

Contagious Ecthyma and its Zoonotic Importance: A Review

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Abstract: Contagious Ecthyma, an acute, contagious and eruptive viral skin disease that affects mainly sheep and goats which has zoonotic importance and is worldwide in distribution. The causative agent of the disease is orf virus, which is transmitted through direct and/or indirect contact with infected animals and contaminated animal products, aerosol and iatrogenic transmission. Transmission to humans is by contact with an infected animal and its lesions are most commonly occurring on the hands. The rates of morbidity and mortality are higher, particularly in young's 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 lesion, negative-stain electron microscopy, serological tests and PCR 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 products (trade-ban). Since it is a viral disease, there is no effective treatment but if there are secondary bacterial complications, the appropriate application of topical or systemic antibiotics is used to reduce the multiplication and severity of the agents. Isolation of sick and susceptible animals and herd vaccination during an 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 infection.

Key words: Contagious Ecthyma • Goats • Parapoxvirus • PCR Analysis • Sheep • Zoonosis

INTRODUCTION

Orf, also known as ecthyma contagious, contagious pustular dermatitis, infectious labial dermatitis, scabby mouth, or sore mouth, contagious ectema is a viral disease caused by the parapox virus. It is one of the most common skin diseases of domesticated and wild ruminants [1, 2]. Contagious ecthyma is an acute, contagious, debilitating and economically important viral skin disease that is responsible for producing skin lesions in the area of mouth, lips and nose for the incubation period of approximately, one week [2-4].

As per the World Organization for Animal Health, Orf is a notifiable and zoonotic disease transmitted from animals to humans [5]. The disease is prevalent in all the continents with several enzootic areas all over the world. Although the disease has been considered as a benign disease it has taken a serious turn in the last decade and certain countries, a severe malignant form of the disease

has been reported [6, 7]. Contagious ecthyma spreads to animals either by direct contact or indirectly via environmental contamination [8].

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 the slaughtering of farm animals and children visiting zoos and livestock fairs [8]. 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' [9].

Clinical signs of the disease range from contagious pustular dermatitis to the formation of scabs in the mucous membrane of the oral cavity, tongue, lips and teats of affected animals. The diagnosis is generally based

on clinical signs, which are typical [10] and by negative-stain electron microscopy from scabs of affected animals where the characteristic ovoid shape of the virion is demonstrated [11]. The documented data and studies are scarce concerning the contagious ectema. To get updated information about the disease, the literature should be available in an accessible manner priorly. Therefore, the objective of this paper is to generally overview contagious Ecthyma and its public health importance.

General Overview

Etiology: It is caused by the Orf virus, which is type species of the genus Parapoxvirus of subfamily chordo-poxvirinae of family poxviridae [12]. In addition to the orf virus (parapox ovis), the genus includes the viruses of bovine papular stomatitis (parapox bovis 1) pseudocowpox (parapox virus bovis 2) and a parapox virus of deer 1-3. The orf virus withstands drying and is capable of surviving at room temperature for at least 15 years. Restriction endonuclease digests of DNA shows considerable heterogeneity between different field isolates [13].

Morphologic and Physicochemical Characteristics:

Para poxviruses are distinguished from other poxvirus genera by their ovoid shape, the crisscross pattern on the particle surface, the relatively small size and the high G + C content (approximately 64%) of the genome. The viral genome is composed of ~135 kb linear, ds DNA with closed hairpin loop ends and genes located on both strands with a bi-directional orientation [14]. Para poxviruses are ether sensitive and quite resistant and survive for several months in a cool and dry environment but are destroyed by high and very low temperatures, UV light and wetting [15]. At room temperature, the maximum survival of the virus in a dried state is 15 years [16]. The exposure to heat at 100°C for one minute inactivated the virus but it survived at 56°C for one hour [17].

Epidemiology: Contagious Ectema 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 a dry climate and remain viable on the wool of animals (infected and recovered) and contaminated materials for significant periods [12].

Host Range: It is a disease of sheep, goats, cattle, alpacas, camels, reindeer, bighorn sheep, Sichuan takin, domestic Shetland sheep, deer, pronghorn antelope, wapiti and seal squirrels [18-22]. Boer goats are highly susceptible to orf virus infection and exhibit severe lesions. Sheep have been found to be completely refractory to infection with the camel orf virus and vice versa [23]. Humans are occasionally affected and dogs can contract the infection from the consumption of orf-contaminated carcasses [24]. Reports do not exist regarding the occurrence of orf due to the consumption of unpasteurized milk but the Food and Agricultural Organization recommends discarding the milk from affected animals. Several countries report incidences of orf viral infections in humans, among which the UK reports on an average of 3 cases per year from 2004- 2014 [25].

