Two cases of human orf resembling intravascular lymphoma, angiolymphoid hyperplasia with eosinophilia, and lymphomatoid papulosis

Anita S. Savell, BS,[a] and Michael R. Heaphy, Jr, MD[a,b]
Reno, Nevada

INTRODUCTION

Orf, also known as ecthyma contagiosum, is a zoonosis caused by *Parapoxvirus ovis*, which is a member of Poxviridae.[1,2] The virus is endemic in goat and sheep populations around the world, and in humans it is most frequently observed in shepherds and farmers after direct contact with nodules or vesicles on livestock or through fomites.[1] The CD30 reactivity caused by *Parapoxvirus* viruses has been established,[3] and in milker's nodules, for example, CD30 reactivity was first described by Rose et al[4] in 1999. However, CD30 reactivity in orf was not reported until 2018.[5] Here, we present 2 cases of orf with CD30 reactivity that histologically resembled other conditions.

RESULTS

Case 1

A 17-year-old male adolescent who raised sheep presented to the clinic with a 3-week history of 2 nodules on his forehead (Fig 1). Sheep he handled were known to be infected with "sour mouth disease." Although the patient was informed the nodules would self-resolve, he requested they be removed because of cosmetic concerns. Histologic sections demonstrated irregular epidermal acanthosis and a brisk lymphocytic infiltrate that included numerous eosinophils (Fig 2, *A* and *B*). Small intracytoplasmic, eosinophilic inclusion bodies were noted within epidermal and follicular keratinocytes (Fig 2, *B*). Increased numbers of vessels lined by plump endothelial cells were also evident on staining for endothelial cell marker CD31 (Fig 2, *C*). Several ectatic vessels contained large, hyperchromatic lymphocytes, many of which showed strong immunoreactivity for CD30 antigen (Fig 2, *D*).

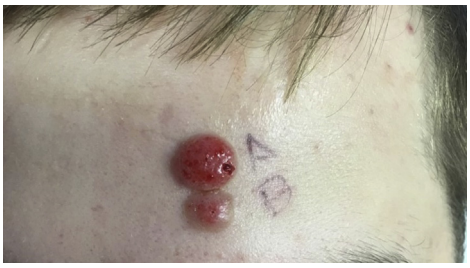

Fig 1. Nodules on forehead of 3 weeks' duration.

Case 2

A young woman who raised sheep presented to the clinic with a 2-week history of a nodule on her hand (Fig 3, *A*) and a newly formed papular eruption with vaguely annular patches on the face (Fig 3, *B*), arms, palms, and soles. Palmar (not shown) and plantar lesions resembled erythema multiforme (Fig 3, *C*). Biopsy of the nodule on the dorsal aspect of the left hand demonstrated an acanthotic and ulcerated epidermis (Fig 4, *A*) with rare eosinophilic inclusion bodies in the cytoplasm of keratinocytes (Fig 4, *B*) and a brisk lymphocytic infiltrate (Fig 4, *C*) with numerous large, atypical $CD30^+$ cells (Fig 4, *C* and *D*). A punch biopsy of the rash taken from the arm showed a superficial and deep perivascular lymphocytic infiltrate with many eosinophils and no epidermal changes. These histopathologic features are consistent with a dermal hypersensitivity reaction and could easily be mistaken for a reaction to a drug (Fig 5).

From the University of Nevada Reno School of Medicine[a]; and Skin Cancer and Dermatology Institute, Reno.[b]
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Correspondence to: Michael R. Heaphy, Jr, MD, 640 W Moana Ln, Reno, NV 89509. E-mail: mheaphy@skincancerderm.com.

