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Ovine Pulmonary Adenocarcinoma (Jaagsiekte)

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Ovine Pulmonary Adenocarcinoma (OPA) is a contagious lung cancer which constitutes about 70% of the total lung cancers of sheep. Disease was reported in South Africa for the first time but now it is prevalent in all parts of world including India (Tamil Nadu, Andhra Pradesh, Rajasthan, Delhi, U.P., H.P. etc having occurrence between 0.50% to 10%). The total livestock population of India is 512.05 million, of which sheep and goats account for 65.06 and 135.17 million, respectively. Among pathological conditions, pneumonia is the second most contributors, which accounts for about 28.57% mortality in small ruminants. The infectious etiologies found to be major contributor to pneumonia and results in reduced weight gain, decrease in milk and wool production, reduced fecundity and higher mortality rates. OPA is one of the important progressive disease involving lungs responsible for mortalities and economic losses to the farmers and remains undetected at field level. Thus owing to its economic importance and animal welfare problem, awareness regarding OPA is needed to be done.

Etiology

OPA is a naturally occurring neoplasm of sheep lungs caused by Jaagsiekte Sheep Retrovirus (JSRV), a member of the genus beta retrovirus, family *Retroviridae*. JSRV is a RNA virus of around 7460 nucleotide bases. Genome is made up of 4 genes: *gag, pro, pol* and *env*. *Gag* encode the structural proteins of the virus capsid (MA, CA, NC); *pro* and *pol,* which encode the viral enzymes, including an aspartic protease (PR), reverse transcriptase (RT) and integrase (IN); and *env*, which encodes for the envelope glycoproteins (SU and TM) present on the surface of the virus particle which plays important role in the pathogenesis of the virus.

Transmission

JSRV mainly spreads by direct contact through aerosols having long incubation period of 2 to 4 years, thus is usually seen in adult sheep. Disease may spread through milk and colostrum to lambs via infected ewes.

Epidemiology of OPA

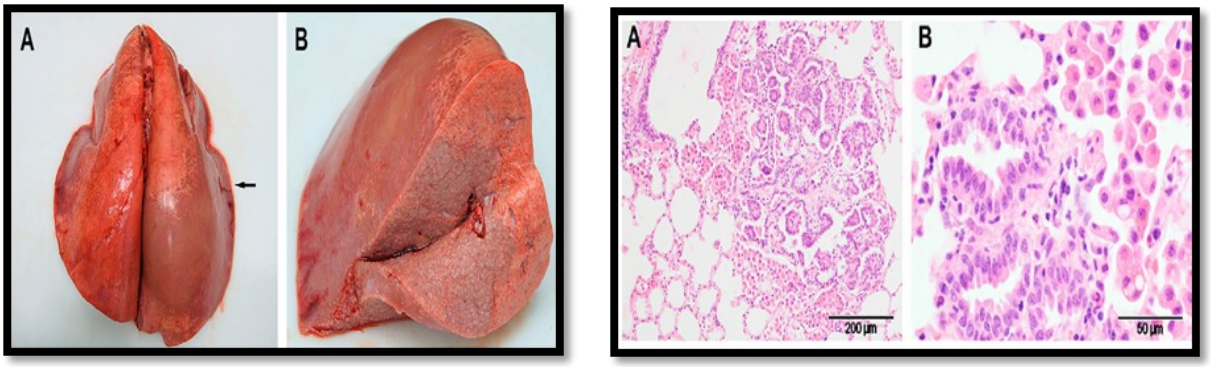
The disease was reported firstly in 1915 at South Africa and is currently present worldwide except New Zealand, Australia and the Falkland Islands, Iceland. Introduction of the JSRV virus in sheep flock causes higher mortality in beginning but once disease is endemic mortality rate falls to 1-5% and remains neglected in the farm.

