytomegalovirus, and recently discovered during the pandemic is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[6,7] Mycoplasma pneumoniae infection is the second most prevalent cause, especially in young children.[4,8] Drugs such as non-steroidal inflammatory drugs (NSAIDs), anti-epileptic drugs, antibiotics (erythromycin, nitrofurantoin, penicillin, sulphonamides, and tetracyclines), and vaccinations (most common cause in infants) are some medications that may induce EM. Hepatitis C, malignancy, and inflammatory bowel diseases (Crohn's disease) are among the systemic diseases that are related to EM.[1]

According to current theory, EM associated with HSV has served as the foundation for the mechanisms of EM. HSV DNA polymerase gene which is involved in cell-mediated immunity against viral antigen-positive cells, is thought to be the cause of EM.[2,8]

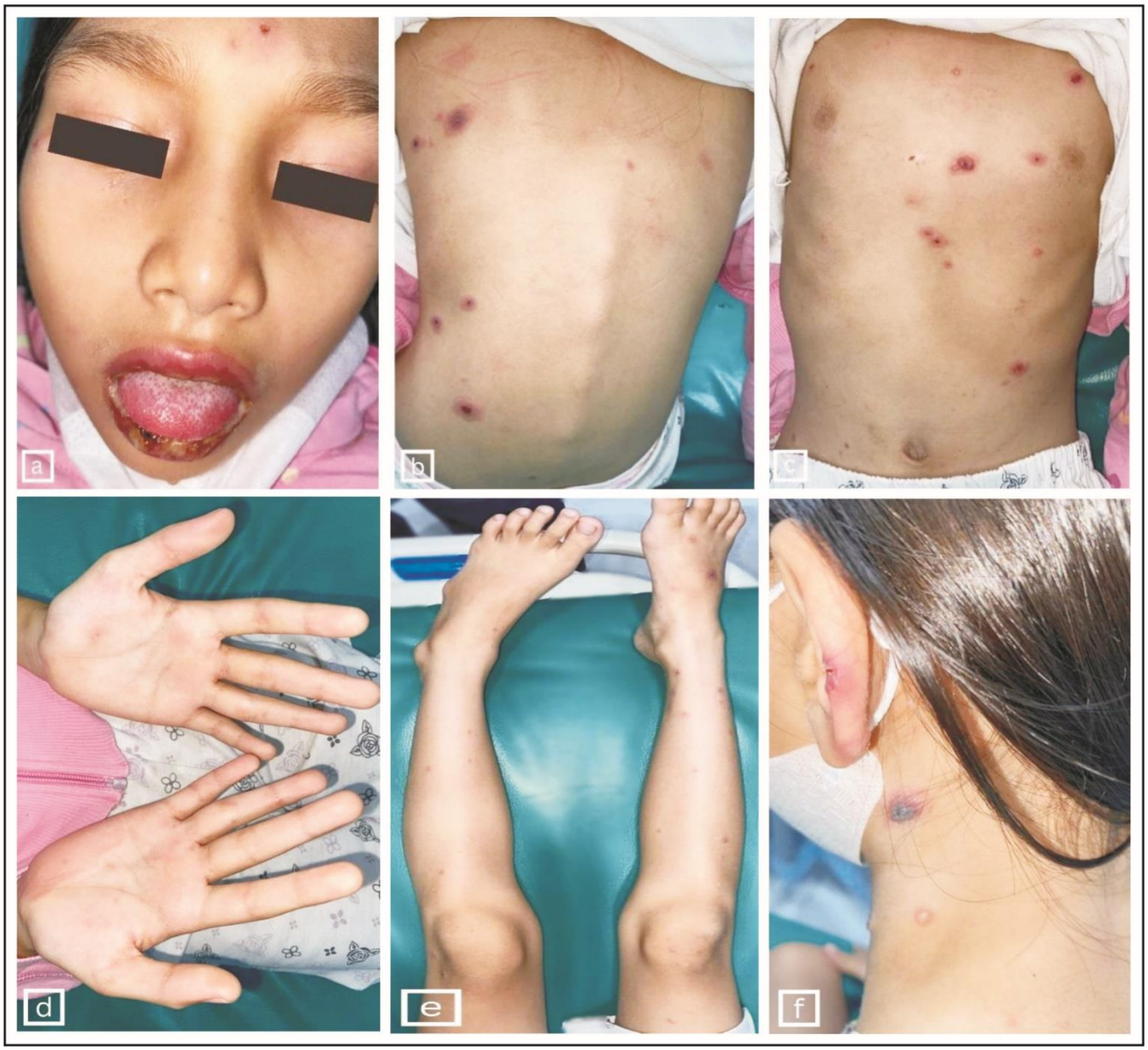

Figure 1: Multiple discrete vesicular lesions with erythematous base and erosion-excoriation lesions with yellowish-black crusting on the lips (a), Multiple circumscript discrete vesicular lesions with erythematous-violaceous base on the back (b), chest and abdomen (c), both palms (d), and both extremities (e), neck (f).

Figure 2: Localized conjunctival injection on the temporal side of the RE.

