ERYTHEMA MULTIFORME AS A COMPLICATION IN A WOMAN WITH HERPES ZOSTER

Agnes Stephanie Tanuwijaya[1*], Niken Kusumaningrum[2], Hari Darmawan[3]

[1]Bachelor of Med, Faculty of Medicine, Tarumanagara University, Jakarta
[2]Dermatology and Venereology Specialist, K.R.M.T. Wongsonegoro Regional General Hospital, Semarang
[3]Department of Dermatology and Venereology, Faculty of Medicine, Tarumanagara University, Jakarta

Email Correspondence: agnes.406231063@stu.untar.ac.id

Disubmit: 19 Oktober 2025 Diterima: 15 Mei 2026 Diterbitkan: 01 Juni 2026
Doi: https://doi.org/10.33024/mahesa.v6i6.23169

ABSTRACT

Globally, the incidence of erythema multiforme (EM) is estimated to be between 0.01 and 1%, with a frequency of approximately 1.2 to 6 cases per million people per year. This condition can be triggered by viral infections, one of which is the varicella-zoster virus (VZV). Herpes zoster occurs due to reactivation of VZV and can cause EM. This condition requires special attention due to its potential severity and diagnostic difficulties. This case presentation describes this rare occurrence in a 43-year-old woman, exploring the clinical presentation, diagnostic approach, and therapeutic management of this unusual combination of virus-induced dermatological manifestations. The patient was given a combination of systemic corticosteroids and antivirals, as well as antibiotics and medications for other symptomatic symptoms. After a three-day hospital stay that showed clinical improvement, the patient was discharged with continued outpatient follow-up and a process to continue the prescribed oral and topical treatment with an appropriate reduction in the systemic corticosteroid dose.

Keywords: Erythema Multiforme, Herpes Zoster, Herpes Zoster-Associated Erythema Multiforme (HAEM), Corticosteroid, Antiviral.

INTRODUCTION

Globally, the incidence of EM has been estimated between 0.01 and 1%, with a frequency of approximately 1.2 to 6 cases per million individuals per year, though the exact prevalence remains difficult to determine (Wollina & Gemmeke, 2009; Trayes et al., 2019). The condition predominantly affects young adults between 20 and 40 years of age, with approximately 20% of cases occurring in children, and is reported to occur equally across all ethnic groups worldwide (Hafsi et al., 2024). While herpes simplex virus (HSV) infection accounts for 70-80% of EM cases, varicella-zoster virus (VZV)-associated EM represents a rare but clinically significant variant that warrants particular attention due to its potential severity and diagnostic challenges (Zhu et al., 2022).

The Asia-Pacific region, including Southeast Asian countries, experiences a substantial and increasing burden of both herpes zoster (HZ) and its associated

complications, with epidemiological trends demonstrating that HZ incidence is rising at approximately 5% per year (Chen et al., 2017; Chan et al., 2023). The average incidence of HZ in Asia-Pacific countries has been documented at 3-10 cases per 1,000 person-years, with prevalence rates ranging from 203 to 224 per 100,000 persons in some populations, with the highest prevalence observed in individuals aged 70-79 years (Chan et al., 2023; San Martin et al., 2023). While comprehensive epidemiological data specific to EM in Asia-Pacific countries remain limited, clinical case reports and hospital-based studies suggest substantial healthcare resource utilization for patients experiencing EM and its complications (San Martin et al., 2023). Of particular concern, patients with immunocompromised or autoimmune inflammatory conditions in the Asia-Pacific region demonstrate significantly elevated risks for HZ and its complications, including EM, suggesting that vulnerable populations warrant targeted surveillance and preventive interventions (Chen et al., 2024).

Indonesia, as the most populous Southeast Asian nation, presents a unique epidemiological landscape for both HZ and EM, though comprehensive national-level data remain scarce. Data from Prof. Dr. R. D. Kandou Hospital Manado documented 0.68% cases of HZ in 2013, with peak incidence occurring in individuals aged 45-64 years (78,57%), demonstrating a female predominance in most hospital-based cohorts (Dilly et al., 2016). Hospital-based studies from Prof. Dr. I.G.N.G. Ngoerah General Hospital in 2019-2022 have reported higher proportions among elderly populations aged 60 years and above who frequently present with multidermatome involvement and post-herpetic neuralgia complications (Hosea & Praharsini, 2025).

