ABSTRACT

Erythema multiforme major (EMM) is a hypersensitivity reaction usually secondary to medications, viruses or other infections. Its presentation is fairly typical with a symmetrical distribution of vesicles, bullae or targeted lesions on the upper body, arms, legs, palms, feet and oral mucosa. The authors present a delineated case of EMM in association with chronic lymphocytic leukemia (CLL) and non-Hodgkin’s lymphoma (NHL) with a very unusual clinical presentation evolving overtime into a unique, almost dermatomal distribution. Typical therapies were not initially helpful and intravenous immunoglobulin antibody had to be administered.

Keywords: Erythema multiforme major lymphocytic, Chronic lymphocytic leukemia, Non-Hodgkin’s lymphoma.

INTRODUCTION

Erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were once believed to be on a spectrum of severe cutaneous adverse reactions. In the past few years, it has been debated that EMM is, in fact, a separate entity from SJS. It is often symmetric, with the distribution beginning acrally (dorsal surfaces of hands, feet, elbows and knees). Oral lesions are found in 70% of cases but are not required for diagnosis. A flu-like prodrome is common 7 to 14 days before lesions are visible.1,2 The initial rash is in a morbilliform pattern beginning in the face, neck, chin and central trunk. The spread is rapid and lesions often coalesce. The Nikolsky sign is often present. Mucosal involvement is extensive. Treatment options are limited for these conditions and many are controversial. There are no standard guidelines for treatment of either EMM or SJS. Studies have shown that treatment with corticosteroids may lengthen the duration of these reactions, whereas others show that it may offer some benefit. For patients with EMM, early treatment of HSV is believed to be the best option.

Chronic lymphocytic leukemia (CLL) is a B-lineage neoplasm of prefollicular center cells that is usually associated with circulating neoplastic small lymphocytes. From a morphologic and immunophenotypic perspective, the malignant cells of CLL are identical to those of nodal-based small lymphocytic lymphoma (SLL), and these two malignancies are thought to represent different manifestations of the same disease. CLL is the most common type of leukemia in the Western hemisphere; its prevalence in Europe and America ranges from 29 to 38% of all leukemias.3 The most common oral manifestations of the leukemias are gingival hypertrophy, petechial hemorrhage and ecchymosis, infection, ulceration and necrosis. Less commonly, as a result of leukemic infiltrates, multiple localized tumor like growths can occur in the gingiva. Similar localized leukemic infiltrations occurring elsewhere in the oral cavity have only rarely been reported in the literature.

The lymphoproliferative disorders continue to be the subject of intensive and rewarding investigation. It is the very heterogeneity of these diseases at a cellular level which largely explains the difficulty; no where are the potential fallacies of comparing the treatment of patients by different groups and centers greater than in the diverse malignancies which we group together as non-Hodgkin’s lymphomas (NHL).4

Erythema multiforme in association with the chronic lymphocytic leukemia and the NHL have been rarely reported in literature as this has been found in merely about 2% of the cases of CLL and NHL. This triad of disorders is mostly seen in African and the South American group of population and rarely in the South-East Asian countries. Patients suffering from this triad of diseases tend to have a remarkably poor prognosis and are often fatal.2,5,6

CASE REPORT

A 65 years old female patient, a local resident from Bangalore, reported to the Department of Oral Medicine and Radiology in our college complaining of pain and burning sensation in the jaw for the past 3 months. The history revealed generalized redness over the lip and within the oral cavity along with burning sensation and pain. The patient experienced difficulty in eating and swallowing. The patient was a known victim of chronic lymphocytic leukemia/non-Hodgkin’s lymphoma since 2002. The last cycle of treatment was carried out about an year ago and was currently on regular follow-up. Treated for RTI...
(respiratory tract infection) in the 2nd week of April, the patient developed oral mucositis which later subsided on taking medication, however, had recurred severely within 10 days and there was difficulty in swallowing as well. Generalized erythematous maculopapular rash and generalized weakness were also associated with reduced appetite. There was no history of diabetes, hypertension, asthma, etc.

Extraoral examination revealed maculopapular rash present along with all the features of erythema multiforme involving the palms and legs (Figs 1 and 2), maculopapular rash on the back (Fig. 3). The lips were ulcerated and showed severe crustations (Fig. 4). Characteristic target lesions/iris lesions (Fig. 5) were very prominent on the skin of abdomen and the back.

The intraoral examination revealed erosion of the labial or the buccal mucosa along with the reddish erythematous appearance. Gingiva appeared soft and edematous. The tongue appeared depapillated and ulceration was noticed on the dorsal surface of the tongue. Due to patient’s unhygienic oral conditions, there were very few teeth present in the oral cavity. Difficulty in mouth opening was also noticed. This case was provisionally diagnosed as erythema multiforme and differential diagnosis of lichen planus, paraneoplastic pemphigus, viral exanthems and other hypersensitivity reactions are given.

The patient was investigated for routine complete hemogram that showed elevated neutrophil and lymphocytic count. The peripheral blood smear showed normocytic normochromic blood picture with marked lymphocytosis and atypical/immature lymphocytes. A mild increase in the number of basophils was also noted. Microscopic sections (Fig. 6) showed flattened stratified squamous epithelium of skin with the reticular dermis showing dense collagen. Papillary dermis showed congested capillaries with perivascular lymphocyte infiltrate. Melanin incontinence was also seen. Skin adnexae were unremarkable. There was no epithelial clefting or bullae seen. There was no definitive evidence of paraneoplastic pemphigus or lichen planus. The direct immunofluorescence test which was carried out as a
confirmatory test was negative for IgG, IgA, IgM, C1q and C3c confirming erythema multiforme.

