



Review Article

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Contagious Ecthyma and its Public Health Significance



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Abstract

Contagious ecthyma is an acute, contagious, debilitating and economically important zoonotic viral disease of sheep, goats and some other domesticated and wild ruminants. The causative agent of the disease, orf virus, is a member of the genus parapoxvirus, which is transmitted through direct and/or indirect contact with infected animals and contaminated animal's products, aerosol and iatrogenically. Transmission to humans is by contact with an infected animal and its lesions are most commonly seen on the hands. The rates of morbidity and mortality are higher, particularly in young animals experiencing the disease for the first time. It is characterized by proliferative lesions which are mainly found on the mouth and muzzle. It can be diagnosed by characteristic lesions, negative-stain electron microscopy, serological tests and polymerase chain reaction analysis. Further, the lesions of the disease often jeopardize the productivity and reduce the market value of the meat, leather and wool besides its zoonotic importance as well as the disruption of national and international trades of animals and animal's products. Since it is a viral disease, there is no effective treatment but if there are a secondary bacterial complication, the appropriate application of topical or systemic antibiotics are used to reduce the multiplication and severity of the agents. Isolation of sick and susceptible animals and herd vaccination during outbreak are helpful to control the spread of the orf virus. Finally, those people who are always in contact with animals should take care of themselves during handling, vaccinating, milking and /or slaughtering animals to reduce the risks of human's infection.

Keywords: Contagious ecthyma; Goats; Para poxvirus; Sheep; Zoonosis; Vaccinating; Virus; Oxyribonucleic Acid; Cytokine; Livestock; Malignant orf; Epidemiology; Diagnosis; Cytoplasm; Etiology; Mortality; Plasma membrane; T-cell

Abbreviations: CDC: Center for Disease Control and Prevention; CE: Contagious Ecthyma; DNA: De-Oxyribonucleic Acid; EEV: Extracellular Enveloped Virion; ICTV: International Committee on Taxonomy of Virus; mRNA: Messenger-Ribonucleic Acid; OIE: Office International Des Epizooties; PCR: Polymerase Chain Reaction; UK: United Kingdom; WV: Wrapped Virion

Introduction

Contagious ecthyma, is a skin viral disease, highly contagious and zoonotic, that affects sheep, goats and some other domesticated and wild ruminants, manifested by appearance of skin lesions which are painful and often occur on the mouth and muzzle, where they can cause anorexia or starvation [1-3]. Orf virus is the causative agent of contagious ecthyma. It is a member of the genus Parapoxvirus, subfamily Chordopoxvirinae of the Poxviridae family [4,5]. The family Poxviridae is characterized by viruses with linear double stranded deoxyribonucleic acid (DNA) molecule of 130 to 300 kilobase pair (kbp) with a hairpin loop at each end [6]. Viruses belonging to this family replicate entirely in the cytoplasm because their virosomes contain enzymes that synthesize messenger ribonucleic acid (mRNA). Para poxviruses are distinguished from other members of the family by having an ovoid shape, with a crisscross patterned tubule-like structure on the particle surface and relatively small size and high guanine and cytokine (GC) content of the genome [7,8].

The synonyms of disease used in various outbreaks includes, contagious, Infectious pustular dermatitis, Infectious labial

dermatitis, Sore mouth, Scabby mouth and Orf [9]. As per World Organization of Animal Health, Orf is a modifiable and zoonotic disease transmitted from animals to humans [10]. It spreads to animals either by direct contact or indirectly via environmental contamination. The transmission of infection from animals to humans is by direct or indirect contact with infected materials and animals and has been reported to be associated in adults involved in slaughtering of farm animals and in children visiting zoos and livestock fairs [11]. The virus usually enters the host through damaged skin leading to scabs typically observed at the site of infection. During outbreaks, morbidity can approach 100%, whilst mortality is usually less than 1%. However, mortality can increase by 20% to 50% following secondary complications such as stress, immunosuppressant or concomitant disease and can exceed 90% in the case of 'malignant orf' [12].

Clinical signs of the disease range from contagious postural dermatitis to formation of scabs in mucous membrane of the oral cavity, tongue, lips and teats of affected animals. The diagnosis is generally based on clinical signs, which are typical [13] and

by negative-stain electron microscopy from scabs of affected animals where the characteristic ovoid shape of the virion is demonstrated [14].

Therefore, the objectives of this review are:

- a. Giving highlights about etiology, epidemiology, characteristic lesions, diagnosis, treatment and control of the disease and
- b. Highlighting of molecular methods and the significance of the disease to the new dimension due to its zoonotic importance.

