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Overview on the Contiguous Ecthyma (Orf) Disease

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Abstract:
Orf, Ecthyma disease a zoonotic disease with a highly infectious viral skin disease that affects sheep, goats, and a few other domestic and wild grazing animals, as well as humans. It manifests as painful skin lesions that frequently appear on the mouth and muzzle. The disease is found all over the world and can strike at any time of year, but it is most commonly recorded in the spring and summer, mostly among lambs and kids. Contagious ecthyma virus, Orf virus , Contagious pustular dermatitis, painful mouth, sore mouth and scabby mouth. The sheep species that are most frequently impacted by contagious ecthyma virus are lambs and adults that have not had a vaccination. Mortality is uncommon, but severe morbidity is common, with significant economic losses often linked to aspiration pneumonia or following bacterial or parasitic diseases. In this review focus on the Contiguous Ecthyma (Orf) Disease and immune response.

Key words: Contiguous Ecthyma, Orf, immune response

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Introduction:

Ecthyma disease is a highly infectious viral skin disease that affects sheep, goats, and a few other domestic and wild grazing animals. as well as humans. It manifests as painful skin lesions that frequently appear on the mouth and muzzle, where it can lead to anorexia or starvation (kamal Alsaadi, et al,2017). The lesion presented with a spectrum of lesions in the commissure of the lips, medial canthus of the left eye, and distal prepuce, ranging from hemorrhagic papules, vesicles, and pustules to multifocal necrotic scabs (Gwynne E. Kinley ,et al , 2013) .the clinical presentation of these lesions in young lambs during a spontaneous epidemic of the disease. On the gingiva, tongue, and dental pad, lesions could be visible. They developed from small, erythematous papules to bigger, frequently consolidating papules that, in some instances, were ulcerated. Within seven days, the resolution process began, and it was finished in 22 days (Ma´ire C, et al , 2007). After a 3 to 7 days incubation period, human orf lesions typically manifest themselves on the fingers, hands, or forearms. Typically, a lesion will grow over time from a small, erythematous macule or papule to a big nodule with a red center, a white halo, and peripheral erythema(M. Ganter.,2015 ; Turid Vikoren,et al , 2008). At least 71% of human diseases are zoonotic, and over the previous decade, pathogens originating from animals or from products derived from animals have been responsible for nearly 75% of all newly emerging human pathogens(Rodolaki A , 2014).

The virus-caused disease is endemic throughout the world and highly transmissible, primarily affecting small ruminants, all strains were identified from sick animals' skin lesions (Charalambos Billinis ,et al , 2012) . Walley (1890) first described the disease in sheep and referred it as contagious dermatitis or Orf the term contagious ecthyma was first used by Mossu . Peterkin (1937) described the zoonotic importance of the disease .Since then the disease in man has been referred to as Orf ,and the virus named Orf virus (Robinson and Balassu ,1981). The disease is found all over the world and can strike at any time of year, but it is most commonly recorded in the spring and summer, mostly among lambs and kids (Pratyush.K ,et al , 2019). The disease, which affects the skin, is characterized by the growth of a sizable vascularized benign tumor-like lesion and can be managed with antiretroviral medications (Tedla M, et al ; 2018). Electron microscopy may not always detect the oval virus, which is comparable to the virus of Milker's nodules . Milker's nodule, which is produced by the same

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group of viruses (poxvirus, parapox, and orthopox); is difficult to differentiate, even in ultrastructural analyses (Gill MJ ,et al, 1990) . Aynaud conducted a thorough investigation of the infectious pustular dermatitis of sheep and published a report in 1923 that noted that the illness might be spread by a "filterable" agent. From 1957 to 1963, reports on the isolation of parapoxvirus (PPV) in cell culture were published. In 1933, comprehensive accounts of how each illness spread to humans was published (ORFV). The PPV DNA sequence was initially described in 1989, and the PPV genomes were first molecularly investigated in 1979 (D. Haig ,et al , 2008).