The concurrent presentation of EM major with active HZ represents a particularly unusual clinical manifestation, combining the localized vesicular pathology of HZ with the disseminated hypersensitivity response characteristic of EM major. This case presentation describes such a rare occurrence in a 43-year-old female, exploring the clinical presentation, diagnostic approach, and therapeutic management of this unusual combination of viral-induced dermatological manifestations.

LITERATURE REVIEW

Erythema multiforme (EM) is an immune-mediated, self-limiting mucocutaneous hypersensitivity reaction characterized by distinctive target-shaped lesions that reflects the body's complex immunological response to various triggering factors (Sokumbi & Wetter, 2012). The condition represents a type IV hypersensitivity reaction involving T-lymphocyte-mediated targeting of skin keratinocytes triggered by specific antigens resembling those of infectious agents or foreign substances (Alkhaleefa et al., 2022). EM presents across a spectrum ranging from mild to severe forms, with the distinction between EM minor and major determined primarily by the extent of mucosal involvement and systemic manifestations. EM minor typically presents with limited mucosal involvement and symmetrical target cutaneous lesions on extremities with a self-limited course, while EM major is characterized by extensive mucosal membrane involvement affecting two or more sites and carries greater morbidity (Hasan et al., 2018; Hafsi et al., 2024).

RESEARCH METHODS

We conducted a case report-based study at Wongsonegoro Hospital. Data collection was conducted using patient medical records, including patient history, physical examination, supporting procedures, and therapy. Follow-up was then conducted one-month post-hospitalization.

CASE REPORT

A 43-year-old housewife presented with complaints of redness and itching all over her body for the past three days, which had worsened since yesterday. Initially, the patient had a fever with a nonspecific pattern, accompanied by weakness, nausea, and intermittent headaches and joint pain (VAS 4/10). The patient also complained of clustered, fluid-filled, reddish blisters on her chest and abdomen, accompanied by itching, burning, and fever. She then sought treatment from a midwife and was prescribed acyclovir ointment. However, the following day, the redness spread to her feet and hands, accompanied by increasingly severe itching, burning, and fever. Other complaints, such as red eyes and sensitivity to light, were denied. Vomiting and a sore throat were denied. Frequent bowel movements and urination were also reported.

Regarding her medical history, the patient denied any previous history of allergic reactions to medications or foods. Notably, she could not recall a documented episode of chickenpox during childhood or adolescence. She specifically denied any previous episodes of the current presentation. Significant systemic diseases including diabetes mellitus, malignancy, autoimmune disorders, and human immunodeficiency virus infection were all explicitly denied. The patient reported no recent close contact with individuals displaying similar symptoms, and subsequent investigation of family members, neighbors, and community contacts revealed no additional cases.

