

CONCISE COMMUNICATION

Poxvirus-induced angiogenesis after a thermal burn

Dilek BIYIK OZKAYA,¹ Banu TASKIN,² Betul TAS,³ Zehra ASIRAN SERDAR,⁴
Cuyan DEMIRKESEN,⁵ Ozlem SU,¹ Nahide ONSUN¹

¹Dermatovenerology Department, Medical Faculty, Bezmialem Vakif University, ²Dermatovenerology Department, Florence Nightingale Hospital, Bilim University, ³Dermatovenorology, Bagcilar Research and Training Hospital, ⁴Associate Professor Zehra Asiran Serdar's Clinic, and ⁵Pathology Department, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey

ABSTRACT

Orf (contagious ecthyma) is a zoonotic infection caused by a dermatotropic parapoxvirus that commonly infects sheep, goats, and oxen. Parapoxviruses are transmitted to humans through contact with an infected animal or fomites. Orf virus infections can induce ulceration, and papulonodular, pustular, or ecthymic lesions of the skin after contact with an infected animal or contaminated fomite. Rarely, orf virus provokes extensive vasculo-endothelial proliferation as a skin manifestation. Here, we present the case of an 8-year old female with poxvirus-induced vascular angiogenesis that developed 10 days after a thermal burn. An 8-year-old female presented at our outpatient clinic with red swellings and a yellow-brown crust on them. After a thermal burn with hot water, she went to a clinic and the burn was dressed with nitrofurazone and covered for 2 days. When the dressing was removed after 2 days, nodules were seen in the burnt areas. When the clinical findings were considered with the histopathological features, a reactive vascular proliferation due to a viral agent was suspected. Following PCR, parapoxvirus ovis was detected. Viral infections such as pox virus can trigger pyogenic granulomas or pyogenic granuloma-like vascular angiogenesis. Infectious agents must be considered when dealing with pyogenic granuloma-like lesions.

Key words: burn, orf, pyogenic granuloma, pox virus, vascular angiogenesis.

INTRODUCTION

Orf (contagious ecthyma) is a zoonotic infection caused by a dermatotropic parapoxvirus that commonly infects sheep, goats, and oxen. Parapoxviruses are transmitted to humans through contact with an infected animal or fomites.¹ Orf virus infections can induce ulceration, and papulonodular, pustular, or ecthymic lesions of the skin after contact with an infected animal or contaminated fomite. The incubation period is 7 days.^{1, 2} Subsequently, an erythematous nodule develops that goes on to ulcerate and heals with a firm necrotic crust. An iris-like lesion can develop with a red centre, white middle ring, and erythematous periphery. The lesions heal slowly over several weeks usually without scarring, unless there has been secondary infection.³

Rarely, orf virus provokes extensive vasculo-endothelial proliferation as a skin manifestation.

Here, we present the case of an 8-year old female with poxvirus-induced vascular angiogenesis that developed 10 days after a thermal burn.

CASE

An 8-year-old female presented at our outpatient clinic with red swellings and a yellow-brown crust on them. After a

thermal burn with hot water, she went to a clinic and the burn was dressed with nitrofurazone and covered for 2 days. When the dressing was removed after 2 days, nodules were seen in the burnt areas.

On examination of the left arm, granulomatous yellow-brown infiltrated nodules with an erythematous eroded base were seen. The nodules ranged in size from 5 × 3 to 2 × 1 cm (Fig. 1). There was no regional lymphadenopathy and the rest of physical and systemic examination was normal. A punch biopsy was taken from a lesion at the left wrist. Histopathologically, the biopsy was interpreted as a pyogenic granuloma in a different pathology department. When the biopsy was sent to us for consultation, the histopathological examination revealed massive capillary proliferation in an oedematous dermis (Fig. 2). The overlying epidermis contained keratinocytes with pale cytoplasm and a parakeratotic crust within the stratum corneum. When the clinical findings were considered with the histopathological features, a reactive vascular proliferation due to a viral agent was suspected. Following PCR, parapoxvirus ovis was detected (Fig. 3).

Since the lesion was dressed with nitrofurazone and covered for 2 days, we first considered allergic contact dermatitis and a secondary infection and started treatment with amoxicillin clavulonic acid 625 mg bid and chloroquine-diflucortolone

Correspondence: Dilek Biyik Ozkaya, M.D., Dermatovenerology Department, Medical Faculty, Bezmialem Vakif University, Adnan Menderes Bulvarı (Vatan cad). PK:34093 Fatih/Istanbul, Turkey. Email: dilekcozkaya@gmail.com
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Figure 1. (a, b) Clinical photographs of the initial lesion and (c, d) 6 weeks later.

valerate bid. After the histopathology showed a pyogenic granuloma, we started silver nitrate. After 2 weeks, the lesion started to heal. Six weeks later, only post-lesional pigmentation was observed. First, we thought that the lesions had regressed because of the treatment, but after the PCR result we realised that the regression was spontaneous.