Causative agent of Ecthyma disease

Contagious ecthyma virus ,Orf virus , Contagious pustular dermatitis, painful mouth, soremouth and scabby mouth are additional names for the illness (kamal Alsaadi, et al , 2017 ; Gwynne E, Kinley,et al ,2013 ; Esposito J.J, et al,1995).The virus epitheliotropic ,prototype species and has ovoid-shaped ,enveloped, virions measuring 260 by 160 nm and a linear double-stranded positive-sense DNA virus ,genome measuring 134-139 kb, an unusually high average G + C content of 63%–64%, and is a member of the family Poxviridae, subfamily Chordopoxvirinae, and genus Parapoxvirus (Nandi S , et al, 2011 ; Delia Lacasta ,et al , 2021 ; C.M. Fauquet, et al ,2005). Poxviruses are cytoplasmic-parasitic DNA viruses that multiply and assemble in viral factories. The actions of the Parapoxvirus genus, with ORFV as a typical species, differ significantly from those of Orthopoxvirus, and the plots of viral practical solutions for avoiding host immunity are sophisticated.and interesting, especially when it comes to anti-host and host antiviral mechanisms(Yongzhong Yu ,et al , 2022) . The tubular, filamentous arrangement of the outer coat of the viral particle is the virus's most distinctive physical characteristic(Martins M ,et al, 2021 ; D. Haig,et al , 2008). The viral genome is divided into two parts: a conserved core piece and changeable terminal portions that encode the components essential for viral attachment to cell hosts (Fleming et al , 2015). The core conserved region contains multiple genes involved in viral replication, notably the B2L gene, which encodes a key immunogenic envelope protein homologue of vaccinia virus. (Gelaye et al , 2016 ; Olivero, et al , 2018 ; Murat Şevik , 2019 ; Candice Schmidt,et al , 2013 ; Madhusudan Hosamani ,et al , 2008). The core region and the variable region make up its genome. The core region, which is conserved in the majority of the poxviruses, codes for critical proteins needed for structural elements, nucleotide biosynthesis, genome replication, transcription, and assembly. The variable areas, on the other hand, are located at the 5′ and 3′ terminal ends. The

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primary regulators of viral pathogenicity and host range are the proteins that these terminal genes encode (Delhon et al , 2004). In a PCR procedure, DNA was isolated from skin and scab tissue samples taken from animals that had tested positive for contagious ecthyma (CE) . PCR sequence analysis the B2L gene was chosen extensively utilized for molecular identification and genetic assessment of parapoxvirus species (P. Forster, et al , 2001 ; Kottaridi C, et al , 2006). Both the ORFV 059(F1L) and ORFV 011(B2L) full-length genes were cloned . The variable terminal sections of the genome contain genes that are not required for virus multiplication; some of them are unique to ORFV and encode proteins critical for ORFV virulence or pathogenesis, as well as regulating the host's antiviral immune response (Hinds et al, 2007). The viral interferon resistance (VIR) protein, which is encoded by the highly conserved gene ORF020 (homolog of VACV E3L), is involved in inhibiting the antiviral action of the host interferon response (C.J. McInnes, et al , 1998). The interferon resistance gene (VIR), which is situated in the left terminal of the orf viral genome, was used to study the genetic variability of Greek and Italian orf virus isolates at the amino acid level (McInnes C, et al , 1998 ; Christine Kottaridi ,et al , 2006). For molecular diagnosis and genetic characterisation of ORFVs in diverse epidemics, the VIR gene has been a target (G. Venkatesan, et al , 2011). The immunomodulator proteins that ORF virus has evolved with is called E3L, and it confers resistance to interferons on poxviruses (Monu Karki, et al, 2019).

Pathogenicity of Ecthyma Virus

Ordinarily, skin damage, fractures, and abrasions allow the Orf virus to enter the host's tissue and reproduce in keratinocytes that are undergoing epidermal regrowth (B.Markey ,et al , 2013). The cytoplasm of cells serves as the site of autonomous poxvirus replication. Virion produces early enzymes and early virion proteins after uncoating late proteins and late enzymes. Poxviruses have toxic effects on cells, which cause rounding ,and clumping of the cells, the breakdown of the cell's structural integrity, and the development of cytoplasmic vacuoles. By inoculating the skin, many poxviruses can cause a localized, self-contained illness (orf) these replication "factories" can be seen under a light microscope as basophilic-staining B-type inclusion bodies and are distinct from the host nucleus. Recombination occurs spontaneously in the genome (Dayna G,et al ,2001). When the infectious ecthyma virus invades, immunoglobulins are generated that attach to it particularly to form complex immune responses, which are then removed by the immune system to protect tissues from injury (Y,DAI,et al, 2017). The viral replication caused cutaneous