Distribution: Contagious ectema has been reported in many countries [26]. It was initially reported by Zeller in 1920 from South West Africa. Since then, it has been reported from almost all parts of the 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 [27]. An outbreak of CE was investigated in June 2012 with the morbidity rate of 22% in the Adet Sheep Research Sub-center in Ethiopia. During this, five scab samples were obtained from sheep suspected of CE and all are confirmed by PCR assay as CE positive [26].

Transmission: In animals, the natural transmission of disease occurs through direct or indirect contact between infected susceptible animals. Transmission from wild to domestic goats when infected herds had prolonged contact with areas where salt blocks were provided artificially on highways and campgrounds is also possible [10]. In outbreaks of CE, it was suggested that with the presence of spiky weeds in the pastures, the ecthyma virus was being inoculated into the mouth. The disease also can be transmitted by fomites (inanimate objects that carry infectious organisms [28]). 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 [27]. Iatrogenic transmission of orf virus may also occur during minor or major surgical

intervention, hand contact, drenching and ear tagging. Animals with immune defects and persistently infected animals play an important role in the maintenance of the orf virus in nature [12].

In humans, veterinarians and veterinary attendants can contract the infection by handling the CE infected material or animals [29]. The disease can be transmitted from a mother who milked the sheep to her child [30] through scratching. During the Islamic religious worship practice of Eidul-Adha from infected sheep to in-contact humans [31, 32]. Though there is no demarcation between the sexes regarding orf infection in humans, the male is at higher risk compared to female as a male comes with direct contact with the infected animals in slaughterhouses and other places as well as during vaccination [5].

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 [33]. Extension of lesions in internal organs is rare. The disease is most serious in young animals which may refuse to nurse and can die of starvation [34]. Morbidity can go as high as 100%, the mortality rate is usually less than 1% but secondary infections of bacteria and fungus can increase the number to between 20 and 50% but depending on the age of the animal it can go as high as 93% [35]. Following clinical disease or vaccination, animals are partially protected with recurrent infection being possible to occur in 1-3 months but with less severe lesions and healing is rapid [12].

Pathogenesis: Skin is the main predilection site and essential for the establishment and development of lesions. Initially, the virus replicates in the epidermal cell layers derived from the walls of the wool follicle. At the time of grazing, the dried steamy and spiny feed may abrade the tissues of lips, nostrils, mouth as well as for stomach [15]. 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 [9].

The viral replication leads to edematous and granulomatous inflammation of dermal cells. Typical lesions are initially erythematous spots followed by the 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 [12]. Kids below two months of age also develop similar

lesions on the lips then spread to the skin of the face, ears, feet, flanks and scrotum. In lactating animals, lesions may appear on the udder or teats. Lesions can also appear on the skin of the vulva of ewes and scrotum of ram causing the venereal form of orf. The lesions as being proliferative, cauliflower-like in appearance that commences on the lips, muzzle, mucocutaneous junctions, nostrils, gums and sometimes spread to internal organs including the tongue even in the absence of systemic involvement. Systemic involvement has been reported where the infection extends to the alimentary tract and trachea leading to severe gastroenteritis and bronchopneumonia [3, 12].

Host Response to Orf Infection: Host immune response is very much important for controlling the magnitude of orf virus multiplication. The infected animals produce monoclonal antibodies against five immune-dominant antigens such as 39 kDa and 42 kDa of the envelope protein, 10 kDa putative fusion protein and uncharacterized 22 kDa and 65 kDa proteins and these antigens are extremely useful for the differentiation of different para poxviruses [36].

The polyclonal antibody raised against sheep orf virus neutralizes sheep orf virus more efficiently than the goat orf virus, so there may be some differences in neutralizing epitopes of the orf virus of ovine and caprine origin and would explain the failure of the sheep orf vaccine to protect goat kids [3]. The host response by orf virus infection is primarily characterized by initial infiltration of neutrophils followed by accumulation of dendritic cells, CD4+ T cells, CD8+ T cells and B cells around the virus-infected epidermal cells. CD4+ T cells are more numerous than CD8+ T cells at the lesion site [37]. 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 the 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 [33].

Virus Virulence Factors and Evasion from Host Immunity: 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 [38].

It has been observed that the orf virus often repeatedly infects and replicates in animals despite recovery from a primary attack. There are several possible reasons for this phenomenon. Firstly, the virus infects epidermal cells and undergoes limited replication before host anti-viral effector molecules reach the infection site. Secondly, by targeting regenerating epidermal cells, the virus is less likely to stimulate apoptosis in the cells. Finally, the virus possesses mechanisms to interfere with the components of a protective immune response [39]. The important virulence genes of orf virus are the mammalian virulence endothelial growth factor gene, orf virus homologous ovine gene encoding cytokine IL-10, orf virus interferon resistance gene and a gene which inhibits the inflammatory cytokine granulocyte-macrophage colony-stimulating factor [40].