Pathology and pathogenesis of OPA

Grossly two forms of OPA are classified, classical and atypical. The classical form is more common and is characterized by the enlargement of lungs, development of grayish extended neoplastic lesions, and production of excess lung fluids. Atypical form is usually subclinical in nature and is characterized by the presence of few to multiple pale and dry nodules in the lung parenchyma. Microscopically, classical form shows lepidic pattern of alveoli, with proliferation of type II pneumocytes, forming papillary and acinar projection into the alveolar lumen. While in atypical OPA case there is extensive fibrous tissue proliferation, with mononuclear cells infiltration in the interstitium along with pneumocyte proliferation. Type II alveolar epithelial cells are the principal neoplastic cell type (82%), with Clara cells (7%) and undifferentiated cells (11%).

Grossly, (A&B) picture is showing enlarged, firm and meaty lungs with neoplastic nodules (depicted with arrow marks). Microscopically, (A&B) it reveals typical papillary and acinar pattern of type II pneumocytes in alveolar lumen and type II pneumocytes proliferation.

The SU subunit of the (*env*) glycoprotein specifically binds to cell *Hyal2* receptor, followed by endocytosis of the virus and subsequent fusion of the viral and endosomal membranes releases the viral core into the cytoplasm. The entry of the JSRV core into the cytoplasm activates reverse transcription leading to the formation of double-stranded DNA. Integrase mediates the integration of the viral DNA into the host chromosomal DNA to form the provirus. Two major JSRV transcripts are produced by alternative splicing: (i) the full-length viral



Source: (Griffiths *et al.*,2010)

RNA, used for the expression of *gag, pro* and *pol* proteins and also for the encapsulation into new virus particles, and (ii) a spliced sub genomic RNA, which is used for the translation of *env* proteins. Retroviral protein synthesis occurs on free ribosomes in the cytoplasm for *gag, pro* and *pol*, whereas, *env* proteins are targeted to the endoplasmic reticulum and subsequently transported to the plasma membrane. While budding they acquire a lipid envelope and their *env* glycoprotein.

Immune response against OPA

An important feature of JSRV infection is the absence of specific cellular or humoral immune responses against viral proteins because of the exposure of enJSRV proteins in foetal thymus, which produces central tolerance. Besides, immunosupression also occurs due to the excess production of surfactant proteins. MHC I downregulation and MHC II upregulation has been seen in many cases.

Wheel barrow test in sheep (Grffiths *et al.*, 2010)

Diagnosis of OPA

A field test for OPA, known as the wheel barrow assay, is performed by elevating the hind quarters of the sheep, following which lung fluid drains from the nose of infected sheep. Upto 200-400 ml of lung fluids can be collected by this test which signifies the disease.

JSRV is associated with both typical and atypical forms of OPA, but antibodies against it have not been detected, therefore serological tests are of no use, whereas, PCR is a sensitive and specific assay for the detection of OPA. Single step and hemi-nested JSRV specific PCRs have been developed, based on the primers derived from the U3 region of the JSRV- LTR. These can detect JSRV in several tissues, including peripheral blood MNCs of in contact sheep in the flocks with OPA, as well as in experimentally infected lambs and in bronchioalveolar lavage samples.

Real time PCR (qPCR) can be used as diagnostic tool for JSRV infection as well as for the measurement of viral load in OPA affected sheep. Immunohistochemistry can be used to demonstrate the viral antigen in the alveolar cells and macrophages by using antibodies raised against viral antigens. Computed tomography, X ray and Ultrasonography has been used to image subclinical tumors in OPA.

Summary and conclusion

Ovine Pulmonary Adenocarcinoma is an important disease that affects nearly all sheep-rearing countries around the world and caused by beta retro virus in the family *retroviridae* causing lung tumor leading to respiratory distress and thus huge economic loss worldwide. The virus is transmitted by droplets from respiratory fluid, milk, and colustrum. OPA is important diseases as it has been used as an animal model to study human lung cancer, because histologically it is similar to human adenocarcinoma in situ of the lung. It is a challenging disease to diagnose during its early stages, which probably accounts for its under-reporting. There is no specific treatment or vaccine available as the disease is progressive and no specific antibodies have yet been detected. Affected sheep must be culled as soon as clinical suspicions. Effective control, and possible disease eradication, has been hampered by the lack of a suitable diagnostic test or vaccine. Research is going on to develop improved diagnostic tests.

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