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cell edema and granulomatous inflammation (V,Spyrouo and G.Valiakas ,2015). Vacuolar degeneration, expanding degeneration, and eosinophilic cytoplasmic inclusions in keratinocytes, viral cytopathic changes that might have been induced by an ORFV infection, Granulocyte-macrophage colony-stimulating factor, which could have been produced by an ORFV infection, Granulocyte-macrophage colony-stimulating factor, which could have been caused by an ORF the cause of transient viral elusion, is inhibited by viral activity, allowing for viral reproduction in cells. (Deane.D,et al ,2000 ; Kui Zhao ,et al , 2010). The immunomodulator proteins shed light on disease development and vital elements of a host defense response. This information will be utilized to create a logical prevention plan. (David M. Haig and Colin J. McInnes,2002). When orf infects the skin or mucosa, it causes papules, pustules, or highly vascularized, proliferative cauliflower-like lesions that affect the host's immune system and encourage angiogenesis When diagnosing sheep and goats with proliferative and papilloma-like skin lesions, Orf virus should always be considered..(G.P. Burrai,et al , 2021).

Orf is clinically identified by the formation of papules, vesicle pustules and and quickly expanding scabs limited to the infected animals' lips and snout (J.F Carguelutti ,et al , 2011). These lesions often develop a crust, quickly develop scabs, then heal on their own after 4 weeks. The scabs are an indicator of future infections and contribute to the contamination of pastures and sheds because they contain large concentrations of the virus and protect it from environmental inactivation for months or years (Haig D M,et al , 2002). Epidermal keratinocytes, especially those repairing the damaged skin, have been found to contain ORFV antigen when ORFV envelope proteins are targeted by antibodies. A virus may also be present in the basal keratinocytes at the base of hair follicles (D. Haig.et al , 2008). The pathological findings in this instance revealed considerable vascular proliferation, viral cytopathic changes in keratinocytes, included vacuolar degeneration, ballooning degeneration, and eosinophilic cytoplasmic particles, which might have been caused by an ORFV infection(KuiZhao et al,2010). after slaughtering a sheep to commemorate the Muslim holiday Eid al-Adha, acquired numerous severe erythematous, purple-colored plaques on his hands. Viral multiplication is followed by morphological and metabolic alterations that ultimately result in cell demise. On the basis of the history of exposure, the histology, and the typical skin lesions, the diagnosis of orf virus infection was made. Although farmers and doctors are typically those with frequent animal contact who contract the orf virus (Ashley Velluccia,et al ,2020) .

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The sheep species that are most frequently impacted by Contagious ecthyma virus are lambs and adults that have not had a vaccination. Mortality is uncommon , but severe morbidity is common, with significant economic losses often linked to aspiration pneumonia or following bacterial or parasitic diseases (Mauldin EA.et al , 2016).

There have been reports of secondary bacterial infections including Arcanobacterium pyogenes and Staphylococcus aureus in orf instances. First symptoms can be seen in lambs as early as day 4, and they can last for up to three weeks or more before they fully recover, which can take up to eight weeks(A Bala, et al ,2019). through abraded skin and replicates in epidermal cells(I.R.Tizard,2013) The many phases of skin lesions-erythema, macule, papule, vesicle, pustule, scab, and scar-proceed in a systematic manner. The infection is limited to the squamous epithelium and may affect the mouth, eyelids, teats, and coronary band, making the affected animals more susceptible to secondary infections. (L.J.savory et al, 2000). Clinically, ORFV mostly affects the skin surrounding the lips, oral and nasal mucosa, and udders, and is linked with cutaneous lesions that appear in various phases as maculopapular, vesicular pustules, and scabby proliferative lesions(Adedeji ,et al , 2018) Lesions usually disappear in 2 to 4 weeks after the onset of contagious ecthyma, and it is not usually fatal. However, if secondary problems such bacterial infections or myiasis develop, mortality may occur(D.J.Wilson .2012) Ecthyma lesions that can cause anorexia or even famine and are painful. Lesions on an animal's udder can lead it to forsake its young, and young animals may refuse to nurse them. Lameness may be brought on by foot lesions(Lowa .s.unviresity, 2015).