The virulence endothelial growth factor gene plays an important role in the 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 [12]. The ovine encoding cytokine IL-10 gene has interferon resistance function which is a clear indication that interferon plays a crucial role in host resistance to orf virus-infected animals [40]. When Orf affects the teats of lactating ewes or does, changes in the local defense mechanisms of the host can occur potentially and predisposing the animals to mastitis [33].

Clinical Signs and Symptoms

In Animals: The incubation period of the disease varies from 4 to 8 days with an initial rise in temperature, development of papules and pustules often at oral commissures, the skin of lips, nose, face, ears, feet and flanks followed by thick, tenacious scabs covering a raised area of ulceration, granulation and inflammation [11]. Small erythematous to larger coalescing ulcerated papules were observed on the gingiva, tongue and over the dental pad and hard palate [41]. The scabs are friable, bleed easily and pain which may result in anorexia or even starvation [23].

In some cases, lesions are hard, dry and crusty and fissure whereas in other cases the lesions are moist, ulcerated and foul-smelling and sometimes the skin of the inner thigh contains a large number of fly (*Ophira species*) larva [3]. When the coronets are affected in finishing lambs, they are often proliferative, granulomatous and persistent and result from infection

with dermatophilosis and are referred to as 'strawberry footrot' [42]. The secondary effect of orf infection often leads to mastitis in ewes and incidence is more in unvaccinated ewe's due to infection with *Mannheimiahaemolytica* and staphylococci compared to vaccinated ones [43, 44].

The venereal form of the disease is characterized by the appearance of papules, vesicles and ulcers on the skin of the vulva of ewes and the preputial orifice of rams [3]. In rams, ulcerative lesions characteristic of Orf in the prepuce are accompanied by the inability to mount the ewe, loss of libido and incomplete erection [45]. The ulcers developed in the vulva and penis may undergo necrotic changes due to invasion of *Fusobacterium necrophorum* [13]. 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 [46].

In Humans: Some scholars 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 the formation of black spots and crusts in lesions and finally phase 5 is the healing stage [47]. Clinical signs of orf infection in humans occur in 3-7 days post-entry of the virus. The disease manifests itself by a single skin lesion or a few lesions of a small firm, red to blue papule on a finger, hand, or other bare parts of the body. Other symptoms reported include pain, pruritus, lymphangitis and axillary adenitis, or sometimes fever or malaise. Unless secondary infection gets involved, the lesions heal in 3-6 weeks [12].

Diagnosis: In animals, Contagious ecthyma can be diagnosed based on characteristic lesions on the anatomic areas of predilection [28]. Virus isolation can be attempted in a variety of cell cultures or embryonated eggs. Viral particles may be observed in a vesicular fluid, skin and crusts by using electron microscopy [48]. Laboratory diagnosis of orf disease is achieved by negative-stain electron microscopy from scabs of affected animals where the characteristic ovoid shape of the virion is demonstrated [11].

The serological tests used for orf diagnosis include virus neutralization, agar gel immune diffusion (AGID), complement fixation, or agglutination for the detection of anti-contagious ecthyma antibodies. The development of

PCR methods for the molecular detection of parapox DNA has met the demands for specific and sensitive laboratory diagnosis of orf disease. Several procedures have been developed to detect the parapox virus. However, most of these methods are time-consuming, laborious and sometimes show a lack of specificity and sensitivity with cross-reactions observed. PCR analysis, as proved by many reports, is a rapid, sensitive and specific tool in identifying several infectious diseases of veterinary importance [14].

The efficacy of PCR was comparably (85-87%) to the cell culture/neutralization methods [49]. Recently, PCR targeting microscopy and B2L gene have been developed for confirmatory diagnosis in sheep [26]. ELISA has been used for detecting orf virus antigen and antibodies [50]. In Humans, The diagnosis of disease in humans is usually like that of animals and it is based on a clinically typical skin lesion and patient's history. The diagnosis may be confirmed by isolation and identification of the virus, demonstration of the virus by electron microscopy and PCR analysis [51].

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 the FMD virus does not [28]. Ulcerative dermatosis is characterized by ulcers and crusts on the skin of the face, feet and genitalia. But lesions are not elevated because epithelial hyperplasia is absent [51].

Bluetongue is characterized by oral erosive lesion and has a seasonal incidence (late summer, early fall) which coincides with the activity of insect vector [52]. Dermatophilosis typically results in multiple small superficial pustules and rarely causes prominent skin lesions except in debilitated lambs whereas; staphylococcal dermatitis (periorbital eczema) is characterized by hair loss, edema and deep necrosis of eyelids and adjacent areas [14]. 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 [28]. Facial eczema is distinguished by dermatitis, severe edema and damage to the ears [13].