Literature Review

Etiology

Contagious ecthyma or alternatively called contagious pustular dermatitis is a viral disease of sheep and goat caused by orf virus which belongs to the family of poxviridae and based on the classification of international committee on taxonomy of viruses (ICTV), it is one of the notifiable viral disease known to have a zoonotic importance [10,15]. Other members of genus are: bovine viral stomatitis virus, Para poxvirus of red deer in New Zealand and pseudo poxvirus [16]. Presently, four strains of orf have been sequenced completely: namely OVIA82 and OVSAA00 in America, D1701 in Germany and NZ2 in New Zealand [17].

Characteristics of orf Virus

The orf virus belongs to the poxviruses family and Para poxvirus genus. It is cylindrical, with diameter ranging between 140-170 x 200-300nm, and contains double-chain DNA. Its genomic sequencing has revealed that the genes most probable to induce virulence and immunity are concentrated at the terminal regions. The virus is resistant to ether and other lipid solvents and is inactivated if under 30 °C for 30 minutes [10]. Parapoxviruses are distinguished from other poxvirus genera by crisscross pattern on the particle surface, the relatively small size, their ovoid shape and the high G+C content (approximately 64%) of the genome [18].

Replication Cycle of orf Virus

Orf virus like all other poxviruses contains a double stranded DNA genome with enzymes and transcription factors. Being a large virus, it replicates in the cytoplasm of host cells. When a mature virion comes in contact with the cell membrane of host cell, a signaling cascade is triggered. These results in membrane rearrangement and the formation of actin and ezrin containing protrusions that envelop to the virus. At this stage the core of the virus is released into the cytoplasm. There are no specific proteins receptors identified to date that are required for penetration [6].

Once in the cytoplasm the core synthesizes early messenger RNA (mRNA) that is translated into several proteins including growth factors, immune defense molecules, enzymes and factors for DNA replication and intermediate transcription factors. This

uncoating step releases the viral DNA into the cytoplasm, where it can function as a template for DNA replication and the subsequent waves of intermediate and late transcription [19]. Then transcription of intermediate genes occurs in the progeny DNA and the mRNA produced is translated to form late transcription factors. Virion structural proteins come from translation of mRNA transcribed from late genes. All of the products then start being assembled with the formation of distinct membrane structures. The concatemeric DNA intermediates are resolved into units of genome and packaged in immature virions. Then maturation of the virion progresses to form an infectious intracellular mature virion. Then modified trans-golgi and endosomal cistern wrap up the MVs to form wrapped virions (WV) which are transported to the periphery of the cell along microtubules. Upon reaching the plasma membrane, the WV fuses with the cell membrane resulting in release of extracellular enveloped virion (EEV), which then go about to infect other cells [6].

Epidemiology

Orf is an infection often unknown to practitioners throughout the world [20]. Contagious ecthyma is found worldwide and is more common in late summer, fall and winter on pasture and in feedlots. This seasonality is likely related to increased close contact among animals, as well as increased physiological stress from lambing or cold weather. It has been found to survive for up to 17 years in environments with dry climate and remain viable on the wool of animals (infected and recovered) and contaminated materials for significant periods [1]. It has been reported from many countries [21]. It was initially reported by Zellor in 1920 from South West Africa. Since then, it has been reported from almost all parts of world those involved in rearing sheep, goats, cattle, dogs, camel and both free living wild and captive animals. For instance, the disease outbreaks have been reported in 1992 by FAO/OIE from Norway, China, Indonesia, Iraq, Brazil, Ethiopia and Spain [17].

Host range: Contagious ecthyma is an acute, contagious, debilitating and economically important zoonotic viral skin disease that affecting sheep, goat and some other domesticated and wild ruminants [22,23]. Several countries report incidences of orf viral infections in human, among which UK reports on an average 3 cases per year from 2004- 2014 [24].

Transmission: Orf is transmitted by direct contact inoculation [25]. Man acquire the infection from contact with infected or recently vaccinated animals and/or fomites in conjunction with skin trauma [26]. Human infection typically is associated with occupational animal contact. Children are exposed to the disease after visiting petting zoos and livestock fairs. It also may be observed after the feast of sacrifice in Muslim countries. However, human-to-human transmission has not been reported [27]. Aerosol transmission and transmission by use of contaminated gavage feeding tube or by ear tagging as well as from infected sheep and goats to other species of animals by feeding them raw sheep carcasses are also possible. Iatrogenic transmission of orf virus may also occur during minor or major

surgical intervention, hand contact, drenching and ear tagging. Animal with immune defects and persistently infected animals play an important role in the maintenance of the orf virus in the nature [1].

