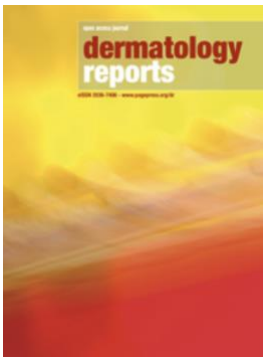

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Erythema Multiforme post-Orf viral infection: a comprehensive review of the literature with a case report highlight

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Abstract

Orf, also known as ecthyma contagiosum, is a highly contagious zoonotic infection linked to direct contact with infected sheep, goats, or reindeer, posing a significant risk to farmers, veterinarians, shepherds, and butchers. This study presents a case of a 41-year-old female who developed Orf, complicated by the rare occurrence of Erythema Multiforme (EM), after handling sheep meat. The patient initially presented with a progressive painful skin eruption on the left dorsum of the little finger, which subsequently worsened and led to the development of generalized painful and itchy skin lesions, including target lesions typical of EM, on the palms, soles, and extremities. The diagnosis was confirmed through clinical examination and skin biopsy. The patient was treated with antihistamines and topical corticosteroids, resulting in a complete resolution of symptoms within three weeks. Our underscores the importance of recognizing EM as a potential complication of Orf infection, particularly in individuals with occupational exposure to animals.

Introduction

Orf, otherwise known as ecthyma contagiosum, is a highly contagious zoonotic viral infection. It is seen secondary to exposure to sheep, goats, or reindeer. Transmission to humans occurs through direct contact with infected lesions on said animals or through contaminated fomites. Farmers, veterinarians, shepherds, and butchers are the most at-risk populations. The infections may be encountered in Islamic countries following Eid Al-Adha's Feast of Sacrifice. During which, presentations may be confused with anthrax.[1]

It typically presents as an asymptomatic lesion on the hand. Over the course of 6-8 weeks, the lesion progresses through 6 clinical stages: Maculopapular, target, acute-nodular weepy, regenerative-nodular dry, papilloma, and regression stages" assuming different morphologies with each stage.[2] Though histology can be used to confirm the diagnosis, a clinical diagnosis is usually sufficient. The disease is self-limiting in immunocompetent patients. However, it can be complicated by Erythema Multiforme (EM) through a secondary immune reaction.

Herein, we report a case of Orf-viral infection complicated with EM, along with a review of the previously reported instances in the literature.

Case Report

A 41-year-old female presented to the Emergency Department complaining of progressive painful skin eruption over the left dorsum of the little finger for two weeks. Her past medical and surgical history were significant for iron deficiency anemia, sleeve gastrectomy, and cholecystectomy.

After delving deeper into the eruption history, the patient conveyed that it started two weeks before her presentation and after inadvertently lacerating her two little fingers with sheep teeth while she was handling sheep meat. One week after the incident, her skin eruption worsened and was draining some fluid. After the deterioration of her condition, she decided to seek assistance at the primary health care clinic, and augmentin 625mg TID for 3 days was prescribed. After administering augmentin, the patient reported a generalized painful and itchy skin eruption over her trunk and extremities on the same day of starting therapy, prompting her to discontinue the medication.

A dermatologic examination of the lesion showed a solitary erythematous nodule that was covered with hemorrhagic crust and surrounded by a well-defined, erythematous, hot, indurated, tender plaque on her right little finger (erysipeloid reaction). In addition, the right ring finger showed a longitudinal hemorrhagic crust (healed nodule). Furthermore, there were generalized well-defined light pink urticated papules and plaques (Figure 1). Some of them exhibited the appearance of target lesions on her palms and soles bilaterally. Multiple light pink macules and patches with scratch marks bilateral were noticed over the forearms, arms, thighs, legs, (Figure 2, Figure 3) upper chest, and buttock area. No ocular, oral, genital, or mucous membrane involvement was noted. The left dorsum of the hand exhibited signs of swelling, tenderness, edema, and hotness, especially when compared to the contralateral limb up to the elbows (erysipelas reaction).

Considering all aforementioned clinical characteristics, the presentation suggestive of ORF complicated by EM minor.