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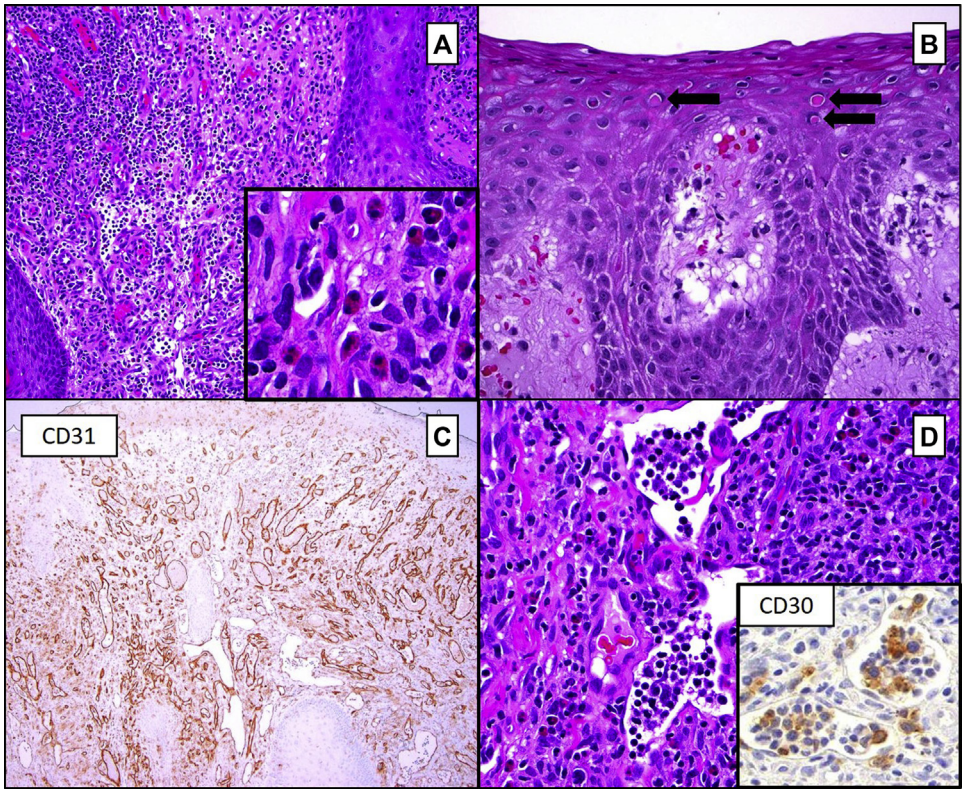

Fig 2. Biopsy of forehead nodule. **A**, Irregular acanthosis, numerous vessels with prominent endothelial cells, and a brisk lymphocytic infiltrate that includes many eosinophils (inset). (Hematoxylin-eosin stain.) **B**, Higher-power view of an acanthotic epidermis with conspicuous intracytoplasmic eosinophilic inclusions (arrows). **C**, Stained for CD31 (brown), more clearly demonstrating an extensively vascularized dermis. **D**, Large, hyperchromatic $CD30^+$ cells (inset, brown) present within ectatic vessels.

DISCUSSION

There are at least 18 distinct *Parapoxvirus* viruses,[6] at least 7 of which have been reported to cause disease in humans and some of which cause nodules or vesicles that bear resemblance to orf.[7] Such lesions include milker's nodules, stomatitis papulosa, Ausdyk disease, sealpox, and those caused by parapoxvirus of red deer in New Zealand and novel deer-associated parapoxvirus.[7] Nodules or vesicles appear at the site of inoculation after up to a 5-day incubation period.[7] Orf nodules are typically solitary[3] and ulcerate after 2 to 3 weeks.[7] In contrast, milker's nodules more commonly appear in groups[8] and without ulceration.[7]

Histologic features of orf vary based on stage but are classically characterized by irregular epidermal acanthosis with a brisk infiltrate and inclusion bodies within epidermal keratinocytes.[1] A highly vascular infiltrate is common because of viral production of a homolog of vascular endothelial growth factor,[3] and as a result, some cases may histologically simulate a vascular tumor.[1] The histopathologic features of the rarely reported widespread or generalized reactions to orf virus infection have not been well documented.

Whether all of the distinct *Parapoxvirus* viruses known to cause disease in humans are prone to elicit a robust infiltrate with many atypical $CD30^+$ lymphocytes is not presently known. Authors of at least 2 popular dermatopathology textbooks have used the aforementioned reference by Rose et al[4] to support the assertion that a $CD30^+$ reaction may occur in orf infections.[1,3] Other reactive inflammatory disorders that may contain a significant number of large $CD30^+$ cells mimicking certain lymphoproliferative disorders include molluscum contagiosum, viral warts, herpes simplex, herpes zoster, arthropod reactions, scabies, and drug eruptions.[3] In the majority of such cases, however, the number and density of $CD30^+$ cells are considerably less than that which is typically observed in the most commonly encountered $CD30^+$ lymphoproliferative disorders, lymphomatoid papulosis and anaplastic large T-cell lymphoma. Rarely do any of the reactive conditions mentioned earlier truly mimic lymphomatoid

