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Clinical History: A 14-year-old, mixed breed, female goat had been coughing on and off for the past year. She had labored breathing with no improvement after taking antibiotics. She was euthanized when she became dyspneic.

Necropsy Findings: There are multifocal to coalescing tan to yellow proliferative lesions expanding the parenchyma and elevating the majority of the pleural surface.

Gross and Microscopic Images:

Figure 1. Lung. Proliferative lesions affect the majority of the parenchyma.
Figure 2. Lung (cross section). The affected area comprises 90% of the parenchyma.

Figure 3. Lung (cross section, close up). Neoplastic tissue is adjacent to unaffected bronchi and vasculature.
Figure 4. Lung. Neoplastic cells are forming papillary projections. A large bronchus (*) contains abundant eosinophilic fluid. 20X, H&E.

Figure 5. Lung. Neoplastic columnar epithelium is piling up but few mitotic figures are observed. 400X, H&E.
**Figure 6.** Lung. Copious eosinophilic fluid is expanding alveolar lumens and a terminal airway (*). 20X, H&E.

**Figure 7.** Lung. Copious amount of inspissated eosinophilic fluid, believed to contain surfactant, is produced by type II pneumocytes. 200X, H&E.
Morphologic Diagnosis: Lung: Adenocarcinoma

Condition: Jaagsiekte, Ovine Pulmonary adenocarcinoma (OPA), Pulmonary adenomatosis

Cause: Jaagsiekte sheep retrovirus (JSRV)

Comments: Ovine pulmonary adenocarcinoma (OPA) is caused by the Jaagsiekte sheep retrovirus (JSRV), which affects sheep, goats and wild mouflons that are one to four years old. The virus is easily spread through aerosolized droplets, milk, or colostrum. JSRV is a simple retrovirus that can induce lung tumors in as little as 10 days, which is shorter than typical insertional activation of host oncogenes by other retroviruses. Experimental infection of young lambs but not adult animals results in the induction of lung adenocarcinoma after a short (several weeks to months) incubation while in naturally occurring OPA cases the lung adenocarcinoma develops slowly after a long (several years) incubation period. The discrepancy between the incubation period in experimentally-induced and naturally occurring OPA may be due to experimental exposure of lambs to a much higher amount of virus and/or to higher susceptibility of target cells to infection by JSRV in young lambs.

The JSRV envelope (Env) glycoprotein is a structural protein that functions as a dominant oncprotein which transforms cells via several signal transduction pathways, including phosphatidylinositol 3-kinase (PI-3K)/Akt and Ras–MEK–mitogen-activated protein kinase (MAPK). A second mechanism involves Env binding to the virus entry receptor, hyaluronidase 2 (Hyal2), Hyal2 degradation, and activation of the RON receptor tyrosine kinase, which is normally suppressed by Hyal2. Unlike other retroviruses, the host range of JSRV is in part limited by species-specific differences in Hyal2, which is not functional as a receptor in mice but is functional in humans in experimental studies. The same differences exist in how sheep respond versus goats. Because JSRV uses a structural protein, the virus does not need a productive infection in order to induce cell transformation; it only needs to enter a target cell, reverse transcribe its genome, and integrate its provirus into the cell, eventually leading to cell transformation.

Most retroviruses use a non-structural protein, but JSRV is a variation of the norm since it uses the envelope structural protein as a virulence factor. Since viruses are non-living, they depend on their host cells machinery to produce the proteins they need for replication. Some proteins are structural proteins that build the capsid and envelope. Other proteins are non-structural proteins that are encoded by a virus but that is not part of the viral particle. By using a structural protein as a virulence mechanism, JSRV replication appears to induce tumors based on the species and their individual response, which is a unique paradigm for oncogenic viruses.

