CHAPTER 3.8.8.

OVINE PULMONARY ADENOCARCINOMA (ADENOMATOSIS)

SUMMARY

Ovine pulmonary adenocarcinoma (OPA), also known as ovine pulmonary adenomatosis and jaagsiekte, is a contagious tumour of sheep and, rarely, of goats. It is a progressive respiratory disease, principally affecting adult animals. The disease occurs in many regions of the world. A betaretrovirus (jaagsiekte sheep retrovirus: JSRV), distinct from the non-oncogenic ovine lentiviruses, has been shown to cause the disease.

Detection of the agent: *JSRV cannot yet be propagated* in vitro*, therefore routine diagnostic methods, such as virus isolation, are not available for diagnosis. Diagnosis relies, at present, on clinical history and examination, as well as on the findings at necropsy and by histopathology and immunohistochemistry. Viral DNA or RNA can be detected in tumour, draining lymph nodes, and peripheral blood mononuclear cells by polymerase chain reaction. Lambs become persistently infected by JSRV at an early age, and, in an OPA-affected flock, most sheep are infected.*

Serological tests: *Antibodies to the retrovirus have not been detected in infected sheep; therefore, serological tests are not available for diagnosis.*

Requirements for vaccines: *There are no vaccines available.*

A. INTRODUCTION

Ovine pulmonary adenocarcinoma (OPA), also known as ovine pulmonary adenomatosis, jaagsiekte (Afrikaans = driving sickness) and ovine pulmonary carcinoma (OPC), is a contagious lung tumour of sheep and, more rarely, of goats. It is the most common pulmonary tumour of sheep and occurs in many countries around the world. It is absent from Australia and New Zealand and has been eradicated from Iceland.

Historically, a number of different viruses have been linked to OPA, including a herpesvirus and lentiviruses, which have been propagated from tumour tissue. However, the former does not have an aetiological role in OPA and the latter exhibit characteristics of non-oncogenic lentiviruses. It has been demonstrated clearly that OPA is caused by a betaretrovirus that cannot yet be cultured *in vitro,* but the virus has been cloned and sequenced. The term jaagsiekte sheep retrovirus (JSRV) is used in referring to this virus.

B. DIAGNOSTIC TECHNIQUES

At present, diagnosis of OPA usually relies on clinical and pathological investigations but, more recently, specific techniques to identify JSRV proteins or nucleic acid can be employed. In particular, polymerase chain reaction (PCR) offers hope for ante-mortem diagnosis of OPA as a flock test (Lewis *et al.,* 2011). In flocks in which the disease is suspected, its presence must be confirmed, at least once, by histopathological examination of affected lung tissue to identify the characteristic lesions and, preferably by immunohistochemistry or PCR, to confirm the presence of JSRV. For such an examination, it is imperative to take specimens from several affected sites and, if possible, from more than one animal. This is because secondary bacterial pneumonia, which might be the immediate cause of death, often masks the lesions (both macroscopic and microscopic) of the primary disease. In the absence of specific serological tests that can be used for the diagnosis of OPA in live animals, disease control relies on strict biosecurity to prevent the introduction of the disease to OPA-free countries and flocks; where the disease already exists, control relies on regular flock inspections and prompt culling of suspected cases and, in the case of ewes,

their offspring. However, clinical examination has been shown to be unreliable for detection of early OPA cases (Cousens *et al.,* 2008), although transthoracic ultrasound examination can detect a proportion of subclinical cases (Cousens & Scott, 2015). There is no known risk of human infection with JSRV. Biocontainment measures should be determined by risk analysis as described in Chapter 1.1.4 *Biosafety and biosecurity: Standard for managing biological risk in the veterinary laboratory and animal facilities*.

Table 1. Test methods available for the diagnosis of ovine pulmonary adenocarcinoma and their purpose

Method	Purpose					
	Population freedom from infection	Individual animal freedom from infection prior to movement	Contribute to eradication policies	Confirmation of clinical cases	Prevalence of infection – surveillance	Immune status in individual animals or populations post-vaccination
Detection of the agent						
PCR	++	+	+	+++	++	–
Histopathology	–	–	+	+++	+	–
Immuno-histochemistry	+	–	+	+++	+	–

Key: +++ = recommended for this purpose; ++ recommended but has limitations;
+ = suitable in very limited circumstances; – = not appropriate for this purpose.
PCR: polymerase chain reaction in either blood or tumour samples.