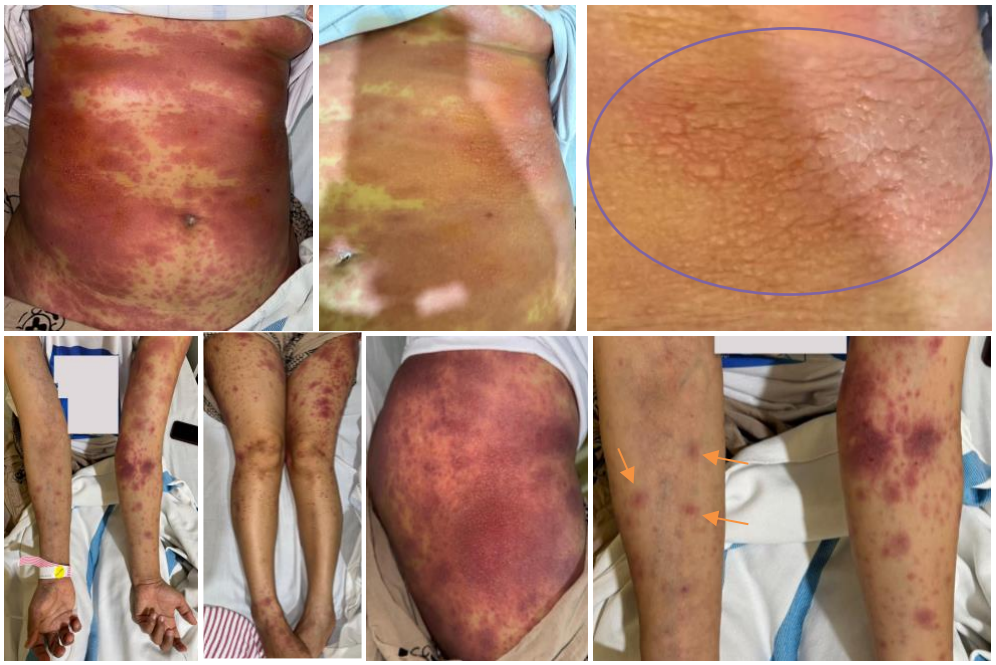

Figure 1. Patient's Dermatological Status
The purple circle is dermatomal lesion in HZ; the yellow arrows are target lessions in EM.

Physical examination revealed a patient with compos mentis and vital signs within normal reference ranges, demonstrating hemodynamic stability despite the severe cutaneous presentation. Abdominal palpation demonstrated epigastric tenderness without peritoneal signs. Peripheral perfusion assessment revealed acral skin warmth bilaterally with capillary refill time less than two seconds, indicating preserved microcirculation.

The dermatological examination constituted the most striking finding: the patient demonstrated widespread, well-demarcated lesions distributed across the anterior trunk, abdomen, bilateral upper and lower extremities in a generalized distribution pattern. The lesion morphology displayed remarkable polymorphism erythematous macules transitioned to purplish papules of miliary to plaque dimensions, with many lesions exhibiting the pathognomonic target or iris morphology. Particularly notable were miliary to lenticular-sized vesicles clustered and confluent across bilateral thoracic and hypochondriac regions (Figure 1).

The ECG examination was found within normal limits. A complete blood count, blood sugar, and liver and kidney function tests were within normal limits. A Tzanck test revealed multinucleated giant cells. The HIV test was non-reactive, and only hyponatremia (129 mmol/L) was found.

Based on the history and examination results, the patient was diagnosed with erythema multiforme major with ongoing herpes zoster. The treatment given to the patient was IVFD NaCl 0.9% 500 cc continued at 20 tpm, ranitidine injection 2x50 mg, dexamethasone injection 3x5 mg, and diphenhydramine injection 2x10 mg. Patients are also given oral medications such as loratadine tablets 2x10 mg, acyclovir tablets 5x800 mg for 7 days, gabapentin tablets 1x300 mg, and erythromycin tablets 3x500 mg. Topical medications such as a combination cream containing desoxymetasone 30 grams + lanolin 30 grams + fucilex 10 grams were used 3 times a day on the red area other than the vesicles. In the area with vesicles, betadine spots were applied 3 times a day, and a combination cream containing acyclovir and fusidic acid was given 3 times a day after the betadine spots were applied.

The patient was also placed under close coordination with an internal medicine specialist to ensure comprehensive medical supervision and management of systemic complications. Throughout the three-day hospitalization period, the patient demonstrated marked clinical improvement. The widespread erythematous lesions progressively faded, with target lesions becoming less prominent and the inflammatory erythema substantially reduced (Figure 2). The vesicular eruption showed accelerated crusting and epithelialization, and no increase in lesion size occurred. Systemic symptoms, including fever, malaise, and arthralgia, largely resolved. Pruritus significantly reduced, and the patient regained functional capacity.

After three days of hospital-based treatment demonstrating clinical improvement, the patient was discharged to home with continued outpatient follow-up and instructions to continue the prescribed oral and topical medications with appropriate tapering of systemic corticosteroids.