For the diagnostic workup, left hand X-ray and Magnetic Resonance Imaging (MRI) yielded negative results, and ruled out osteomyelitis. Additionally, one 4 mm punch skin biopsy was taken from the eruption site in the leg to rule out drug eruption from Augmentin. Microscopic examination of the hematoxylin, and eosin (H & E) stained tissue sections from the skin punch biopsy revealed mild dermal edema, dilatation of small blood vessels, and mild perivascular lymphocytic infiltrate (Figure 4). Skin biopsy from left little finger for H&E and tissue culture with viral PCR were not taken due to patient refusal because of pain.

Regarding the treatment plan, she was prescribed antihistamine (loratadine 10 mg daily and chlorpheniramine 4 mg HS), and topical mometasone furoate 0.1% ointment to be applied on all skin lesions. She was also prescribed to apply topical imiquimod 5% cream on the left little finger nodule three times a week, and cover the lesion with mepilex AG dressing. In addition, the patient was instructed to clean the left index finger with normal saline daily and apply urea topical cream on all skin eruptions or vaseline ointment twice daily. Upon follow-up in the clinic after 3 weeks, the eruption subsided and outcomes were favorable.

Discussion

Orf, alternatively referred to as ecthyma contagiosum or contagious pustular dermatitis, is a viral infection that predominantly affects individuals engaged in occupations such as farming, shepherding, veterinary medicine, and butchery due to occupational exposure.[3] It is attributed to an epitheliotropic, double-stranded DNA virus belonging to the parapoxvirus genus within the poxviridae family.[3] Orf presents with singular or multiple nodules typically observed on the hands

and fingers, but can also manifest on the feet, legs, neck, and face. Following an incubation period lasting 3-7 days, the lesions progress through six distinct clinical stages: i) maculopapular stage (days 1-7), characterized by erythematous macules or papules; ii) target stage (days 7-14), featuring a necrotic center surrounded by a red outer halo; iii) acute stage (days 14-21), marked by the onset of nodular weeping; iv) regenerative stage (days 21-28), during which the nodule begins to dry; v) papilloma stage (days 28-35), where the lesion adopts a papilloma-like appearance and forms a dry crust; vi) regression stage (after 35 days).[4]

Orf-induced lesions may be accompanied by symptoms such as lymphangitis, lymphadenopathy, malaise, fever, and erysipelas as a secondary bacterial infection.[5] Uncommon occurrences of papulovesicular eruptions have been documented, including a bullous pemphigoid-like eruption.[6] The immune reaction triggered by Orf infection is believed to be accountable for EM.[7] However, the occurrence of EM subsequent to Orf infection is uncommon and rare. Our case reports a 41-year-old female who developed an Orf infection complicated by the rare occurrence of EM minor lesions.

To the best of our knowledge, a total of 43 cases, including the one documented herein, have been reported to acquire EM post-Orf viral infection. A summary review and comparison of documented occurrences of EM associated with Orf infection from oldest to most recent are provided in (Table 1). Out of all cases reported, twenty-three were females and sixteen patients were males, with the ages ranging from (6 to 56 years). A total of twenty-one patients documented specific exposure to animals, predominantly sheep in ten cases, lamb in five cases, goat in three cases, and calf in one case, as well as interactions with raw meat in six cases. Regarding the diagnostic approach, in most instances, the final diagnosis was established with clinical cutaneous examination only, in twenty-eight cases. A combined clinical exam and skin biopsy of lesions

were employed in twelve cases. Treatment approaches for Orf-induced EM vary, with five cases managed conservatively with no specific intervention. Topical corticosteroids were utilized in ten cases. Two cases showed no response or resistance to topical steroids and were managed with topical imiquimod as the next step approach. In more severe cases with further complicated painful lesions, oral and intravenous antibiotics for secondary superimposed bacterial infection, oral corticosteroid, cetirizine, antihistamine, and intravenous corticosteroids were employed.