Clinical presentation is typically used to diagnose diseases. However, given that several of the differential diagnoses include notifiable diseases, such as foot-and-mouth disease (FMD), bluetongue (BT), sheep pox, and peste des petits ruminants(PPR), laboratory testing and confirmation may be crucial (Lacasta D , 2021; Watson P, 2002). All of the affected kids vital signs-temperature, pulse, and breathing effort/rate-were normal. Auscultation of the heart and lungs was normal. Musculoskeletal and neurological behavioral issues . The muzzle lesions were best described as proliferating, crusty lesions with macules, papules, pustules, and scabs (L. macula spot, L. papule, and L. pustula containing pus) (SpicklerAR , 2015). .
Contact with an infected animal or exposure to a polluted environment or object, such as grazing, are the two main ways that transmission happens. The virus replicates in epidermal cells after entering the host through skin breaks, causing lesion growth(Jamilu Abubakar

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Bala ,et al; 2019). Transmission from person to person is uncommon(Hosamani M,et al , 2009). Zoonoses are most usually spread when afflicted animals are lambed, sheared, docked, soaked, or slaughtered, The majority of human infections are localized and self-heal(Delhon G,et al , 2004).

Immounlogical response to Ecthyma Virus

The immune response to infected by Contagious Ecthyma virus in sheep include Both innate and adaptive mechanisms make up the immune response to ORFV infection.(Vikoren,T ,et al, 2008). Because of a lack of immunological memory, innate immunity is the initial line of defense against an invading virus. Once internalized, neutrophils, MHC class II, dendritic cells (DCs), and natural killer (NK) cells of the innate immune system combat the viral infection (Zahoor, M.A, et al , 2016). Adaptive immunity refers to cell-mediated and antibody-mediated responses that aid in the detection of invading viral antigens by host cells (McLane L.M,et al , 2019). Depletion of lymphocyte subsets provides a unique opportunity to investigate the involvement of various cellular components of the sheep immune system during Orf virus infection (J.B loyd, et al ,2000). Virus was discovered in the skin of one of three sheep: CD8-depleted, WC1-depleted, and control. CD8+ lymphocytes weren't found to be necessary for viral clearance later in the infection, but the presence of CD4+ T-cells and Orf-virus-specific antibodies is essential for viral replication control in infected sheep skin (J.B loyd et al; 2000). When compared to CD8+ cytotoxic T-cells and B-cell responses, significant amounts of CD4+ T-cells were identified in infected animals, demonstrating that the immunological response to ORFV infection is normal (Umer M, et al , 2020 ; David M. Haig and Colin J. McInnes, 2002). Antiviral characteristics of the immune response to Contagious Ecthyma Virus (CEV) infection in the skin and adjacent lymph nodes include CD4+ and CD8+ cells,cytotoxic T lymphocytes,interferons,antibodies, and other additives (Haig D , 1998).

ORFV can partially avoid the human immune response because it rapidly produces a variety of virulence proteins that impair host immunity after acute infection of the mucocutaneous borders of the epidermis (Jamilu Abubakar B ,et al,2020). ORFV encodes a number of immunomodulatory genes (IMGs), including chemokine binding protein (CBP), interleukin-10 (IL-10), vascular endothelial growth factor (VEGF), the GM-CSF inhibitory factor (GIF), and interferon-resistance gene (OVIFNR), which inhibits protein synthesis by preventing an enzyme called dsRNA-dependent kinase from working (Martins M, et al, 2021). Genetic variation has

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been seen to exist even within genes at conserved areas, changing structural proteins that could be the target of a future universal vaccination(Hassana Kyari M, et al ,2022). ORFV elicits a strong immune response in sheep, involving neutrophils, cutaneous dendritic cells, CD4+ and CD8+ T cells, interferon gamma, B cells, and antibody production. CD4+ T cells, interferon gamma, and, to a lesser extent, CD8+ T cells aid to defend against ORFV infection, although antibodies had little impact (Haig DM and McInnes CJ, 2008). The ORFV chemokine-binding protein (CBP) binds to chemokines that regulate monocyte, macrophage, lymphocyte, and neutrophil recruitment to the site of infection, such as monocyte chemotactic protein-1, macrophage inflammatory protein-1 alpha, RANTES (regulated upon activation, normal T cell expressed and secreted), and lymphotactin (Haig DM , 2006).

