Ovine Pulmonary Adenocarcinoma

Ovine Pulmonary Adenomatosis, Ovine Pulmonary Carcinoma, Jaagsiekte, Sheep Pulmonary Adenomatosis

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Importance

Ovine pulmonary adenocarcinoma is caused by a virus that can be transmitted between sheep in respiratory secretions or milk. Infections result in fatal pulmonary neoplasia in some animals, while others remain subclinically infected for life. The economic impact can be significant: 30-80% of the flock may be lost on first exposure to the virus, with continuing annual losses that can be as high as 20% in some flocks, although 1-5% is more usual. Excluding this disease from a flock is difficult, in part because no diagnostic test can reliably detect animals in the preclinical stage. No effective treatment or vaccine is available, and eradication is challenging. Ovine pulmonary adenocarcinoma occurs in most sheep-raising areas of the world, with the exception of a few countries such as New Zealand and Australia. Iceland is the only country known to have successfully eradicated this disease.

Etiology

Ovine pulmonary adenocarcinoma results from infection by jaagsiekte sheep retrovirus (JSRV), a member of the genus *Betaretrovirus* in the Retroviridae. JSRV is also known as the pulmonary adenomatosis virus. It has never been cultured from infected animals, which must be identified with viral nucleic acids or antigens. However, infectious virus has been constructed from molecular clones of JSRV, and these viruses can cause tumors in experimentally infected sheep.

Species Affected

Ovine pulmonary adenocarcinoma mainly affects sheep. Cases have also been reported in captive mouflon (*Ovis musimon*) and rarely in goats.

Zoonotic potential

Some authors have speculated that JSRV or a related human virus might be involved in the pathogenesis of certain types of lung cancer in people. Studies to investigate this hypothesis have produced conflicting findings, and it is controversial. One recent study reported that JSRV could infect some human cells *in vitro* but found no serological evidence for human infections in an endemic region.

Geographic Distribution

Ovine pulmonary adenocarcinoma has been reported from a number of sheep-raising countries in Europe, Africa, Asia and the Americas, and is suspected to occur in others. It is absent from Australia, New Zealand and Iceland.

Transmission

JSRV is thought to be transmitted mainly by the respiratory route, probably via aerosols or droplets. Infectious virus is shed in the respiratory exudates of infected sheep, including subclinically infected animals. Horizontal transmission has been demonstrated in sheep of all ages, but young lambs are particularly susceptible to infection. Close contact is thought to increase transmission. JSRV also occurs in milk and colostrum, which can transmit the virus to nursing animals. Viral nucleic acids were detected in the fetuses of some clinically affected sheep. The ability to eliminate JSRV by rearing neonates on uninfected colostrum and milk suggests that *in utero* transmission might not be significant in the epidemiology of this disease, but this is not definitive. Infected animals become carriers for life.

Enveloped retroviruses like JSRV are not thought to remain viable for long periods in the environment. One study that used an indirect estimate for virus survival, the ability to amplify viral RNA by RT-PCR, detected JSRV RNA for up to 6-8 weeks when the virus was suspended in lung fluids at 4°C (39°F) or 20°C (68°F), and between 3 days and 2 weeks when it was dried and held at 4-37°C (39-99°F). The study's authors propose this as a possible upper limit for the survival of infectious JSRV, which has not been studied. Studies on other retroviruses (e.g., HIV-1, HTLV-1) have found that live viruses may survive for a week or two, and perhaps longer, when suspended in liquids such as tissue culture fluid, which protect the virus and prevent it from drying out. One group reported recovering a human retrovirus for up

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to 7 days at 23°C (73°F) when it was dried at high concentrations on plastic, but the relevance of this study to natural conditions, where virus concentrations are much lower, is uncertain.

Disinfection

Retroviruses are susceptible to common disinfectants that can inactivate enveloped viruses, such as sodium hypochlorite, 2% glutaraldehyde, 70% ethanol, hydrogen peroxide and iodine. They can also be destroyed with UV light or moist heat of 121ºC (250ºF) for at least 15 minutes.