DISCUSSION

Our patient visited an outpatient clinic with red swelling after a thermal burn. The initial biopsy was interpreted as a pyogenic granuloma. Parapoxvirus ovis (Orf virus) is an *Orthopoxvirus*. Analysis of the parapoxvirus genes has shown that viral vascular endothelial growth factor E (VEGF-E) stimulates angiogenesis in the skin, without the side effects seen with cellular VEGF-A.³ These molecules mediate endothelial cell proliferation, vascular permeability, angiogenesis, and lymphangiogenesis via the endothelial cell receptors VEGFR-1 (Flt1), -2 (KDRy Flk1), and -3 (Flt4). The VEGF-like protein of orf virus strain NZ2 (ORFV2-VEGF) is most closely related in primary structure to VEGF.⁴

Vascular endothelial growth factor (VEGF or VEGF-A) plays a pivotal role in the regulation of normal and pathological angiogenesis.⁴ VEGF-E is a potent angiogenic factor with a bioactivity similar to that of VEGF-A; *i.e.* *in vivo*, it induced tissue-factor

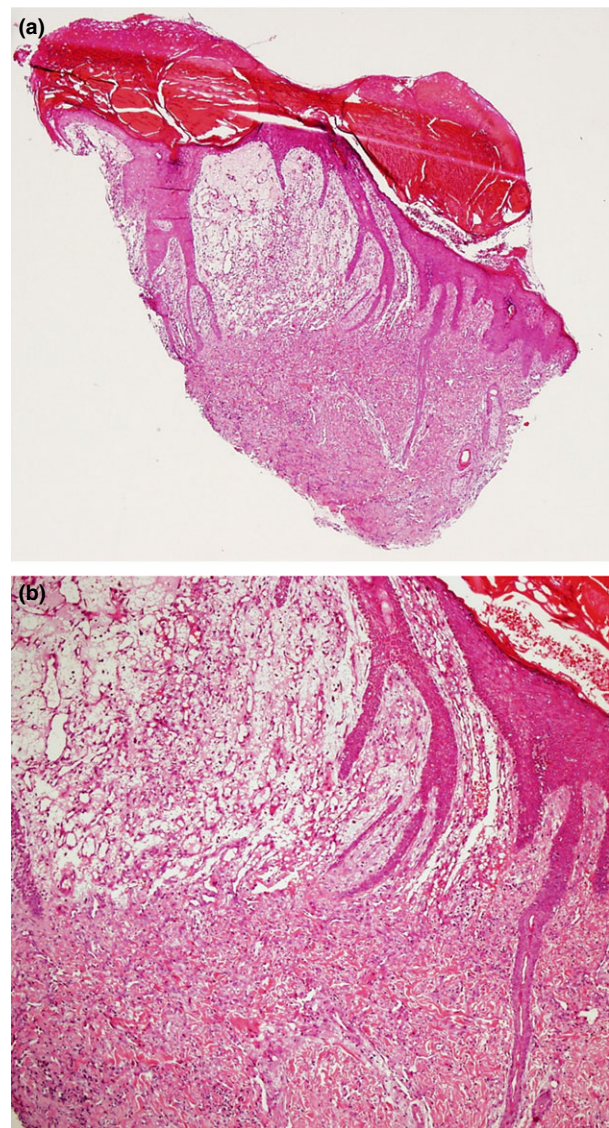


Figure 2. Massive capillary proliferation in oedematous dermis, with replacement of the dermal collagen fibres. Note the acanthotic epidermis with parakeratotic crust (a, HE×40; b, HE×200).

(TF) expression, the proliferation, migration, and sprouting of cultured vascular endothelial cells, and angiogenesis.⁴

Orf virus causes pyogenic granuloma-like lesions, which are characterised histopathologically by massive capillary proliferation and dilation. Our patient's first biopsy was interpreted as a pyogenic granuloma. There are similar reported cases.^{5–10} De Kaminsky *et al.*⁵ reported multiple pyogenic granulomas in a 15 month old girl burned with boiling milk. Bozkurt *et al.*⁶ described a 2-year-old boy with multiple pyogenic granulomas in an area burned with hot milk. Aliagaoglu *et al.*⁷ reported pyogenic granulomas with multiple and satellite involvement after a burn in a 5-year-old child. Ceyhan *et al.*⁸ reported an