Public Health Importance: The scholars agree that 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 products of animal origin [53]. But CE was considered as a neglected disease which is zoonotic and an occupational hazard [54, 55].

ORFV in humans was first described clinically in 1934, Delhon *et al.* [56]. The infection in human beings is still known as 'human orf' [14]. 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 [33]. 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 [53].

The infections occur most frequently during lambing, shearing, docking, drenching, or slaughtering of affected animals and resulted in localized lesions that can heal spontaneously [56]. In Greece, in October 2010, a managed 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, a man of Ethiopian descent aged 35 years, residing in Massachusetts, cut his left thumb with a knife while slaughtering a lamb as part of Easter festivities. Subsequently, small, pink and white papules are noted in both guys at the site of injury that enlarged over the following week [57].

Economic Importance: The presence of CE in a country limits the trade of new breeds and the development of intensive animal production. The level of impact varies from country to country both qualitatively and quantitatively. CE is one of the animal bioterrorist agents as it (i) causes high morbidity and mortality, (ii) has the potential for rapid spread, (iii) potential to cause serious socio-economic disturbances (trade limitations), or public health consequences [58].

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 [51].

ORFV infections pose an economic loss to farmers especially in the rural poor population of developing countries who rely on small ruminants for food security and a source of income and other social benefits.

Losses do not only result from death but also reduced growth rate, premature culling of ewes and does due to orf-induced mastitis. Reduction in the Reproductive performance of a flock when rams are infected with the venereal form of orf making them unwilling to mate, extra cost for veterinarian involvement and delays in trading and slaughtering [35].

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 [28]. During the 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 common, therefore topical and systemic antibiotics must be used in the treatment schedule. Occasionally levamisole as an immune-stimulant is indicated in orf virus infection [12].

Palliative treatment is indicated along with the feeding of a balanced diet and debilitated animals need to be treated with 10% glucose saline intravenously. Lesions should be washed with KMnO₄ lotion and application of boric acid, mild antiseptic or antibiotic ointment topically with parenteral antibiotic injection is recommended. Removal of scabs and applications of ointments or lotions are practiced but the delay in healing has occurred in many cases .the provision of palatable feed is recommended [13].

Prevention and Control

In Animals: The infection is prevented by maintaining a virus-free herd or flock by not introducing infected individuals to the existing ones [52]. Vaccines have been proved to be important for the reduction of the severity of symptoms in infected flocks [59]. Proper disinfection of premises of animal house and incineration of all infected materials extracted from sick animals are required to reduce the risk of a new infection. Vaccination with a live virus vaccine should not be recommended on a farm having any previous history of orf outbreak as the live virus may contaminate the environment [28]. Attenuated vaccines are usually preferred because of improved efficacy. Attenuated tissue culture has been proven that occasionally the vaccine virus strain may cause disease, whilst at the same time failing to confer strong immunity and thus prevent reinfections [60].

Several measures have been suggested to prevent the spread of the disease during an outbreak in flocks or flocks. These include quarantine of new animals before

mixing with other animals on the farm. Sick animals must be separated, fed and treated. People should avoid consumption of milk from infected ewes and does presenting lesions on the teats and udder. Animal handlers should wear gloves and facemasks when handling sick animals to avoid getting infected. Proper disinfection of premises of animal houses and proper handling of all contaminated materials should be carried out. These measures are essential to reduce the risk of a new infection. Finally, the migration of animals from one place to another particularly the infected ones should be prohibited. Most important is for farmers to supply a well-balanced diet to their animals which can help build their immunity and resist infection by ORFV which once enters a flock or flock is difficult [12].

In Humans: As CE is a zoonotic disease, 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 [59]. Non-permeable gloves should be used during direct contact with lesions in humans, despite that human-to-human transmission has not been reported [53]. Also, 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 [32].

CONCLUSION AND RECOMMENDATION

Contagious Ecthyma, caused by the 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 an initial rise in temperature and skin lesions in the area of the 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 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. Orf has gained higher importance throughout the world in recent years due to its zoonotic perspective and disturbances of economic safety. The policymakers (OIE, Minister of livestock and fishery in Ethiopia and even in the World) should give attention to alleviate the hazards caused by this disease especially by the improved management system and avoiding the causal negligence of the disease.

This is done by giving awareness to the global society through education, consultancy and agitation. The religious and cultural practices of slaughtering and handling animals should be in good hygienic conditions. Generally, the following necessary measures should be taken as a recommendation:

- Minimize transportation stress.
- A systematic vaccination of the entire herd is recommended only during outbreaks.
- Incinerate gloves and all tissues that meet lesions extracted from sick animals.
- Always wear gloves when handling sick animals and vaccines as humans can contract the disease.
- Avoid the consumption of milk from does that present lesions on the teats and udder.
- Education of the farmers through animal health extension activities.

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