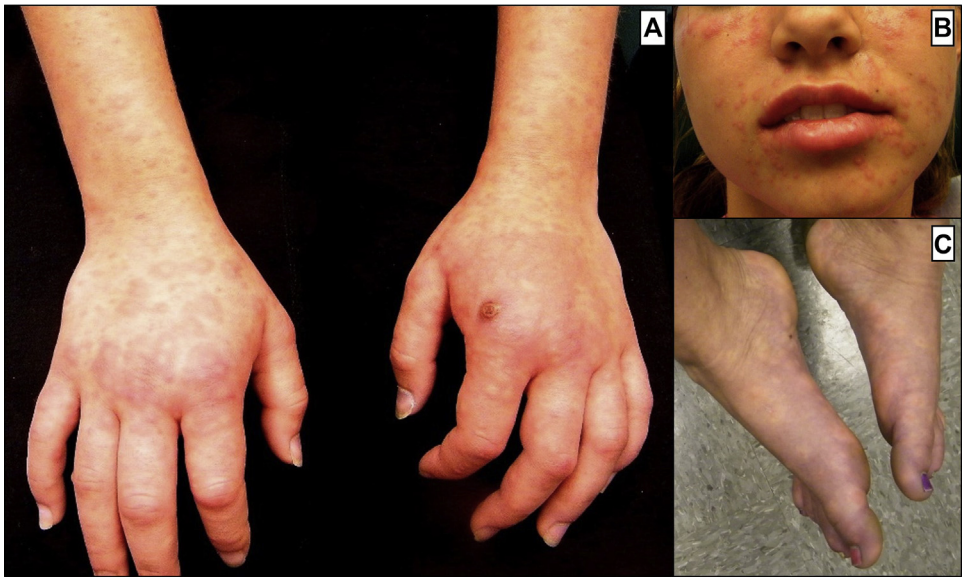

Fig 3. **A**, Nodule on dorsal surface of the left hand, with associated annular patches and edema of the bilateral aspect of the hands. **B**, New-onset papular eruption on the face. **C**, Erythema multiforme–like reaction of the plantar aspect of the foot.