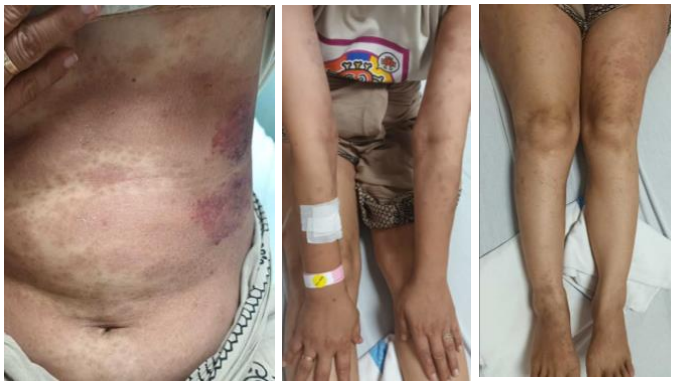

Figure 2. Post-Therapy Dermatological Status

DISCUSSION

The simultaneous presentation of EM mayor and HZ in this patient represents a critical understanding of how viral infections trigger aberrant immune responses in the skin (Trayes et al., 2019). To comprehend the pathogenesis of this case, one must recognize that HZ did not simply coexist with EM mayor—rather, the reactivated VZV served as the primary immunologic trigger that initiated the systemic, immune-mediated cascade characteristic of EM mayor (Wollina et al., 2009). The initial presentation of clustered vesicles on the thorax and abdomen reflected active viral replication within sensory nerve ganglia and their dermatomes; however, the subsequent rapid, widespread, and symmetrically distributed erythematous target lesions extending to acral sites represented a fundamentally different pathologic process reflecting aberrant host immunity (Hafsi et al., 2024). Erythema multiforme exists at the intersection of viral infection and exaggerated adaptive immune responses involving cell-mediated hypersensitivity (Soares et al., 2021). The pathogenesis begins when viral antigens—in this case, VZV glycoproteins or nucleoproteins expressed on the surface of infected keratinocytes—are presented to circulating CD4+ T lymphocytes through major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (Hafsi et al., 2024). The molecular mechanisms of keratinocyte destruction in EMM operate through multiple converging pathways leading to programmed cell death (Sankari et al., 2015).

The inflammatory microenvironment amplifies the cascading tissue destruction through autocrine and paracrine cytokine signaling (Alkhaleefa et al., 2022). Activated Th1 cells and infiltrating macrophages continuously secrete pro-inflammatory cytokines including TNF-α, interferon-gamma (IFN-γ), interleukin-1 (IL-1), and interleukin-6 (IL-6), which increase vascular permeability and promote recruitment of additional inflammatory cells to affected skin (Hafsi et al., 2024). These cytokines upregulate expression of adhesion molecules and chemotactic factors, creating a self-perpetuating cycle of immune cell recruitment and activation (Soares et al., 2021). The systemic manifestations observed in this patient—fever, malaise, weakness, nausea, and electrolyte disturbances—reflect the spillover of these inflammatory mediators beyond the skin into systemic circulation (Hafsi et al., 2024). The presence of hyponatremia likely

resulted from syndrome of inappropriate antidiuresis (SIADH) induced by cytokine-mediated non-osmotic release of vasopressin, a well-documented consequence of acute viral infections and systemic inflammatory responses (Krolicka et al., 2020). This finding underscored that the patient's pathologic process extended beyond a localized dermatologic eruption and represented a systemic inflammatory emergency requiring comprehensive therapeutic intervention (Michaels, 2009).

The differential diagnosis for this case is erythroderma et causa drug eruption. However, because there is no mucosal involvement or previous medical history, normal complete blood count results, and multinucleated giant cells on the Tzanck test, the differential diagnosis of drug eruption can be ruled out. The therapeutic approach employed in this case exemplifies modern EM management based on understanding of its immunopathogenesis. The antiviral component of therapy targeted VZV replication through high-dose acyclovir administration. Acyclovir operates through a mechanism of competitive inhibition of viral DNA polymerase following conversion to its active triphosphate form by viral thymidine kinase (Taylor et al., 2023). Once activated, acyclovir triphosphate competes with natural substrate deoxyguanosine triphosphate for incorporation into viral DNA, effectively terminating chain elongation and preventing viral DNA replication. The high oral dosage of 800 mg five times daily was selected to achieve cutaneous and systemic concentrations sufficient for VZV suppression; studies have demonstrated that acyclovir initiated within 72 hours of zoster onset reduces viral shedding, accelerates lesion healing, and limits pain duration (Gnann, 2007).