1. Detection of the agent

JSRV has been designated as a betaretrovirus because of its genetic organisation and its structural proteins. Although the ovine genome contains approximately 20 copies of endogenous betaretroviruses that are highly related to JSRV (Spencer & Palmarini, 2012), JSRV is clearly exogenous and associated exclusively with OPA (Palmarini *et al*., 1996). JSRV is detected consistently in the lung fluid, tumour, peripheral blood mononuclear cells, somatic cells in colostrum and milk, and lymphoid tissues of sheep affected by OPA or unaffected in-contact flockmates, and never in sheep from unaffected flocks with no history of the tumour. Full-length proviral clones of JSRV have been obtained from OPA tumour DNA and cells. JSRV virus particles, prepared from these clones by transient transfection of a cell line, were used for intratracheal inoculation of neonatal lambs. OPA tumour was induced in the lambs, thus demonstrating that JSRV is the causal agent of OPA (DeMartini *et al*., 2001; Palmarini *et al*., 1999).

Although the endogenous betaretroviruses that are highly related to JSRV are not involved in the aetiology of OPA, their expression in the uteroplacental tissues appears to be beneficial (Dunlap *et al.,* 2006) and expression in the fetus may, by induction of tolerance, account for the apparent lack of immune response of mature animals to exogenous JSRV (Palmarini *et al*., 2004).

There are no permissive cell culture systems for propagation of JSRV. Some cell cultures prepared from the tumours occurring in young lambs can support virus replication for a short period (Jassim, 1988; Sharp *et al*., 1985).

1.1. Nucleic acid recognition methods

Single step and hemi-nested JSRV-specific PCRs have been developed, based on primers derived from the U3 region of the JSRV LTR (Table 2) (Palmarini *et al.,* 1997). These can detect JSRV in several tissues, including peripheral blood mononuclear cells and lung fluid, from OPA-affected sheep, as well as experimentally infected lambs (De las Heras *et al*., 2005; Holland *et al*., 1999; Salvatori *et al.,* 2004). Importantly, JSRV can be detected by PCR in blood (Gonzalez *et al*., 2001), colostrum and milk (Borobia *et al.,* 2016), and in bronchoalveolar lavage samples (Voigt *et al*., 2007) from unaffected in-contact sheep from flocks with OPA.

These PCRs have a high diagnostic specificity but a low diagnostic sensitivity when applied to individual animals, due to low concentrations of target DNA in the blood of clinically healthy animals (De las Heras *et al.,* 2005; Holland *et al*., 1999; Lewis *et al.,* 2011). Longitudinal studies in OPA-affected flocks, supported by studies with lambs fed artificially with colostrum and milk (Grego *et al.,* 2008), have shown that most lambs become infected at a very early age. A high proportion of animals in these flocks are infected, yet only a minority develops OPA (Borobia *et al.,* 2016; Caporale *et al*., 2005; Salvatori, 2005).

Table 2. Primers used in JSRV-specific PCRs

	Primer	**Sequence (5'→3')**
Single step PCR	P1	TGG-GAG-CTC-TTT-GGC-AAA-AGC-C
	PIII	CAC-CGG-ATT-TTT-ACA-CAA-TCA-CCG-G
Hemi-nested PCR (uses product from single-step PCR)	P1	TGG-GAG-CTC-TTT-GGC-AAA-AGC-C
	PVI	TGA-TAT-TTC-TGT-GAA-GCA-GTG-CC

A few reports have described techniques, such as reverse-transcription PCR (RT-PCR) and real-time RT-PCR, to detect JSRV RNA in lung fluid and tumour tissues (Cousens *et al.,* 2009; Lee *et al.,* 2017; Zhang *et al.,* 2014). Although these techniques have not been investigated further, they have the potential to increase the sensitivity of detection and future studies, including comparison with the established PCR protocols, are merited.

2. Clinical signs and pathology

2.1. Clinical signs

There is no reliable laboratory method for the ante-mortem diagnosis of OPA in individual animals, therefore flock history, clinical signs and post-mortem lesions are the primary method for the diagnosis of the disease. OPA has a long incubation period, clinical disease is encountered most commonly in sheep over 2 years of age, with a peak occurrence at the age of 3–4 years. In exceptional cases, the disease occurs in animals as young as 2–3 months of age. The cardinal signs are those of a progressive respiratory embarrassment, particularly after exercise; the severity of the signs reflects the extent of tumour development in the lungs. Accumulation of fluid within the respiratory tract is a prominent feature of OPA, giving rise to moist rales that are readily detected by auscultation. Raising the hindquarters and lowering the head of affected sheep may cause frothy mucoid fluid to run from the nostrils. Coughing and inappetance are not common but, once clinical signs are evident, weight loss is progressive and the disease is terminal within weeks or months. Death is often precipitated by a superimposed bacterial pneumonia, particularly that due to *Mannheimia* (formerly *Pasteurella*) *haemolytica*. In clinically affected animals, a peripheral lymphopenia characterised by a reduction in CD4+ T lymphocytes and a corresponding neutrophilia may assist clinical diagnosis, but the changes are not pathognomonic and are not detected during early experimental infection (Summers *et al*., 2002).