Incubation Period

In experimentally infected sheep, tumors can develop within a few weeks to months in young lambs, but take longer to form in older animals. The course of tumor development is usually slow in naturally infected animals; in most cases, it is thought to be a few months to a few years.

Clinical Signs

Clinical signs are only seen in animals that have developed tumors; JSRV carriers are asymptomatic. Typical signs in sheep include weight loss and progressive emaciation, despite a good appetite, and respiratory compromise, particularly after exercise. Affected sheep often lag behind the flock. Many also have a thin mucoid discharge from the nostrils, and if the head is lowered, a copious exudate may pour from the nares. This exudate may be clear, milky or occasionally pinkish, and is often frothy. Moist rales may be heard on auscultation, although coughing is not usually prominent. Distant metastases are uncommon, but they have been reported to cause locomotor difficulties when they occur in skeletal muscle. Once a sheep becomes sick, the signs are slowly progressive and invariably fatal, ending in severe dyspnea. Some animals can survive for months; however, secondary bacterial pneumonia, exercise or exposure to cold may exacerbate the respiratory signs and cause death within a few days. Goats with tumors seem to be subclinical in many cases.

Post-Mortem Lesions

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The lungs of sheep with ovine pulmonary adenocarcinoma are usually enlarged, and in advanced cases, do not collapse upon opening the chest cavity. Frothy fluid is often present in the trachea and bronchi. The overlying pleura usually appears smooth, although affected areas may be discolored. Tumors tend to be more common in the anteroventral portions of the lungs. They vary from small nodules to solid coalescing masses, and are often sharply demarcated and firm. Their color may range from gray or pinkish-gray to purple or brown. On cut surface, they are glistening and granular, and a frothy fluid may be expressed. Secondary pneumonia, fibrinous pleuritis and/or necrotic foci are also common in the lungs of affected sheep. Extensive secondary lesions may mask some tumors. The bronchial and mediastinal lymph nodes are usually enlarged and edematous, and sometimes contain metastases. More distant metastases occur infrequently. They appear as single to multiple nodules in various organs such as the kidneys, liver, spleen, skeletal muscle and skin, or as focal thickening of the walls of the gastrointestinal tract or mesentery.

Atypical cases, characterized by solitary or aggregated hard, pale nodules with a dry cut surface, can be seen in a minority of sheep. Excess fluid in the lungs is not a prominent feature of this form. Atypical lesions may appear alone or together with classical lesions, and can occur in subclinical cases as well as animals with clinical signs.

There is relatively little information about the lesions in goats, but experimentally infected goats developed small, hard, well circumscribed nodules in the lungs.

Diagnostic Tests

JSRV has not been recovered in culture, to date. In live animals, ovine pulmonary adenocarcinoma is often diagnosed by the clinical signs, combined with a flock history of the disease. The "wheelbarrow test" – raising the hind legs to lower the head of the animal – can be used to check for excess fluid in the lungs. Fluid is occasionally absent even in advanced cases. If excess lung fluid is found, it can be tested for JSRV nucleic acids or antigens by RT-PCR, immunoblotting or ELISAs, respectively. However, sheep are often euthanized immediately after a positive wheelbarrow test. Early cases are difficult to distinguish from other respiratory diseases, but RT-PCR can sometimes detect nucleic acids in bronchoalveolar lavage fluid. One study found that ultrasound is useful for antemortem identification of tumors > 2 cm in size. In affected animals, a bright linear echo formed by normal aerated lung tissue is reported to be replaced by hypoechoic area(s) of hepatoid appearance in the ventral margins of the lung lobes at the fifth or sixth intercostal spaces. Video recordings of typical ultrasound scans are available as a supplement in Cousens and Scott, 2015 (see Internet Resources).