Caporale et al. found that JSRV induces lung tumors in goats that are grossly and histologically different from those in sheep. They also found major differences in the number of virus-infected cells at early stages of infection and concluded that the differences were not related to the number of available target cells, were not related to cell transformation, and were not related to the presence of a host-specific immune response toward JSRV. They concluded that JSRV replication is restricted (i.e., it cannot produce progeny), but it can induce oncogenesis in goats. In goats, JSRV induces neoplastic lesions that appear to be more circumscribed than those observed in infected sheep. This finding could be due to (i) decreased susceptibility of goat cells to JSRV-induced transformation, (ii) reduced ability of the virus to infect and replicate in the target cells for virus transformation, or (iii) difference in the grade of malignancy of the neoplasm induced in the two different species. Tumors in sheep and goats are formed by the same cell type, however, which are the type II pneumocytes.
Sheep possess transcriptionally active endogenous retroviruses (enJSRVs), while goats do not. Sheep appear to be “immune tolerant” since the enJSRV is molecularly similar to JSRV and is not viewed as foreign. Tolerance may originate in the fetal thymus during T lymphocyte development and any JSRV-reactive T cells deemed ‘anti-self’ are selectively removed. Another hypothesis is that tumor cells downregulate their major histocompatibility class-I expression, possibly being the reason for the absence of any virus-specific cytotoxic T cell response (CTL). For this reason, sheep do not mount a cellular or humoral response, which makes them more vulnerable to infection. Sheep have neoplastic foci of different sizes that are adjacent to each other, resulting in large tumors with a “spreading” or “invasive” appearance. This may be due to the ability of JSRV to produce viral progeny that can then infect and transform cells, resulting in multiple tumor foci of polyclonal origin that subsequently coalesce into larger tumor masses.

Death of animals with OPA results from dyspnea attributed to the production of copious amounts of thick inspissated fluid seen in airway and alveolar lumens. The virus attacks mitotically active type II pneumocytes, Clara cells, and undifferentiated cells that are abundant in young lambs during the postnatal development (hence the age-related susceptibility to JSRV infection) or in adults as a result of damage to the bronchioalveolar epithelium. JSRV infected sheep and goats can live a long life if cell proliferation remains low. In older sheep, oncogenesis without acute infection increases cell proliferation, fluid production, and death. Type II pneumocytes produce surfactant, which is believed to be a component of the copious fluid found at the end stage of the disease. The origin and composition of this fluid is not fully understood but it is not edema fluid. Type II pneumocytes are upregulated as more neoplastic cells are formed and, consequently, more fluid is produced. For this reason, death is believed to be due to increased quantity of fluid produced and not due to poorly formed or low quality surfactant.

In sheep, two pathologic forms of OPA are currently recognized: classical and atypical. In classical forms, diffuse or nodular lesions occur in the cranioventral parts of all lung lobes. On the cut surface, the tumor is moist, and thick frothy fluid may pour from the airways on slight pressure. Histologically, there is epithelial cell neoplastic proliferation in both alveolar and/or bronchiolar regions. The tumors proliferate in a mostly papillary pattern, but also form acinar or occasionally solid growths. The tumors generally show a benign histological pattern but intra- and extrathoracic metastases have been detected in some cases. Atypical forms of OPA tend to be more nodular in both early and advanced tumors; are pearly white, very hard in consistency, very well demarcated from the surrounding parenchyma, and have a dry surface. The histology of atypical OPA is similar to that of the classical disease, with increased stromal reaction accompanying the epithelial proliferation. In sheep, the stroma is infiltrated by mononuclear cells and lymphoid hyperplasia is a common feature in these cases. As previously described, goats have a different lesion morphology, consisting of large, well-circumscribed nodules of bronchioalveolar carcinoma that compress the surrounding normal parenchyma and lack significant inflammatory cell infiltrate.

The World Organization for Animal Health (OIE) declared OPA as the most important disease of small ruminants that can affect international trade. OPA also serves as an animal model on pulmonary carcinogenesis because it has similar pathological and epidemiological features to bronchoalveolar carcinoma in humans. The surfactant protein A, proliferating cell nuclear antigen (PCNA), and p53 protein expression were evaluated, with PCNA and p53 protein expression representing potential indicators of malignancy of the pulmonary tumors. Interestingly, animals experimentally coinfected with JSRV and ovine lentivirus (maedi-visna virus) showed spontaneous regression of tumors believed to be involving CD3(+) T cells and production of antibodies against JSRV.

The clinical diagnosis of OPA is elusive since no preclinical assay exists. Characteristic signs to look for in affected animals is drainage of the thick lung fluid from the nose following elevation of the hindlimbs. There are no circulating JSRV specific antibodies at this time because the proteins are sequestered within the tumor. When clinical signs or tumors are observed, JSRV infection can be confirmed in lung fluid or tumors by immunoblotting, ELISA, or polymerase chain reaction (PCR).
References:


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