Orf infection typically presents as a benign, self-limiting condition, typically resolving spontaneously within 6 to 8 weeks without lasting effects. In the majority of cases, symptomatic treatment suffices, advising patients to maintain lesion cleanliness with local antiseptics, initially using moist dressings and later transitioning to dry ones.[24] If a concurrent bacterial infection is suspected, appropriate topical or systemic antibiotic therapy may be considered. Various treatment modalities have been proposed, such as surgical excision, cryotherapy, and the topical application of immune-response modulators like corticosteroids and imiquimod, or antiviral agents like cidofovir. Despite these options, there is insufficient evidence to recommend any specific treatment.[14] The impact of the Orf virus extends widely across global health, environmental, and economic domains, notably affecting the agricultural sector. While human Orf infections are commonly identified among animal handlers such as veterinarians and farm laborers, physicians may also encounter characteristic lesions in individuals engaged in specific cultural rituals, such as the traditional animal sacrifice associated with the Muslim holiday Eid al-Adha. Overall, this case highlights the importance of recognizing Orf infection and its potential complications, particularly in individuals with occupational or cultural exposures. Clinicians should maintain a high index of suspicion for Orf in patients presenting with characteristic skin lesions, especially in settings where animal contact is prevalent.

Conclusions

Despite its rarity, the occurrence of EM following Orf infection underlines the need for awareness and recognition of this potential complication among clinicians. This awareness is crucial for prompt and appropriate management, especially considering the broad differential diagnosis that includes other zoonotic infections.

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Figure 1. A) A single well demarcated erythematous inflammatory nodule covered with a hemorrhagic crust that is surrounded by a clear, erythematous, tender plaque on the little finger. **B)** Generalized, well-defined light pink urticated papules and plaques on the palms of both hands (bilateral).