5.4.3. Morbidity and mortality: In flocks where the disease occurs for the first time, morbidity rates can be up to 70%. Mortality however, is usually low (<1%), although increased rates (up to 90%) have been reported in lambs after secondary bacterial infections [28]. Extension of lesions into internal organs is rare; however, several sheep and goats severely infected with contagious ecthyma have been found dead or moribund [29]. The disease is most serious in young animals which may refuse to nurse and can die of starvation [30].

5.4.4. Risk factor of contagious ecthyma: Risk factors for Orf virus infection include; age, congestion due to increased stocking density, increased orphaned lambs, stress, immunosuppressive diseases, prolonged parturition and forage weed (thorny plants) [24,31].

Pathogenesis

The virus enters the body through broken skin and replicates in the cytoplasm of the host epithelial cell [32]. Primary skin lesions develop two to six days after infection at the portal of entry of the virus to the body and there is no detectable viremia [12]. The viral replication leads to edematous and granulomatous inflammation of dermal cells. Typical lesions are initially erythematous spots followed by formation of papules, vesicles, pustules with a yellowish creamy appearance and scabs that finally become dry and shed with no scar remaining. This development pattern takes place in a period of one to two months.

Host response to infection

An intriguing phenomenon of ORFV is that animals can be reinfected with the virus either by experimental or natural infection although the size and severity of lesions diminishes with each occurrence [33]. In human skin, the histology of the orf lesions is grossly like that of sheep. Apart from this CD8+ T cells are important in host antiviral immunity for killing virus infected cells via MHC class I pathway. Hence, there is a prompt antibody and cell mediated immune response to orf virus infected host that involves CD4+ cells, CD8+ cells, interferon and antibody [28]. CD4+ lymphocytes are further subdivided into Th1 and Th2 on the basis of the type of released cytokines. The Th1 cell subset mainly includes cells secreting IL-2, TNF- α , and INF- γ . The main roles of these cytokines include enhancing killer cell cytotoxicity and cell-mediated immune response. The Th2 cell subset mainly includes cells producing IL-4, IL-6, and IL-10. The role of Th2 cytokines is to promote antibody production and mediate humoral immune response [34].

Virus virulence factor

In fact, the virus encodes immune-modulatory factors that interfere with host inflammatory effect or/and anti-virus immune mechanisms. These are interleukin-10, which

suppresses cytokine production by activated macrophages, and another protein that inhibits the biological activity of granulocyte macrophage colony stimulating factor and interleukin-2 [35]. The virulence endothelial growth factor gene plays an important role in proliferation of epithelial cells allowing the virus to infect the target cells leading to apoptosis whereas the virus IL-10 down regulates the T-cell mediated immune response by altering the function of antigen presenting cells [1]. When Orf affects the teats of lactating ewes or does, changes in the local defense mechanisms of host can occur potentially and predisposing the animals to mastitis.

Clinical Signs

In animal

The Orf lesions appear 6 to 7 days after infection. Proliferative cauliflower lesions are usually confined to the muzzles, lips, nostrils, mucous membranes of the mouth, eyelids and ears, and teats of nursing ewes [36]. (Figure 1). The lesions on the udder are due to direct contamination during nursing that cause mastitis (inflammation of the mammary gland) in does and ewes. Severe to moderate enlargement of the lymphnodes, arthritis, and pneumonia resulting from sore mouth has been reported [37]. The clinical signs in captive wild animals were like domestic sheep and goats which had poor general body condition and difficulty in feeding and loss of body weight [38].



Figure 1: Typical clinical lesions of contagious ecthyma in different body parts a) nostrils and mouth region, b) ear, c) teat and udder. Tedla et al. [71].

In human

Orf usually manifests on the hands, but unusual locations have been described including the nose, scalp, axilla, buttocks, and genitals, after a 3 - 7 days incubation period. Lesion development follows a predictable pattern in the course of 6 - 10 weeks [39]. Most parapoxvirus infections in humans, including orf, are self-limited, except in immune compromised hosts [40]. Symptoms include vesicular or necrotic skin lesions, pain, pruritis, lymphangitis, axillary lymphadenitis, and rarely fever or malaise [41]. Potential complications include erythema multiform, deforming scars, and secondary bacterial infections (Figure 2). Some authors report the cutaneous form in five different phases: phase 1 consists of the formation of small papule, phase

2 consists of larger lesions with red centered, white margins and lens shaped nodules, phase 3 consists of exudation, phase 4 is the regenerative phase leading to formation of black spots and crusts in lesions and finally phase 5 is healing stage [42].