Current medications were triamterene and hydrochlorothiazide, cetirizine, and ethinyl estradiol and levonorgestrel. She had been taking ibuprofen for pain in the past week. She was placed on 70 mg of prednisone orally once daily, as well as valacyclovir, ciprofloxacin and cetirizine. After 12 days of high-dose corticosteroids the patient continued to worsen. The vesicles became bullae and coalesced. The patient was still stable but in constant pain, and the WBC count remained elevated. At this point, approximately 70% of her body surface area was involved. The rash continued to be extremely well-delineated, following dermatomal planes. Treatment options aside, this case is an interesting example of what we believe to be EMM in a very unique and conflicting presentation. The treatment modalities however did not end on a positive note as the lesions proved fatal to the patient despite proper care and adequate drug administration.

**DISCUSSION**

Erythema multiforme is a skin condition considered to be a hypersensitivity reaction to infections or drugs. It consists of a polymorphous eruption of macules, papules and characteristic ‘target’ lesions that are symmetrically distributed with a propensity for the distal extremities.2,3 There is minimal mucosal involvement. Herpes simplex virus (HSV) is the most commonly identified etiology of this hypersensitivity reaction, accounting for more than 50% of cases. Mycoplasma pneumoniae is another commonly reported etiology, especially in children, as is fungal infection. The medications most often associated with erythema multiforme are barbiturates, hydantoins, nonsteroidal anti-inflammatory drugs, penicillins, phenothiazines and sulfonamides. Recurrent erythema multiforme often is secondary to HSV-1 and -2 reactivation, although the HSV may be clinically silent. Erythema multiforme is a self-limited eruption that usually has mild or no prodromal symptoms. Patients may experience itching and burning at the site of the eruption. The papules may enlarge gradually into plaques several centimeters in diameter.7 The central portion of the papules or plaques gradually becomes darker red, brown, dusky or purpuric. Crusting or blistering sometimes occurs in the center of the lesions. The characteristic ‘target’ or ‘iris’ lesion has a regular round shape and three concentric zones: A central dusky or darker red area, a paler pink or edematous zone, and a peripheral red ring. Some target lesions have only two zones, the dusky or darker red center and a pink or lighter red border. Target lesions may not be apparent until several days after the onset. Erythema multiforme is diagnosed clinically. In patients who have target lesions with a preceding or coexisting HSV infection, the diagnosis can be made easily. Skin biopsy is not necessary when the clinical picture is clear because biopsy findings are not specific for erythema multiforme. Because erythema multiforme often resembles urticaria at the onset of the eruption, it is important to distinguish the clinical features. The individual lesions of erythema multiforme in typical cases are present and fixed for at least 1 week, and some evolve into target lesions. When bullous lesions are present, erythema multiforme must be distinguished from the autoimmune bullous diseases. Recurrent erythema multiforme may be treated with continuous oral acyclovir (400 mg two times per day) even if HSV is not an obvious precipitating factor. Oral acyclovir has been shown to be effective in the suppression of recurrent erythema multiforme in a double-blind placebo-controlled trial. Patients with recurrent erythema multiforme despite the use of suppressive antiviral therapy should be referred to a
that specific classification cannot be made. Cutaneous retroperitoneal tumors with such primitive differentiation (dendritic follicular cell sarcomas). Other refers to cases of sarcomas that appear to be of lymph node origin (such as sarcomas associated with lymphocytic leukemia, and Castleman’s disease. The neoplasms associated with erythema multiforme have cases occur, but the three most commonly associated lichenoid lesions, affecting palms and soles, as well as the over blistering on the cutaneous surface. Both blisters and lichenoid lesions, affecting palms and soles, as well as the paronychial tissues. The exact percentages vary as additional cases occur, but the three most commonly associated neoplasms associated with erythema multiforme have always been non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and Castleman’s disease. The sarcomas associated with this are unusual retroperitoneal sarcomas that appear to be of lymph node origin (such as dendritic follicular cell sarcomas). Other refers to cases of retroperitoneal tumors with such primitive differentiation that specific classification cannot be made. Cutaneous treatment of the autoimmune disease is difficult, and most patients die from complications, including pulmonary involvement with respiratory failure.

CONCLUSION

This case is particularly difficult to classify. The rash initially presented on the acral surfaces, which is consistent with EMM; however, the delineated, almost dermatomal appearance that it took as it progressed was unique. Although treatment options are still limited and controversial for these reactions, our patient did not seem to benefit from corticosteroid treatment. Intravenous immunoglobulin treatment, although started late in the course of the reaction, seemed to offer immediate relief to the patient and turned the corner of the disease progression toward the recovery phase but only for a particular period of time. Due to severity of the lesions, the triad of diseases proves fatal for the patient. Although our knowledge in this arena has progressed substantially in the last decade, much is still unknown. The disease occurs rapidly, has a short and stormy progression in many patients, and leaves us with a limited window of opportunity in which to study it in individual cases. We hope that with increased recognition, more details of the mechanisms of autoimmune injury will be defined, allowing us to better treat these affected patients.

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REFERENCES


ABOUT THE AUTHORS

Siva Kumara Shankari (Corresponding Author)
Postgraduate Student, Department of Oral Medicine and Radiology Bangalore Institute of Dental Sciences, Bengaluru, Karnataka, India
e-mail: sivakumarashankari@yahoo.com

K Jayanthi
Professor and Head, Department of Oral Medicine and Radiology Bangalore Institute of Dental Sciences, Bengaluru, Karnataka, India

Bhawna Gupta
BDS-CRII Student, Department of Oral Medicine and Radiology Bangalore Institute of Dental Sciences, Bengaluru, Karnataka, India