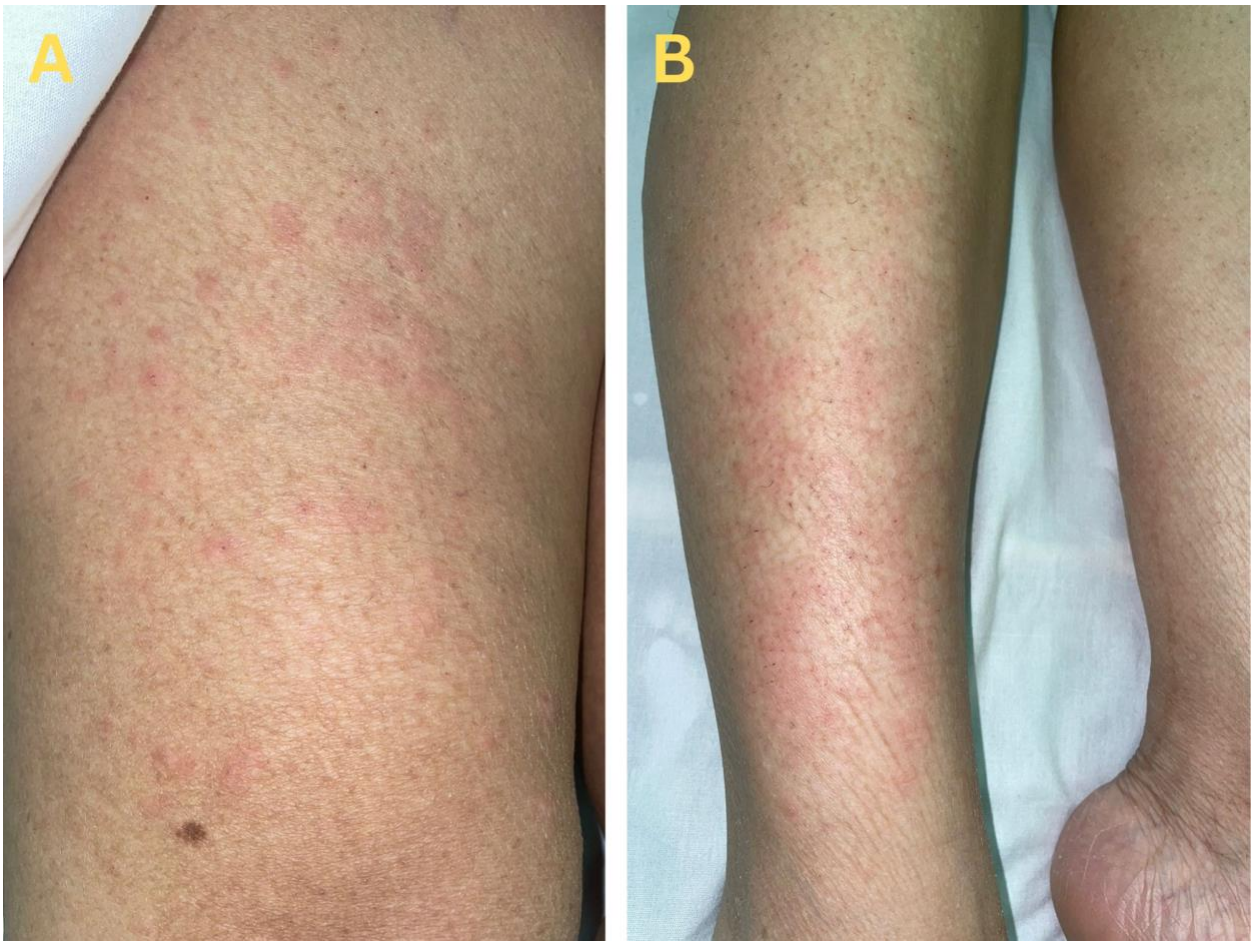

Figure 2. A, B) Multiple well-defined light pink macules and patches, with some exhibiting urticated plaques, over the thighs and legs.

Figure 3. Two well-defined pale pink macules, accompanied by scratch marks on both sides, over the forearms.