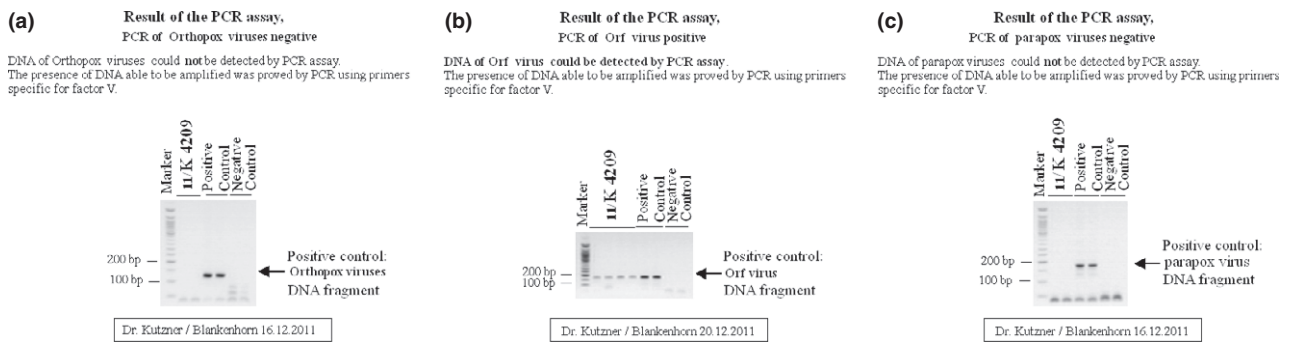


Figure 3. Orf virus was detected in these lesions by PCR. (a) PCR of orthopox viruses negative, (b) PCR of Orf virus positive, and (c) PCR of parapox viruses negative.

Table 1. Pyogenic granulomas after burn and infectious diseases

	Year	Age and sex	Cause of Burn	The time lesions occur	Healing time	Treatment
De Kaminsky <i>et al.</i> ⁵	1978	15- month-old girl	Boiling milk	1 week after burn	–	Electrocoagulation
Momeni <i>et al.</i> ⁹	1995	1.5-year-old boy	Boiling milk	2 weeks after burn	3 weeks	Spontaneously
		5-year-old girl	Boiling milk	2 weeks after burn	3 weeks	Spontaneously
Ceyhan <i>et al.</i> ⁸	1997	35-year-old woman	Boiling milk	Unknown	4 weeks	Spontaneously
		18-month-old girl	Boiling milk	1 week after burn	–	Excision
Aliagaoglu <i>et al.</i> ⁷	2006	5-year-old girl	Unknown	15 days after burn	–	Excision
Bozkurt <i>et al.</i> ⁶	2006	2-year-old boy	Boiling milk	–	–	Excision
Ceyhan <i>et al.</i> ¹⁰	2007	17-month-old boy	Boiling water	2 weeks after burn	12 weeks	Oral erythromycin, 40 mg/kg four times daily, 8 weeks
Albayrak <i>et al.</i> ¹¹	2012	5-year-old boy	Boiling water	8 days after burn	10 weeks	Oral erythromycin, 250 mg four times daily, 10 weeks
El Hayderi <i>et al.</i> ¹²	2013	52-year-old woman	After labial herpes	–	15 days	Treatment with valaciclovir (1000 mg, thrice daily for 15 days)
Midilli K ¹³	2013	11 males (mean age 37) 2 females in a burn unit	Unknown	–	6 weeks	2 patients died (added pseudomonas and acinetobacter infections). Other patients healed spontaneously

18-month-old girl with multiple pyogenic granulomas following a second-degree burn. Momeni *et al.*⁹ reported three patients: a 1.5-year-old male, 5-year-old female, and 35-year-old female; all three had second-degree burns over their face and trunk caused by hot milk. Ceyhan *et al.*¹⁰ reported multiple eruptive pyogenic granulomas in a 17-month-old male that developed on burned skin. In our opinion if PCR had been done in these cases, orf virus might have been seen. They have similar clinical appearance with our case. Albayrak *et al.*¹¹ reported bacillary angiomatosis in a burn; bacillary angiomatosis can also cause pyogenic granuloma-like lesions.

A pyogenic granuloma or lobular capillary haemangioma is a vascular tumour. They are common in children, but can occur

at any age.^{8–10} A pyogenic granuloma usually presents as a solitary, red, rapidly growing papule or nodule and they are generally seen on the hands, forearms, face, or at sites of trauma. Trauma, chronic irritation, some drugs, and pregnancy can trigger a pyogenic granuloma.^{8–10}

El Hayderi *et al.*¹² reported a pyogenic granuloma after HSV-1 infection. Midilli *et al.*¹³ reported a nosocomial outbreak of disseminated orf infection in a burn unit.