Figure 2: shows a nodule caused by orf virus infection after contact with an infected lamb. CDC [27].

Diagnosis

Molecular Identification and Investigation

Several molecular diagnostic methods including polymerase chain reaction (PCR) and quantitative PCR (qPCR) have been developed to detect orf virus [43]. On the other hand, serological tests such as agar gel precipitation test (AGPT), agglutination test, complement fixation test (CFT), enzyme linked immunosorbent assays (ELISAs), serum neutralization test (SNT) could be employed [44,45].

The classical roles for diagnosis, which might depend on histopathological examinations and clinical manifestations were less accurate, since the isolation of the virus is thought to be the golden standard method, but its need time. Nevertheless, with the development of molecular biology, as the PCR technique is widely used to amplify genomic fragments from the specimens of diseased sheep and it has a strong tool in molecular diagnosis [46-48]. Since PCR technique was used for diagnosis of contagious ecthyma there by samples were found positive by PCR showing the predicted PCR amplicon size of 408 bp [49].

Necropsy findings

Significant gross necropsy findings included scattered hemorrhagic papules, vesicles, pustules, and numerous multifocal-to-coalescing proliferative and necrotizing scabs affecting haired skin at the mucocutaneous junctions (commissures) of the lips, extending into and affecting the oral papillae, the medial canthus of the left eye, and the distal prepuce [50]. In malignant cases, lesions are observed with abnormal shapes, congested borders in the oral cavity and upper respiratory tracts, and in rare cases there are esophageal mucosa, abomasums, and small intestine involvement [51]. Specified lesions of the disease are proliferative and after a while the central cells fall, which causes ulcer like lesions [52].

Differential Diagnosis

Orf is differentially diagnosed from sheep pox, foot and mouth disease (FMD), staphylococcal dermatitis, Dermatophilosis, Bluetongue, facial eczema and ulcerative dermatosis. Orf virus induces proliferative lesions whereas FMD virus does not [53,54]. Ulcerative dermatosis is characterized by ulcers and crusts on skin of the face, feet and genitalia. But lesions are not elevated because epithelial hyperplasia is absent [55]. Bluetongue is characterized by oral erosive lesion and has a seasonal incidence (late summer, early fall) which coincides with the activity of insect vector [56].

Dermatophilosis typically results in multiple small superficial pustules and rarely causes prominent skin lesions except in debilitated lambs whereas; staphylococcal dermatitis (periocular eczema) is characterized by hair loss, edema and deep necrosis of eyelids and adjacent areas [18]. On the other hand, sheep pox and goat pox are contagious and devastating diseases characterized by elevated papules over the entire body. The systemic reaction is profound and often fatal [53,54]. Facial eczema is distinguished by dermatitis, severe edema and damage to the ears.

Public Health Significance

At least 71% of all human pathogens including CE are zoonotic and about 75% of all emerging human pathogens over the past 10 years have been caused by pathogens originating from an animal or from products of animal origin [57]. But CE was considered as a neglected disease which is zoonotic and an occupational hazard [58]. ORFV in humans was first described clinically in 1934 [59]. The infection in human beings is still known as 'human orf'. It should not be underestimated regarding its zoonotic potential, as many human cases have been reported worldwide. Recently, a case report of virus infection in hunter indicated a possible transmission by game. In humans, Orf virus infection occurs mainly in relatively well defined 'at risk' populations, which include veterinary surgeons, shepherds and abattoir workers, in whom it is an occupational hazard.

The infections occur most frequently during lambing, shearing, docking, drenching or slaughtering of affected animals and resulted in localized lesions which can heal spontaneously [60]. In Greece, in October 2010, a man aged 42 years assisted with a lamb sacrifice for the Muslim holiday Eid al-Adha, during which he held the lamb's head with his left hand and his hand is punctured with a bone of a recently slaughtered goat and in April 2011 [61].

Economic Importance

Orf can cause welfare and economic impacts usually associated with poor growth in lambs, mastitis in ewes and death in worst case scenarios [62]. Presence of CE in a country limits the trade of new breeds and development of intensive animal's production. The level of impact varies from country to country both qualitatively and quantitatively. CE is one of the animal

bioterrorist agents as it

- a. Causes high morbidity and mortality.
- b. Has potential for rapid spread.
- c. Potential to cause serious socioeconomic disturbances (trade limitations) or public health consequences [63].

