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Evidence of jaagsiekte sheep retrovirus-induced pulmonary adenocarcinoma in Ouled Djellal breed sheep in Algeria

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Article Info	Abstract
<p>Article history:</p> <p>Received: 01 May 2019 Accepted: 17 Sep 2019 Available online: 15 March 2020</p> <p>Keywords:</p> <p>Algeria Immunohistochemistry Pulmonary adenocarcinoma Retrovirus Sheep</p>	<p>We report the occurrence of lung cancer in a six months old lamb of Ouled Djellal breed from Algeria. The main clinical sign was a considerable amount of whitish foamy fluid discharge from the nostrils when the animal head was lowered and the rear end was lifted. The post-mortem examination revealed the presence of enlarged, heavy and edematous lungs with diffuse or foci areas, reddish or white-gray in color. The gross and histological lesions of the lungs were compatible with pulmonary adenocarcinoma. Lung adenocarcinoma in sheep is caused by jaagsiekte sheep retrovirus (JSRV) and originated from differentiated alveolar type II cells and non-ciliated bronchiolar epithelial Clara cells. We evidenced the expression of the oncogenic JSRV by immunostaining of lung slides with specific antibodies against the JSRV envelope. The viral proteins were expressed only in the tumor cells from the affected areas. As already described in other countries, JSRV-induced lung adenocarcinoma is present in the sheep population in Algeria.</p>

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Introduction

Ovine pulmonary adenocarcinoma (OPA) is contagious lung cancer in sheep occurring naturally in almost all countries worldwide with the exception of Australia and New Zealand. It has been successfully eradicated from Iceland with a strict slaughter policy.¹ Ovine pulmonary adenocarcinoma was first described in South Africa in the early 19th century and designed as jaagsiekte, an Afrikaner term for chasing sickness describing the respiratory condition of the sick animals that appeared as if they had been chased.² In some countries like United Kingdom, OPA prevalence can be as high as 30.00% representing significant economic and welfare impact.³ This lung cancer has been reported in mouflon and can be naturally or experimentally transmitted to goats.^{4,5} The ovine pulmonary adenocarcinoma is caused by the infection with jaagsiekte sheep retrovirus (JSRV), a beta type retrovirus, isolated in 1983 in South Africa and fully sequenced in 1992.^{6,7} The JSRV is responsible for the trans-

formation of epithelial cells of the lung parenchyma, namely alveolar type II cells in the alveoli and club cells in the bronchioles. Interestingly, the envelope of JSRV is the main oncogenic determinant; its expression is sufficient to induce cell transformation *in vitro* or tumors *in vivo*.⁸ This oncogenic retrovirus is genetically highly related to enzootic nasal tumor virus (ENTV) inducing the transformation of nasal epithelial cells. We have recently reported ENTV-induced nasal adenocarcinomas in Algeria.⁹

Two anatomopathological forms of OPA including classical and atypical have been reported. In the classical form, the neoplastic lesions appear as nodular to diffuse grey to purple areas particularly in the cranioventral parts of the lung lobes; whereas the atypical form has consisted of well-demarcated solitary or multiple nodules often located in the diaphragmatic lobes.¹⁰ Since 1960s, Algeria has experienced a rapid demographic growth and consequently, an increase of the demand of milk and meat; 27,000,000 sheep are raised for human consumption mostly under traditional extensive husbandry.¹¹ The

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circulation of pathogens must be carefully monitored to avoid the spread of deadly diseases. In this context, we report the first clinical case of ovine pulmonary in Ouled Djellal breed in a 6-month-old lamb associated with expression of JSRV proteins in the lung.

Case Description

In February 2016, a six months old lamb of Ouled Djellal breed was examined with a history of progressive respiratory illness associated with abundant lung fluid secretions, unsuccessfully treated with several antibiotic regimens. The lamb presented a poor body condition, struggled to breathe especially when exercised. The owner reported that one sheep died over the last two years with similar clinical symptoms, but no pathological examination has been performed on this initial case. Using the wheelbarrow test, a large amount (~350 mL in 24 hr) of a whitish foamy fluid was discharged through the nostrils. Necropsy was performed to determine the death cause and samples from the animal were taken for microscopy examination. Lung and mediastinal lymph nodes were fixed in 10.00% formalin, paraffin-embedded, cut in 3.00-5.00 μm sections and stained with Hematoxylin and Eosin (H & E). Detection of the JSRV envelope proteins was performed as previously reported.¹⁰

Results

A six months old lamb of Ouled Djellal sheep was presented with progressive respiratory illness and poor body condition. Necropsy demonstrated frothy fluid filling the trachea and exuding from the nares. The incision of the thoracic cavity revealed the presence of enlarged, heavy and edematous lungs. Both lungs showed reddish areas distributed in both lungs together with whitish nodules of various sizes. Lung sections showed the grey granular moist surface in the tumoral areas with frothy fluid exuding from it (Fig. 1). Except for enlarged and edematous lymph nodes, no other obvious abnormalities were observed. No metastases were found within the mediastinal lymph nodes.