The vascular endothelial growth factor (VEGF) glycoprotein has particular mitogenic action for endothelial cells as well as the potential to improve vascular permeability (M Saleh; 1996). VEGF is essential for the creation of new blood vessels during embryonic vasculogenesis and adult angiogenesis (Lyn M. Wise, et al, 1999). Studies showing that inactivating just one VEGF allele causes embryonic mortality due to faulty vascular development underline the importance of VEGF's involvement (P Carmeliet ,et al ,1996). VEGF also acts as an angiogenesis mediator in a variety of pathological conditions, such as tumor formation. Furthermore, some inhibitors of the VEGF/VEGF receptor system have been shown to have an antiangiogenic mechanism for inhibiting tumor development (M Saleh, 1999).

A fifth member of the vascular endothelial growth factor family, VEGF-E, is encoded by the Orf virus. Unlike VEGFR1 or VEGFR3, this protein only interacts to neuropilin-1 and VEGF-receptor 2 (VEGFR2). In accordance with its receptor binding, VEGF-E displays biological activity that raises vascular permeability and endothelial cells' m When recombinant VEGF-E was expressed in normal skin, it thickened the epidermis and increased the density of endothelial cells and blood vessels in the dermis . In wound skin, VEGF-E promoted wound re-epithelialization and thickened neovascularization, pointing to a potential therapeutic use for VEGF-E in accelerating wound healing (Philippa M Beard , 2021) .

A polypeptide comparable to interleukin-10 (IL-10) has been found to be encoded by a gene in the genome of orf virus (Orf) strain NZ2. The anticipated polypeptide sequence has high levels of amino acid similarity with IL-10 proteins reported in sheep (80%), cattle (75%), humans (67%), mice (64%), Epstein-Barr virus (63%) and equine herpesvirus (67%),

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among other species. Two-thirds of the orf protein, or the C-terminus, is similar to ovine IL-10, suggesting that this gene was stolen from the host sheep during orf creation. The IL-10-like gene is expressed early (S B Fleming ,et al , 1997).

Numerous viruses have evolved along the host immune system, developing a number of defensive mechanisms that prevent immune identification and host annihilation. Viruses that acquire cellular cytokine homology or cytokine detection genes are examples of this. Cellular interleukin-10 (IL-10) is an immunomodulatory cytokine generated by several cell types, include monocytes, macrophages, T- and B-lymphocytes, dendritic cells (DC), keratinocytes, epithelial cells, and mast cells (Barry Slobedman ,et al, 2009). IL-10, a secreted cytokine production inhibitory factor, was discovered 30 years ago. It is generated by T helper (Th) 2 cell clones and has been shown to inhibit Th1 cell cytokine production (Margarida Saraiva, et al, 2020).

The cytokine IL-10 is a crucial facilitator of anti-inflammatory processes that protects a host against exaggerated reactions to infections and microbiota. It also plays crucial roles in a variety of other contexts, including sterile wound healing, autoimmune, cancer, and homeostasis (Margarida Saraiva ,et al , 2020). Apoptosis a process of programmed cell death , a type of cell death different from necrosis, is important in processes such as homeostasis and the elimination of damaged cells and may be initiated by cytokines and immune effector cells (Jin Z and El-Deiry WS , 2005 ; Aderem A , Underhill D.M ,1999) . Contagious ecthyma virus is a potent genetic carrier capable of controlling apoptosis in infected skin cells, a strategy that serves to evade the host's immunological response. It has been claimed that the virus may persist in the skin and produce recurring infections in the same flock (Garrido Farina , et al, 2008). Mammalian interleukin 10 (IL10) is a cytokine that inhibits immunological and inflammatory responses, and it was discovered that ORFV could also make a related anti-inflammatory virokine (ORFV-IL-10) that severely weakened the virus when this gene was taken out(Fleming SB ,et al , 2007) .The current study did not examine the existence of viral immuno-modulatory virulence factors, but it did discover that the ORFV-infected cells' expression level of IL-10 increased after infection (Huaijie Jia,et al , 2017) . 36.7% and 7.8% seroprevalence of CE against IgM antibodies have been recorded in small ruminants, respectively. As humans, CE is worried about zoonotic diseases is also susceptible to infection from cuts and open sores (Buttnerand Rziha, 2000).