Virus released into the blood during reactivation of HSV infection is phagocytosed by circulating peripheral blood mononuclear cells, particularly CD34+ Langerhans cell precursors. The CD34+ cells containing HSV migrate to the epidermis and transfer viral DNA fragments to epidermal keratinocytes leading to the recruitment of HSV-specific CD4+ Th1 cells that produce interferon IFN-γ in response to viral antigens.[8] The release of IFN-γ initiates an inflammatory cascade that promotes the lysis of HSV-

infected keratinocytes and the recruitment of autoreactive T cells. These events lead to epidermal damage and the inflammatory infiltrate that characterizes cutaneous lesions of EM.[8] The process starts a chain reaction of events that results in increased sequestration of circulating leukocytes, monocytes, and natural killer (NK) cells, expression of genes induced by IFN-γ, and autoreactive T-cells produced by molecular mimicry or the release of cellular antigens from lysed cells. It is unclear if EM resulting from different causes follows the same pathways.[8]

Prodromal indicators of EM may include fever, coughing, or rhinitis, which are commonly associated with upper respiratory tract infections. Approximately one-third of EM occurrences manifest with a fever exceeding 38.5°C.[9] In our case, we concluded that potential previous infections may have triggered an EM hypersensitivity reaction, considering the patient's history of fluctuating fever over the past week, along with a dry cough. A classic targetoid lesion with blistering or necrotic centres encircled by an erythematous ring served as a diagnostic hallmark for EM. EM can be primarily diagnosed through clinical presentation however atypical lesion presentations may necessitate serological examination or biopsy for definitive causative diagnosis.

Lesions may present conventionally or unusually across various regions, including the face, cervical, palmar, plantar, flexural surfaces, and trunk. Lesions typically manifest within 48–72 hours and resolve between 7–21 days on average.[2,9]

Initial signs of acute EM/Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) with ocular involvement include ecchymosis, crusting, erythema, and conjunctival hyperaemia in over 90% of observed cases. Notably, severe conjunctival inflammation, chemosis, conjunctival membrane, and pseudo-membrane formation are also evident.[5]

A study consisting of 207 EM/SJS/TEN patients revealed ocular complications in 60.1% of cases.[5] Comparatively, ocular involvement was more prevalent in SJS (81.3%) or TEN (66.7%) cases than in EM cases (22.7%). Ocular features included conjunctivitis, blepharitis, conjunctival membrane involvement and symblepharon. Localized conjunctival injection is a common indicator of ocular involvement in EM, consistent with observations in the majority of EMM cases.[3,10]

Diagnostic investigations include fluorescein staining for identifying any corneal epithelial anomalies. Diagnostic approaches for determining the aetiology of conjunctivitis encompass membrane culture, polymerase chain reaction (PCR), and Gram staining.[10] Moreover, it is imperative to acknowledge that progressive acute ocular inflammation may precipitate late ocular complications, culminating in adverse outcomes such as conjunctival scarring, corneal opacification, keratitis, uveitis, and various eyelid deformities (e.g., symblepharon, entropion, ectropion, lagophthalmos, trichiasis), potentially resulting in irreversible visual impairment.[3,5] Early intervention and comprehensive ophthalmological evaluation during the acute phase of EM with ocular involvement is paramount for minimizing ocular morbidity and mitigating the risk of long-term sequelae.[1,5]

Treatment strategies for EMM should be based on the underlying aetiology of EM. Discontinuation of causative medications is imperative in cases of drug-induced EM. Topical antibiotics such dapsone and azithromycin can be used to treat infections that cause EM and may aid as a preventive measure against eye infections.[4,5] However, it should be remembered that certain antibiotics, including sulphonamides, penicillin, erythromycin, nitrofurantoin, and tetracyclines, can potentially trigger hypersensitive EM reactions.[1,4,5] Topical steroids have been administered to alleviate acute ocular inflammation, yielding favourable outcomes with complete resolution. In cases of extensive mucosal involvement, systemic glucocorticoid therapy alongside with hospitalization may be initiated and gradually tapered over 2-4 weeks.[3,5] However, prolonged administration of steroids has been linked to adverse effects such as cataract formation and glaucoma. Inflammatory processes affecting the ocular surface contribute to the impairment of goblet cells, consequently diminishing mucin secretion and disrupting tear stability, predisposing to dry eye syndrome. The utilization of preservative-free lubricants facilitates ocular surface moisturization and removal of inflammatory agents. Additionally, oral antihistamines serve as adjunctive therapy to alleviate symptomatic manifestations, particularly in cases of acute uncomplicated EM.[4] Structural ocular complications may necessitate additional evaluation and intervention, potentially involving surgical interventions such as corneal transplantation or stem cell transplantation. Notably,

Chang et al, reported that only 6.7% of cases of EM exhibited sequelae.[5] In approximately 2% of EM cases, recurrence is frequently attributed to herpes simplex virus (HSV) infection.

In summary, this case underscores the diverse aetiologies of erythema multiforme (EM), encompassing drug-induced, idiopathic, and infection-related types. Comprehensive evaluation through meticulous history-taking, physical examination, serological investigations, and biopsies, particularly in cases with atypical presentations of EM with ocular involvements is necessary. An optimal multidisciplinary approach and early detection are essential in reducing long-term complications associated with ocular EM. A prompt treatment plan should include ophthalmological evaluation, judicious application of lubricants, modulation of inflammation with topical corticosteroids, and targeted antibiotic interventions to address epithelial barrier injuries. Interdisciplinary collaboration between dermatologists and ophthalmologists is necessary for effective management.

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Conflict of Interest: Authors declared no conflict of interest.

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