In some countries, another form of OPA (atypical OPA) occurs, which generally presents as an incidental finding at necropsy or the abattoir (De las Heras *et al*., 2003).

2.2. Necropsy

OPA lesions are in most cases confined to the lungs, although intra- and extrathoracic metastasis to lymph nodes and other tissues can occur. In typical cases, affected lungs are considerably enlarged and heavier than normal due to extensive nodular and coalescing firm grey lesions affecting much of the pulmonary tissue. Usually lesions are present in both lungs, although the extent on either side does vary. Tumours are solid, grey or light purple with a shiny translucent sheen and often separated from the adjacent normal lung by a narrow emphysematous zone. The presence of frothy white fluid in the respiratory passages is a prominent feature and is obvious even in lesions as small as a few millimetres. In advanced cases, this fluid flows out of the trachea when it is cut or pendant. Samples should be taken at necropsy for histopathology, immunohistochemistry or PCR for JSRV.

Pleurisy may be evident over the surface of the tumour and often abscesses are present in the adenomatous tissue.

In atypical OPA, tumours comprise solitary or aggregated hard white nodules that have a dry cut surface and show clear demarcation from surrounding tissues. The presence of excess fluid is not a prominent feature. Classical and atypical lesions may be found in individual sheep from the same flock and, on occasions, in the same lung.

Adult sheep, which on post-mortem examination appear to have died from acute pasteurellosis, should have their lungs examined carefully, as lesions of OPA may be masked by coexisting bronchopneumonia, verminous pneumonia, chronic progressive pneumonia (maedi-visna) or combinations of these. Samples should be taken at necropsy for histopathology.

2.3. Histopathology and immunohistochemistry

Although JSRV can infect several pulmonary cell types (Martineau *et al.,* 2011) and tumours are heterogeneous (De las Heras *et al.,* 2014), OPA originates from JSRV infection and transformation of type II pneumocytes (Murgia *et al.,* 2011). Histologically, the lesions are characterised by proliferation of mainly type II pneumocytes, a secretory epithelial cell in the pulmonary alveoli. Nonciliated club cells (formerly known as Clara cells) and epithelial cells of the terminal bronchioles may be involved. The cuboidal or columnar tumour cells replace the normal thin alveolar cells and sometimes form papilliform growths that project into the alveoli. Intrabronchiolar proliferation may be present. In advanced cases, extensive fibrosis may develop and, occasionally, nodules of loose connective tissue in a mucopolysaccharide substance may be present.

Several studies have employed rabbit polyclonal antibodies to JSRV CA (capsid protein) or mouse monoclonal antibodies to JSRV SU (surface protein) to demonstrate these proteins in the cytoplasm of the transformed epithelial cells by immunohistochemistry, using standard protocols, thus providing a definitive diagnosis, in addition to PCR, e.g. Palmarini *et al.* 1995 and Wootton *et al.* 2006. Antisera are not available commercially but may be made available through personal collaborations.

A prominent feature is the accumulation of large numbers of alveolar macrophages in the alveoli adjacent to the neoplastic lesions (Summers *et al*., 2005).

Where maedi-visna is concurrent, perivascular, peribronchiolar and interstitial lymphoid infiltrates may be prominent.

The histological appearance of atypical OPA is essentially the same as classical OPA, but with an exaggerated inflammatory response (mostly lymphocytes and plasma cells) and fibrosis (De las Heras *et al*., 2003).

For more detailed accounts of the clinical, post-mortem and histopathological aspects of OPA, the reader is referred elsewhere (De las Heras *et al*., 2003; Sharp & DeMartini, 2003; Summers *et al.,* 2012).

There appears to be a synergistic interaction between OPA and maedi-visna. Lateral transmission of maedi-visna virus appears to be enhanced in sheep affected by OPA (Dawson *et al*., 1985; Gonzalez *et al*., 1993).

3. Serological tests

At present, there are no laboratory tests to support a clinical diagnosis of OPA in the live animal. JSRV has been associated exclusively with both typical and atypical forms of OPA, but antibodies to this virus have not been detected in the sera of affected sheep, even with highly sensitive assays such as immunoblotting or enzyme-linked immunosorbent assay (Ortin *et al*., 1997; Summers *et al*., 2002).

C. REQUIREMENTS FOR VACCINES

There are no vaccines available at the present time.

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NB: At the time of publication (2021) there were no WOAH Reference Laboratories for ovine pulmonary adenocarcinoma (adenomatosis) (please consult the WOAH Web site: https://www.woah.org/en/what-we-offer/expertise-network/reference-laboratories/#ui-id-3).

NB: FIRST ADOPTED IN 1990 AS SHEEP PULMONARY ADENOMATOSIS. MOST RECENT UPDATES ADOPTED IN 2021.