Lee and Lynde have suggested that bacterial microorganisms, including *Bartonella* spp., play a role in pathogenesis of PG, based on the similar clinical and histological features between PG and bacillary angiomatosis.¹⁴ Albayrak *et al.*¹¹ reported pyogenic granuloma like lesions caused by bacillary

angiomas (BA). El Haydari *et al.*¹² reported pyogenic granuloma like lesions after herpes virus infection. Similar to our case Midilli K *et al.*¹³ reported multiple pyogenic granulomas in 13 patients in a burn unit. These cases show that different infectious agents may cause pyogenic granuloma like lesions (Table 1).

In conclusion, wound healing in a burned area can trigger a pyogenic granuloma. In the burned area, local immunosuppression occurs, which can alter the response to infectious agents. In addition, viral infections such as pox virus can trigger pyogenic granulomas or pyogenic granuloma-like vascular angiogenesis. Infectious agents must be considered when dealing with pyogenic granuloma-like lesions. This is a rare and interesting condition, so we decided to report this case.

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CONFLICT OF INTEREST: None.

REFERENCES

- 1 Leavell UW, Jacob RJ. Contagious pustular dermatitis, contagious ecthyma. Orf virus infection. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's Dermatology in General Medicine*, 5th edn. New York, NY, USA, McGraw-Hill, 1999; 2474.
- 2 James WD, Berger TG, Elston DM. Viral diseases: In: James W, Berger T, Elston D, eds. *Andrews Diseases of the Skin: Clinical Dermatology*, 10th edn. Philadelphia: WB Saunders Company Elsevier, 2006; 19: 367.
- 3 Holst FR. Other viral infections. In: Plewig B, Landthaler W, eds. *Braun Falcos Dermatology*, 3rd edn. Heidelberg : Springer Medizin Verlag, 2009; 96–97.
- 4 Meyer M, Clauss M, Lepple-Wienhues A *et al.* A novel vascular endothelial growth factor encoded by Orf virus, VEGF-E, mediates angiogenesis via signalling through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) receptor tyrosine kinases. *EMBO J* 1999; **18**: 363–374.
- 5 de Kaminsky AR, Otero AC, Kaminsky CA, Shaw M, Formentini E, Abulafia J. Multiple disseminated pyogenic granuloma. *Br J Dermatol* 1978; **98**: 461–464.
- 6 Bozkurt M, Kulaççi Y, Zor F, Aşkar I. Multiple giant disseminated pyogenic granuloma in a burn lesion. *J Burn Care Res* 2006; **27**(2): 247–249.
- 7 Aliagaoglu C, Bakan V, Atasoy M, Toker S. Pyogenic granuloma with multiple and satellite involvement after a burn in a 5-year-old child. *J Dermatol* 2006; **33**(2): 150–152.
- 8 Ceyhan M, Erdem G, Kotiloğlu E *et al.* Pyogenic granuloma with multiple dissemination in a burn lesion. *Pediatr Dermatol* 1997; **14**: 213–215.
- 9 Momeni AZ, Enshaieh S, Sodifi M, Aminjawaheri M. Multiple giant disseminated pyogenic granuloma in three patients burned by boiling milk. *Int J Dermatol* 1995; **34**: 707–710.
- 10 Ceyhan AM, Basak PY, Akkaya VB, Yildirim M, Kapucuoglu N. A case of multiple, eruptive pyogenic granuloma developed on a region of the burned skin: can erythromycin be a treatment option? *J Burn Care Res* 2007; **28**: 754–757.
- 11 Albayrak A, Albayrak Y, Unal D, Atasoy M, Uyanik MH. A case of bacillary angiomatosis developed at a burn site. *Indian J Dermatol Venereol Leprol* 2012; **78**(1): 121.
- 12 El Haydari L, Paurobally D, Fassotte MF *et al.* Herpes Simplex virus type-1 and pyogenic granuloma: a vascular endothelial growth factor-mediated association. *Case Rep Dermatol* 2013; **5**(2): 236–243.
- 13 Midilli K, Erkişçi A, Kuşkuç M *et al.* Nosocomial outbreak of disseminated orf infection in a burn unit, Gaziantep, Turkey, October to December 2012. *Euro Surveill* 2013; **18**(11): 20425.
- 14 Lee J, Lynde C. Pyogenic granuloma: pyogenic again? Association between pyogenic granuloma and Bartonella. *J Cutan Med Surg* 2001; **5**: 467–470.