It also causes mortality and weight loss in lambs that are reluctant to eat because of oral and peri-oral lesions. It is one of the 15 animal pathogens listed by Animal World Health Organization (OIE) and 23 by (Animal and Plant Health Inspection Agency USDA) which can be used as an animal biological warfare agent. Hence, its biosecurity is paramount importance (USDA, Agricultural bioterrorism act of 2002. United Kingdom has documented 2,167 million CE affected sheep, leading to £10 million loss, includes both treatment and production losses. It is reported that prevalence of Orf in UK to be 1.88% and 19.53%, in ewes and lambs respectively.

Treatment

Since the CE is a viral disease, there is no definitive treatment for infection in humans or animals. Antibiotics, anti-inflammatory drugs, antiviral drugs, and surgical resection usually have only limited success. During outbreak of contagious ecthyma in flocks or herds, quarantine of new animals before introducing to the existing herd is very important. As secondary bacterial contamination in orf virus infection is not uncommon, therefore topical and systemic antibiotics must be used in treatment schedule. Occasionally levamisole as an immunestimulant is indicated in orf virus infection [1]. Palliative treatment is indicated along with the feeding of balanced diet and debilitated animals need to be treated with 10% glucose saline intravenously. Lesions should be washed with 1:100-1:10,000 KMnO₄ lotion and application of 1:10 boric acid, mild antiseptic or antibiotic ointment topically with parenteral antibiotic injection is recommended [64].

Recently several antiviral drugs such as Cidofovir, Sucralfate and Ant nucleoside phosphates (ANPs) particularly(S)-9-[3-Hydroxy-2-(phosphonomethoxy) propyl,6-diaminopurine, cidofovir, an acyclic nucleoside analogue and its adenine-counterpart(S) and hydrox2 (phosphonomethoxy) are highly effective in complicated orf virus infection in sheep, goat and human beings [65]. Vaseline mixed with iodine can also be used. If insects are a problem at the time of infection, insect repellants applied around, but not on the lesions, may be helpful [66]. Besides the synthetic compound, few traditional herbal therapies such as plant oils obtained from sesame, castor, juice of Calotropis procera and Euphorbias have been found effective in the treatment of orf infection in India and African sub-continent whereas in France and Netherlands, *Ilex aquifolium* is used for curing and preventing contagious ecthyma [1]. Supportive treatment of young animals in bad state due to received feed intake should be performed by administering glycose solution by mean of esophageal intubation.

Control and Prevention

In animals

The infection is prevented by maintaining virus -free herd or flock by not introducing infected individuals to the existing ones. Vaccines have been proved to be important for reduction of the severity of symptoms in infected flocks [67,68]. Proper disinfection of premises of animal house and incineration of all infected materials extracted from sick animals are required to reduce the risk of new infection. Vaccination with live virus vaccine should not be recommended on a farm having no previous history of orf outbreak as the live virus may contaminate the environment.

Recently, a wild virus strain attenuated through serial passages on primary chicken embryo fibroblast tissue cultures was used successfully as a vaccine, being able to block the normal cause of the disease and induce rapid recovery [69]. An older commercial vaccine with scab material is available with effective immunity lasting for two to three years. A vaccine containing a caprine strain of the virus has been shown to be more effective when used in goats than a commercial vaccine licensed only for sheep.

In humans

Contagious Echyma is zoonotic disease so, farmers and veterinarians should wear protective gloves and facemasks when dealing with sick animals and meticulous washing of skin wounds with soap and water after handling animals is important. Non-permeable gloves should be used during direct contact with lesions in humans, despite that human-to-human transmission has not been reported. In addition, slaughterhouses should verify that all animals to be sold or butchered are in good health; animals with orf lesions should be disposed of in a safe manner [70-72].

Conclusion and Recommendations

Contagious ecthyma, caused by parapox virus, is one of the most common skin diseases of sheep, goats and other domesticated as well as wild ruminants. It is responsible for producing skin lesions at the area of mouth, lips and nose for the incubation period of approximately, one week. At present, the CE and its allied impediments have the status of disease of worldwide occurrence which can arise in rural as well as urban areas due to less awareness, casual negligence and through religious or cultural practices involving animal handling and slaughtering. Though the disease is self-limiting, secondary bacterial infections lead to complications that may lead to mortality. Since the CE is a viral disease, there is no definitive treatment for infection in humans or animals. Antibiotics, anti-inflammatory drugs, antiviral drugs, and surgical resection usually have only limited success.

Therefore, based on the above conclusions the following recommendations are forwarded:

- a. Always quarantine new animals before introducing them to the rest of the herd.
- b. A systemic vaccination of the entire herd is recommended only during outbreaks.
- c. Always wear gloves when handling sick animals and vaccines as humans can contract the disease.
- d. Avoid the consumption of milk from does that present lesions on the teats and udder.

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