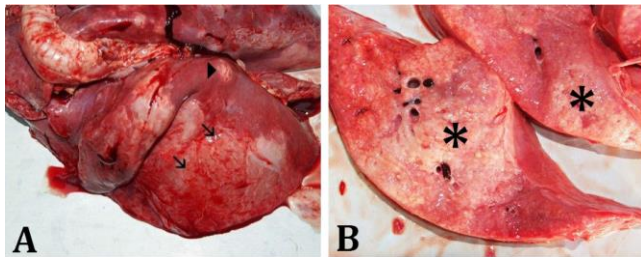


Fig. 1. Clinical and macroscopic presentation of naturally occurring pulmonary adenocarcinoma. **A)** Lungs with lesions consistent with those of lung cancer. Bilateral, diffuse (arrows) and foci areas (arrowhead) of the tumor, reddish or white-gray in color. **B)** Greyish and granular moist (asterisk) surface of the tumoral area.

The pathological examination showed alveoli lined by neoplastic cuboidal to columnar cells arranged in papillary, acinar or glandular patterns (Fig. 2A). Neoplastic cells were well-differentiated and the mitotic index was not remarkable (Fig. 2B). Infiltration of lymphocytes and plasma cells into the interstitial tissue was observed in tumoral areas. Macrophage infiltration was mainly observed in normal or moderately-affected alveoli in the vicinity of tumoral lesions. Importantly, JSRV-envelope proteins were expressed in the cytoplasm of epithelial cells within the lesions as shown by immunohistochemical labeling (Fig. 2C). In conclusion, the young animal presented with JSRV-induced pulmonary adenocarcinoma with mixed lesions and a pneumonic presentation.

Discussion

In our study, we evidenced OPA in six months old Ouled Djellal lambs. The clinical signs, the gross presentation, and the microscopic lesions were compatible with OPA. Pathological examination showed the presence of a typical epithelial tumor and the cells expressed the envelope of JSRV as demonstrated by the immunohistochemical analysis using JSRV-specific antibodies. No systematic follow-up was implemented in this flock, but the owner reported the death of an adult sheep a year before with the same clinical signs (i.e., respiratory distress and mucoid fluid production through the nostrils). This suggests that JSRV was circulating in the flock before we identified the disease and virus in the lamb.

First described in South Africa, JSRV-induced lung cancers in small ruminants are present worldwide. No effective methods for controlling virus spread have been implemented, but the surveillance of disease and virus dissemination into the flocks is essential to limit the economic impact.¹ Adult sheep can be infected when naive and infected animals are kept together; that stresses the importance of respiratory route for inter-animals JSRV transmission.¹² This route of virus spread has been reported as early as 1934 during the Icelandic epidemic outbreak.¹³ Besides transmission through aerosolized particles in adults, the detection of JSRV at birth suggests *in utero* transmission to the fetus and its presence in colostrum and milk supports its spread to kids.^{12,14,15} Younger lambs may be more sensitive to infection because of the increased numbers of dividing type II pneumocytes and Clara cells as seen in normal neonates of other species.¹ Thus, the surveillance of the disease is of importance to rapidly identify and eliminate sick animals and limit virus spread.

We report lung adenocarcinoma in a young sheep of Ouled Djellal breed. This is the first report of JSRV-induced cancer in sheep in Algeria. This highlights the need for a better clinical diagnosis of this deadly disease to determine its extension within the Algerian ovine population.

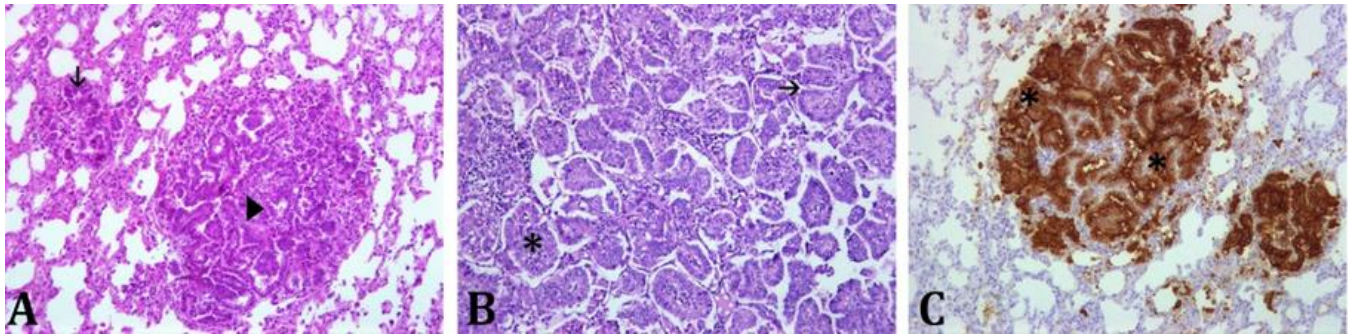


Fig. 2. Pathological and immunohistological presentations. **A)** Non encapsulated lesions (arrowhead) surrounded by normal alveoli infiltrated by macrophages (arrow), (H & E, 100×); **B)** Papillary (arrow) and acinar (asterisk) structures lined by regular cuboidal or columnar cells and interstitial tissue infiltrated by lymphocytes and plasma cells, (H & E, 100×); and **C)** Strong expression of the JSRV-Env marker by adenocarcinomas (asterisk), (IHC, 100×).

The nature of Algerian JSRV strains is under investigation and phylogenetic tools will help us to decipher the origin of the virus present in North Africa.

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Conflict of interest

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing the publication.

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