Systemic corticosteroids exert their therapeutic effects in EMM through multiple complementary mechanisms that directly address the aberrant immune activation responsible for keratinocyte destruction (Hodgens et al., 2023). Corticosteroids operate through both genomic and non-genomic mechanisms, with the rapid non-genomic effects occurring within seconds to minutes of glucocorticoid receptor activation and providing immediate anti-inflammatory benefit (Hodgens et al., 2023). At the non-genomic level, corticosteroids activate membrane-bound glucocorticoid receptors and intracellular glucocorticoid receptors, triggering rapid inhibition of phospholipase A2—the critical enzyme responsible for releasing arachidonic acid from cell membranes (Hodgens et al., 2023). This phospholipase A2 inhibition represents a critical therapeutic target because arachidonic acid serves as the precursor for synthesis of inflammatory eicosanoids including prostaglandins and leukotrienes that amplify inflammatory cell recruitment and vascular permeability (Hodgens et al., 2023). By blocking this pathway, corticosteroids immediately reduce the inflammatory mediator milieu driving vascular dilation, edema, and immune cell infiltration into affected skin (Hodgens et al., 2023). Beyond these acute non-genomic effects, corticosteroids exert profound immunosuppressive effects through genomic mechanisms operating over hours (Hodgens et al., 2023). Critically, acyclovir does not directly suppress the aberrant immune response already set in motion; rather, it removes the stimulus perpetuating immune activation (Trayes et al., 2019). This

distinction is crucial to understanding why antiviral monotherapy alone would likely have been insufficient and why the combination of corticosteroids and acyclovir proved so effective in this case (Trayes et al., 2019). Acyclovir suppresses the source of antigen, while corticosteroids suppress the aberrant response to that antigen, together achieving synergistic therapeutic benefit (Katz et al., 1999).

The underlying reason for this synergy becomes evident when one considers the temporal dynamics of immune activation in herpesvirus infections (Katz et al., 1999). Early in infection, viral replication, and antigen production drive immune activation; attempting to suppress immune responses without addressing viral replication removes the brakes without turning off the engine driving pathology (Trayes et al., 2019). Conversely, suppressing viral replication without dampening the aberrant immune response allows existing pathogenic T cells and their cytokine-mediated effects to continue causing tissue damage (Trayes et al., 2019). Several studies showed effectives of combination theraphy with recurrent oral HAEM was treated with acyclovir (1,000 mg/day) plus prednisone (10 mg/day) for 7 days, along with topical corticosteroids and antiseptic. The lesions healed completely with no sequelae (Muryah et al., 2017). Susanto et al. showed treatment included oral methylprednisolone and oral acyclovir, plus topical steroid,

CONCLUSION

This case exemplifies the power of understanding disease pathophysiology to guide rational therapy and predict clinical response. The superior outcome achieved here resulted from simultaneous targeting of both the viral trigger and the aberrant immune response, supported by adjunctive therapies addressing specific secondary pathophysiologic processes including histamine-mediated inflammation, neuropathic pain, electrolyte derangement, and topical tissue destruction.

REFERENCES

Alkhaleefa, A., Campbell, B., Omotajo, D., & Hardin, J. (2022). Erythema multiforme (EM): Pathophysiology and clinical findings. Calgary Guide [Internet]. https://calgaryguide.ucalgary.ca/erythema-multiforme-em-pathophysiology-and-clinical-findings/erythema-multiforme/

Chan, X.B.V., Tan, N.C., Ng, M.C.W., Ng, D.X., Koh, Y.L.E., Aau, W.K., Ng, C.J. (2023). Prevalence and healthcare utilization in managing herpes zoster in primary care: a retrospective study in an Asian urban population. Frontiers in Public Health, 11, 1213736. https://doi.org/10.3389/fpubh.2023.1213736

Chen, J., Abrahamson, P. E., Ke, Y., Ong, C. R., Parikh, R., & Shantakumar, S. (2024). A systematic literature review of the epidemiology and burden of herpes zoster in selected locales in Asia Pacific. Human vaccines & immunotherapeutics, 20(1), 2344983. https://doi.org/10.1080/21645515.2024.2344983

de Souza Camargo, H., de Oliveira, D.D.S., de Oliveira Barbeiro, C., Esteves, V.Z., Bufalino, A., Massucato, E.M.S., Navarro,

C.M. (2024). Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 137(6), e204. https://doi.org/10.1016/j.oooo.2023.12.279

Dilly, J. T., Kapantow, M. G., & Suling, P. L. (2016). Profil herpes zoster di poliklinik kulit dan kelamin RSUP Prof. Dr. R. D. Kandou Manado periode Januari - Desember 2013. E-CliniC, 4(2). https://doi.org/10.35790/ecl.v4i2.14563

Gnann Jr., J. W. (2007). Antiviral therapy of varicella-zoster virus infections. In A. Arvin (Eds.) et. al., Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge University Press.