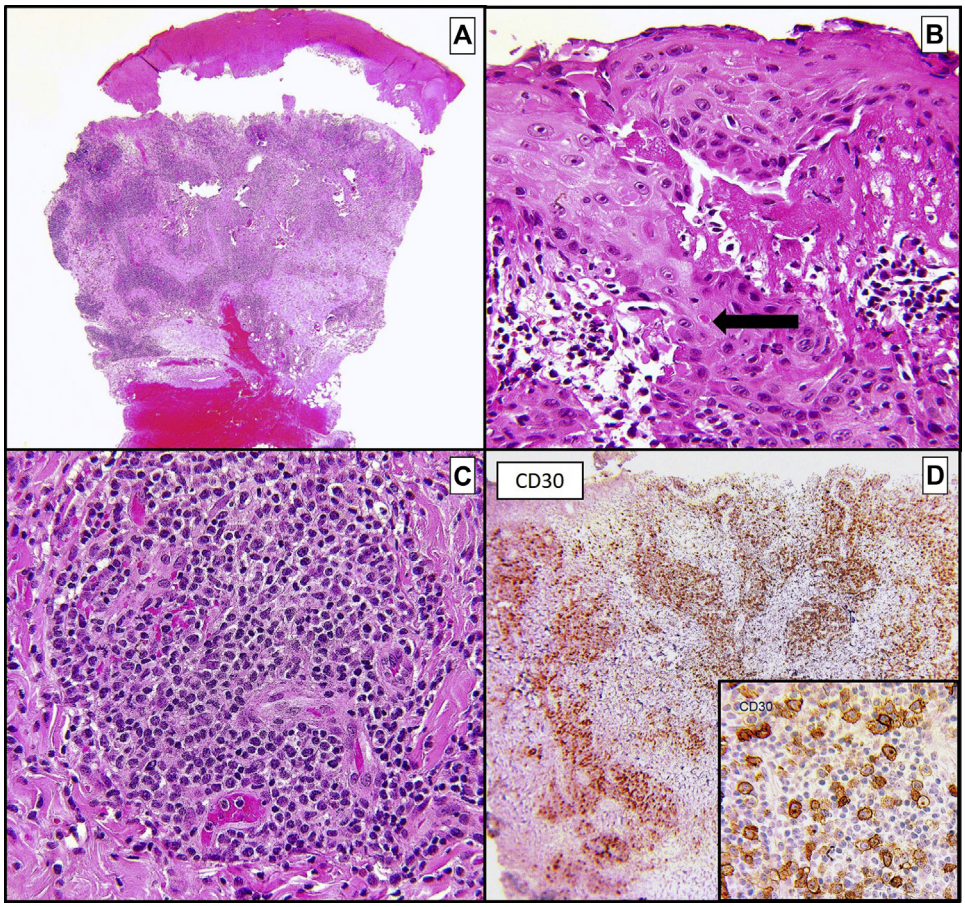

Fig 4. Biopsy of the nodule on the dorsal aspect of the hand, demonstrating eroded, irregularly acanthotic epidermis with a dense dermal infiltrate (**A**), rare eosinophilic inclusion (arrow) (**B**), a brisk infiltrate composed of many large, atypical lymphocytes (**C**), and numerous atypical $CD30^{+}$ lymphocytes (brown) (**D**). (Hematoxylin-eosin stain.)

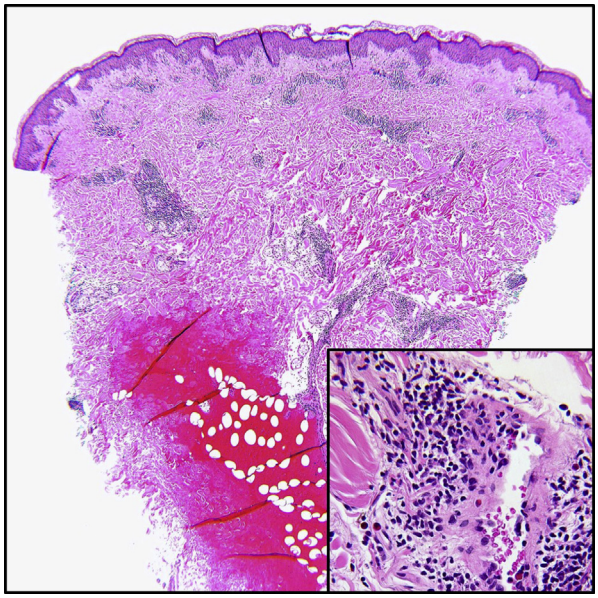

Fig 5. Biopsy from annular eruption on the arm, showing a high-power view (inset) of the dermal perivascular lymphocytic infiltrate with admixed eosinophils (dermal hypersensitivity reaction). (Hematoxylin-eosin stain.)

papulosis or anaplastic large T-cell lymphoma, and confusion with these entities by the dermatopathologist is not common.

Case 1 is to our knowledge the first report of orf with $CD30^+$ atypical lymphocytes confined to the intravascular space in widely dilatated vessels, resembling intravascular lymphoma. Although milker's nodules have a long-established record of CD30 reactivity, with multiple case reports since their initial description,[9] the presence of $CD30^+$ atypical lymphocytes in orf has only recently been documented in 2 cases and such cells were present only within the dermis.[5,10] In case 1, the reactive vascular proliferation with vessels lined by plump endothelial cells accompanied by a brisk lymphocytic infiltrate with many eosinophils also bore some histologic resemblance to angiolymphoid hyperplasia with eosinophilia, the pathogenesis of which has also been tied to local production of vascular endothelial growth factor.[11] Histopathologic resemblance of *Parapoxvirus*-induced lesions to angiolymphoid hyperplasia with eosinophilia has not been described in literature, to our knowledge.

Case 2 demonstrated $CD30^+$ atypical lymphocytes densely clustered throughout the dermis and was histologically indistinguishable from lymphomatoid papulosis and a generalized maculopapular reaction that clinically and histologically resembled a hypersensitivity reaction to a drug. In contrast, exanthematous reactions to viral infections typically show a rather nonspecific superficial perivascular lymphocytic infiltrate without eosinophils.

In conclusion, we present the first case, to our knowledge, of orf resembling intravascular lymphoma and angiolymphoid hyperplasia with eosinophilia, and we highlight the potential for orf to resemble lymphomatoid papulosis and to induce a widespread maculopapular eruption that histologically resembles a drug-induced hypersensitivity reaction.

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