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The farms with the highest seroprevalence of CE infection and recent CE infection outbreaks were those that did not adopt proper biosecurity. From the past, it appears that this farm imports and trades sheep from questionable sources, which may be the cause of the recent outbreak in the farms. This supports the findings of our prior study, which found that farms with poor health practices had greater levels of CE IgM detection (Jesse ,et al , 2018). According to a recent seroprevalence investigation, the incidence of IgM antibodies in smaller animal populations was greater in goats than sheep (A.Abdullah ,et al , 2015). Despite of the animals' lymphocyte depletion status, Orf lesions healed faster in sheep with high Orf-virus-specific antigen titres at the time of infection than in sheep with low antibody levels. (J.B loyd, et al , 2000). The contagious ecthyma virus is also a powerful genetic carrier capable of controlling apoptosis in infected skin cells, a defense strategy used to avoid the host's immunological reaction. It's possible that the virus will persist in the skin and produce recurring infections in the same flock (Garrido-Fariña ,et al , 2008) .

The important role of INF-γ in the host immune response in reducing disease severity . IFN-γ -mRNA-expressing cells were found after reinfection but not after original infection (Ian E Anderson ,et al , 2001). When compared to primary infection, the orf virus may infect sheep several times with reduced lesion size and duration to resolution. It is due, at least in part, to the action of viral immuno-modulator proteins, that disrupt host immune and inflammatory responses. They include an interferon resistant protein, a viral orthologue of human IL-10 (vIL-10) anti-inflammatory cytokine, and a novel GM-CSF and IL-2 (GIF) inhibitor. In addition, the virus contains a virulence protein that is an orthologue of mammalian vascular endothelial growth factor (David MHaig and Colin JMcInnes , 2002). ORFV-IL-10 inhibits the actions of MHC II (major histocompatibility complex class II) molecules, reducing the recruitment of innate immune cells such as mast cells, macrophages, monocytes, and dendritic cells (DCs) to areas of skin injury. ORFV-IL-10 may also affect or decrease T-cell proliferation (Lacasta D, et al, 2021).

Short-term immunity is produced by the orf virus's distinct ability to evade the immune system both during natural infection and after vaccination (Monu karki ,et al , 2019). On scab samples, PCR was run with the immunogenic CE virus envelop protein (B2L) gene as the target. Polymerase chain reaction and serology were used to identify positive samples (PCR) (Jamilu Abubakar B,et al , 2018).

In order to distinguish between recently infected animals and sero-converted animals, The existence of IgG antibodies

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in seroconverted animals will be an excellent predictor of long-term CE infection. The goal of this study was to use IgG antibody detection to determine the seroepidemiology of CE in small livestock farms. (Jamilu Abubakar B,et al , 2018). H2O2 generated by O3 reactions can infiltrate leukocytes and increase neutrophil phagocytic activity, as well as facilitate the release of cytokines that aid in the immune response, such as interferon-γ (IFN-γ) and IL-8, as well as several acute-phase proteins (Bocci, V.et al , 2011). The GM-CSF/IL-2 inhibition factor is a viral protein that is encoded by the ORF 117 gene and is a secreted dual inhibitor of granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2) (GIF). GIF's dimeric structure allows it to bind to molecules of human target cytokines, but not ovine target cytokines (D. Haig.et al , 2008). there are Orf vaccines available, they should only be utilized in the case of serious outbreaks because they may result in the spread of live virus into the environment(C Macaldowie,et al , 2011).

Conclusion: Ecthyma disease is a zoonotic as well as a very infectious viral skin disease could transfer to human. The immune response to infect by Contagious Ecthyma virus include both innate and adaptive mechanisms make up the immune response to ORFV infection. The most defense has antiviral features CD4+ and CD8+ cells, cytotoxic T lymphocytes, interferons, and antibodies are all examples of immune cells.

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