Hafsi, W., & Badri, T. (2024). Erythema Multiforme. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470259/

Hasan, S., Jangra, J., Choudhary, P., Mishra, S. (2018). Erythema Multiforme: A Recent Update. Biomedical and Pharmacology Journal, 11(1). https://dx.doi.org/10.13005/bpj/1358

Hodgens, A., & Sharman, T. (2023). Corticosteroids. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK554612/

Hosea, F. E., & Praharsini, I. G. A. A. . (2025). Characteristic of Herpes Zoster in the Elderly at Prof. Dr. I.G.N.G. Ngoerah General Hospital: An Epidemiologic Study. Berkala Ilmu Kesehatan Kulit Dan Kelamin, 37(2), 84–89. https://doi.org/10.20473/bikkk.V37.2.2025.84-89

Katz, J., Livneh, A., Shemer, J., Danon, Y. L., & Peretz, B. (1999). Herpes simplex-associated erythema multiforme (HAEM): a clinical therapeutic dilemma. Pediatric dentistry, 21(6), 359–362.

Królicka, A. L., Kruczkowska, A., Krajewska, M., & Kusztal, M. A. (2020). Hyponatremia in Infectious Diseases-A Literature Review. International journal of environmental research and public health, 17(15), 5320. https://doi.org/10.3390/ijerph17155320

Menaldi, S. L., Halim, P. A., & Kurniawan, K. (2022). Efficacy of gabapentinoids for acute herpes zoster in preventing postherpetic neuralgia: a systematic review of randomized controlled trials. Dermatology online journal, 28(5), 10.5070/D328559238. https://doi.org/10.5070/D328559238

Michaels B. (2009). The role of systemic corticosteroid therapy in erythema multiforme major and stevens-johnson syndrome: a review of past and current opinions. The Journal of clinical and aesthetic dermatology, 2(3), 51–55.

Muryah, A.E., & Sufiawati, I. (2017). Successful treatment of herpes simplex-associated erythema multiforme with a combination of acyclovir and prednisone. Journal of Dental, Jaw and Face Development and Science, 2(3).

Sankari, S. L., Babu, N. A., Rajesh, E., & Kasthuri, M. (2015). Apoptosis in immune-mediated diseases. Journal of pharmacy & bioallied sciences, 7(Suppl 1), S200–S202. https://doi.org/10.4103/0975-7406.155902

San Martin, P., Aunhachoke, K., Batac, M. C. F., Lodrono-Lim, K., Kwanthitinan, C., Santoso, D., Fonseka, T., Nguyen, M., & Guzman-Holst, A. (2023). Systematic Literature Review of Herpes Zoster Disease Burden in Southeast Asia. Infectious diseases and therapy, 12(6), 1553–1578. https://doi.org/10.1007/s40121-023-00822-0

Soares, A., & Sokumbi, O. (2021). Recent Updates in the Treatment of Erythema Multiforme. Medicina (Kaunas, Lithuania), 57(9), 921. https://doi.org/10.3390/medicina57090921

Sokumbi, O., & Wetter, D. A. (2012). Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. International journal of dermatology, 51(8), 889–902. https://doi.org/10.1111/j.1365-4632.2011.05348.x

Susanto, H., Nurhilailah, Ganesha, R., Hendarti, H.T., Hadi, P. (2021). Herpes-associated erythema multiforme in a postmenopausal woman. Majalah Kedokteran Gigi Indonesia, 7(1), 51-59. http://doi.org/10.22146/majkedgiind.43299

Taylor, M., & Gerriets, V. (2023). Acyclovir. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542180/

Trayes, K. P., Love, G., & Studdiford, J. S. (2019). Erythema Multiforme: Recognition and Management. American family physician, 100(2), 82–88.

Wollina, U., & Gemmeke, A. (2009). Herpes zoster - associated erythema multiforme. Journal of dermatological case reports, 3(1), 11–13. https://doi.org/10.3315/jdcr.2009.1025

Zhu, Q., Wang, D., Peng, D., Xuan, X., & Zhang, G. (2022). Erythema multiforme caused by varicella-zoster virus: A case report. SAGE open medical case reports, 10, 2050313X221127657. https://doi.org/10.1177/2050313X221127657