At necropsy, the diagnosis can be confirmed by the gross lesions, histopathology and the detection of viral antigens or RNA in the lungs and regional lymph nodes. Antigens are usually detected by immunohistochemistry, and RNA by RT-PCR. Because secondary bacterial pneumonia can mask the tumors, several samples should be taken from different parts of the lungs for histopathology.

There is currently no reliable way to identify subclinically infected animals. RT-PCR may detect nucleic acids in the peripheral blood mononuclear cells (PBMCs) of some individuals, but there are usually very few infected cells and this test misses too many infected animals to be useful. It might be employed as a herd test, but its fitness for this purpose has not yet been evaluated. RT-PCR was unable to identify infected animals in bone marrow samples, probably because the number of infected cells is too low, or saliva and nasal secretions. Serology is not

helpful, as infected animals do not normally have detectable antibody titers to JSRV.

Treatment

There is no treatment for animals with tumors and no method to eliminate retroviruses from animals.

Control

Disease reporting

Veterinarians who encounter ovine pulmonary adenocarcinoma should follow their national and/or local guidelines for disease reporting. In the U.S., this disease is reportable in many states. State guidelines should be consulted for specific requirements.

Prevention

Ovine pulmonary adenocarcinoma is usually introduced into a flock in an infected sheep, often one that is subclinically infected. Because there is no reliable test to detect these animals, preventing entry is difficult. Herd replacements should be bought only from flocks with no history of ovine pulmonary adenocarcinoma; however, this does not guarantee that the animals are free of JSRV, as the incubation period is long. Quarantining herd additions has been suggested, but it may be impractical. There is no effective treatment for animals with lung tumors, and no known method to prevent the infection from progressing to this stage. No vaccine is available.

Removing affected sheep and the offspring of infected ewes may reduce losses, but it cannot eradicate JSRV from a flock. Maintaining single age flocks has also been recommended. One study suggested that ovine pulmonary adenocarcinoma may be significantly reduced or eradicated by removing lambs at birth and hand-rearing them with colostrum substitutes or cow colostrum, followed by milk replacer. Good disinfection and general infection control measures should be used when handling these lambs, and they should be placed in an uncontaminated environment. Ovine pulmonary adenocarcinoma was eradicated from Iceland by slaughtering all sheep in affected areas. Embryo transfer may be used to save the genetic potential from valuable flocks that are euthanized.

Morbidity and Mortality

Ovine pulmonary adenocarcinoma is rare in sheep less than 7-9 months of age. Most clinical cases occur in animals over the age of two years, with a peak incidence in 3- to 4-year-olds. Once the clinical signs appear, cases always end in death. Recently infected flocks have high morbidity and mortality rates, with up to 30-80% of the flock dying of tumors. When JSRV has been present longer, the annual rate of loss is usually 1-5%, although losses up to 20% have been reported on some farms. The incidence of infection is much higher than the morbidity rate; most sheep in an infected flock do not develop tumors during their commercial lifespan. One recent study suggested that some nodules might regress either partially or completely in subclinically infected animals. However, these sheep were coinfected with ovine lentivirus, and the nodules that regressed were observed only by computed tomography at their earlier stages. Thus, additional research is needed to confirm this finding.

Clinical cases seem to be very rare in goats. JSRV does not seem to spread readily in the lungs of this species, although goat kids that were experimentally infected with high viral doses developed tumors. These tumors were smaller than the tumors in lambs, and they were less likely to be clinically apparent.

Internet Resources

Cousens C, Scott PR. Assessment of transthoracic ultrasound diagnosis of ovine pulmonary adenocarcinoma in adult sheep. Vet Rec. 2015;177(14):366. (includes video recordings of typical ultrasound scans)
http://dx.doi.org/10.1136/vr.103298

Food and Agriculture Organization of the United Nations (FAO). FAO Manual on Meat Inspection for Developing Countries
http://www.fao.org/3/t0756e/T0756E00.htm

The Merck Veterinary Manual
http://www.merckvetmanual.com/

World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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