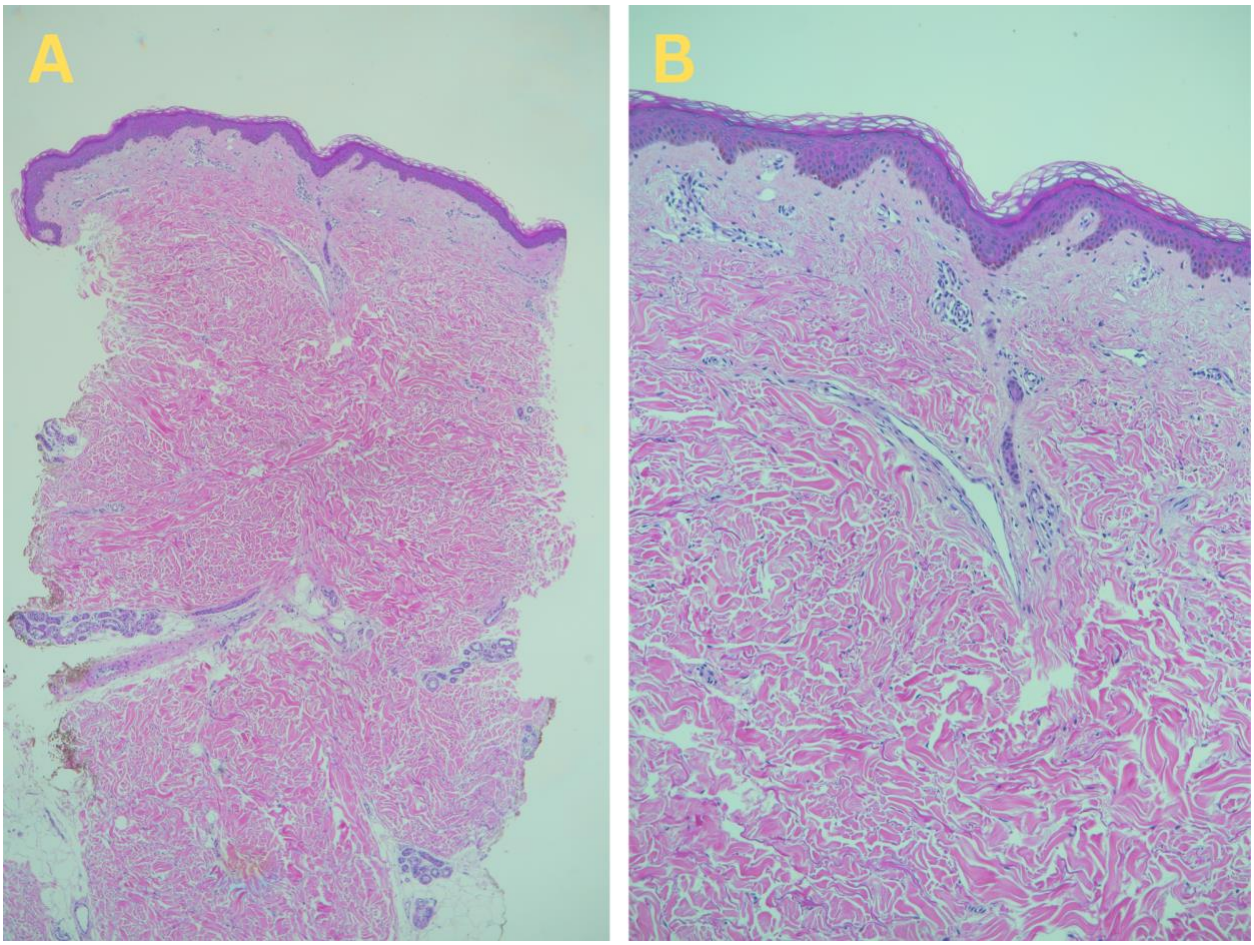

Figure 4. Skin biopsy showed mild dermal edema, dilatation of small blood vessels and mild perivascular lymphocytic infiltrate. **A)** (H & E, original magnification x4); **B)** (H & E, original magnification x10).

Fig. 5

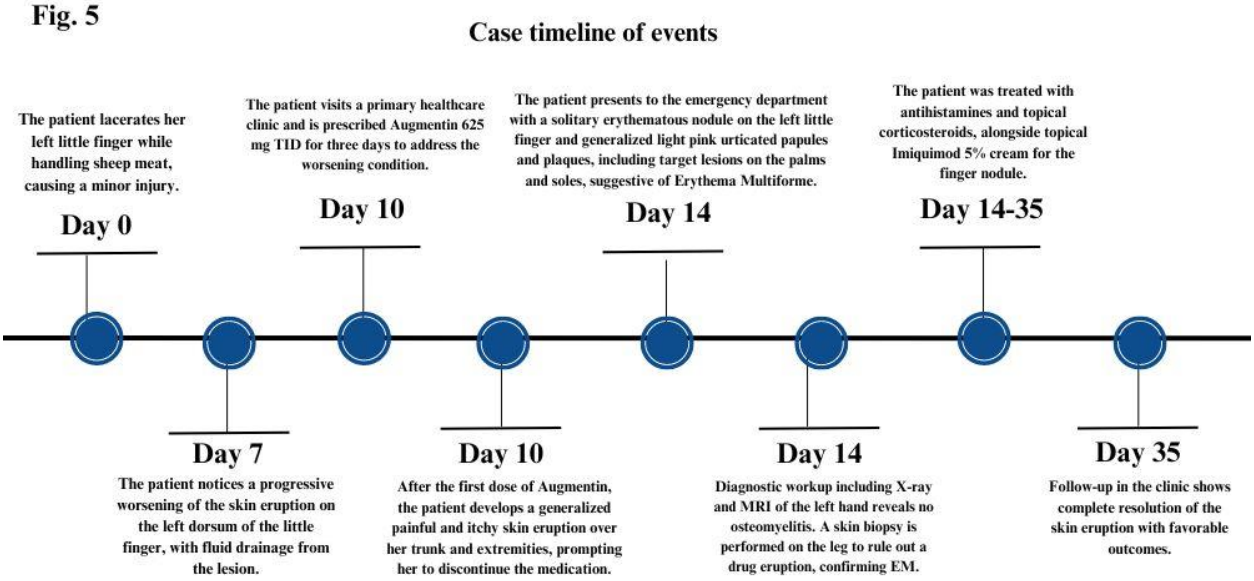

Figure 5. Case timeline of events.

Table 1. Summary review of reported cases involving erythema multiforme triggered by Orf-viral infection.

Case (year)	**Number of patients**	**Gender/Age (years)**	**Animal**	**Diagnosis**	**Management**
Johannessen JV *et al.*[8] (1975)	16	9 males/NA 7 females/NA	NA	Clinical	NA
Agger WA *et al.*[9] (1983)	1	Female/35	Lamb/Goat	Clinical	Oral corticosteroid, Schamberg's topical solution
Bassioukas K *et al.*[10] (1993)	2	Female/30 (1) Female/31 (2)	Sheep (1) NA (2)	Clinical and biopsy (1) Clinical (2)	Intravenous corticosteroid (1) No treatment (2)
Erbagci Z *et al.*[11] (2005)	2	Female/25 (1) Female/56 (2)	Raw meat (1) Sheep (2)	Clinical (1)(2)	Topical imiquimod cream (resistant to topical steroid) (1)(2)
Schmidt E *et al.*[12] (2006)	1	Male/44	Lamb	Clinical	Topical corticosteroid
Coskun O *et al.*[13] (2008)	1	Male/37	Lamb	Clinical and biopsy	Topical corticosteroid
de Wet C *et al.*[14] (2011)	2	Male/47 (1) Female/42 (2)	Sheep (1)(2)	Clinical (1)(2)	Oral antibiotic (flucloxacillin) (1)

					Oral antibiotic (clarithromycin), and systemic antihistamine (2)
Ozturk P *et al*.[15] (2012)	1	Male/30	Raw meat	Clinical and biopsy	Intravenous corticosteroid, topical mupirocin, oral cetirizine, and wet dressing with antiseptic solution
Durdu M *et al*.[16] (2014)	2	NA	NA	Clinical and biopsy	Topical corticosteroid
Shahmoradi Z *et al*.[17] (2014)	1	Female/37	Raw meat	Clinical	Oral cetirizine, topical corticosteroid, topical mupirocin, and wet dressing with antiseptic solution
Yorulmaz A *et al*.[18] (2014)	1	Female/50	Lamb	Clinical and biopsy	Topical corticosteroid, systemic antihistamine, and intramuscular corticosteroids
Joseph RH *et al*.[3] (2015)	2	Female/30 (1) Male/38 (2)	Lamb/Sheep (1) Lamb (2)	Clinical and biopsy (1)(2)	Oral antibiotic (sulfamethoxazole-trimethoprim),

					doxycycline, topical and oral corticosteroid (1) Oral antibiotic (amoxicillin), and systemic antihistamine (2)
Gallina L *et al*.[19] (2015)	1	Male/34	Raw meat	Clinical and biopsy	Oral corticosteroid, topical rifamycin, and oral tetracycline
Alian S *et al*.[20] (2015)	1	Female/36	Sheep	Clinical and biopsy	Oral corticosteroid
Biazar T *et al*.[21] (2016)	2	Female/45 (1) Female/32 (2)	Sheep	Clinical (1)(2)	Low dose intravenous corticosteroid, and systemic antihistamine
Maman M *et al*.[22] (2017)	1	Female/9	Sheep	Clinical	Intravenous antibiotic (amoxicillin + clavulanic acid and clindamycin), oral corticosteroid, and systemic antihistamine
López-Cedeño A *et al.*[23] (2018)	1	Male/6	Sheep/Goat	Clinical	No treatment

Khouna A *et al.*[24] (2019)	1	Female/31	Sheep	Clinical	No treatment
Wu K *et al.*[25] (2021)	1	Female/18	Calf	Clinical and biopsy	Topical corticosteroid
Cavalieri C *et al.*[26] (2022)	1	Male/26	Sheep/Raw meat	Clinical	No treatment
Salvi M *et al.*[27] (2024)	1	Female/51	Goat	Clinical and biopsy	No treatment
Alkallabi *et al.* (2024) (our case)	1	Female/41	Raw meat	Clinical and biopsy	Topical corticosteroid, topical imiquimod, and systemic antihistamine

NA, Not Applicable