CHAPTER 2.7.10.

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 beta-retrovirus (jaagsiekte sheep retrovirus: JSRV), distinct from the non-oncogenic ovine lentiviruses, has been shown to cause the disease.

Identification 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 and, therefore, serological tests are not available for diagnosis.

Requirements for vaccines and diagnostic biologicals: There are no vaccines or diagnostic biologicals 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.

A number of different viruses have been linked aetiologically to OPA, including a herpesvirus and lentiviruses that 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 beta-retrovirus 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 relies on clinical and pathological investigations, although polymerase chain reaction (PCR) offers hope for ante-mortem diagnosis of OPA as a flock test. In flocks in which the disease is suspected, its presence must be, at least once, confirmed by histopathological examination of affected lung tissue. 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 regular flock inspections and prompt culling of suspected cases and, in the case of ewes, their offspring.
Chapter 2.7.10. – Ovine pulmonary adenomatosis (adenocarcinoma)

1. Identification of the agent

Although ovine herpesvirus 1 (OvHV-1) had been isolated exclusively from OPA tumours, epidemiological studies and experimental infections provide no evidence for a role in the aetiology of OPA. Ovine herpesvirus 2 (OvHV-2) is the sheep-associated malignant catarrhal fever herpesvirus and has never been linked to OPA.

The association of retroviruses with OPA has been recognised for several years. Ovine lentiviruses have been isolated on a number of occasions, but these viruses have no aetiological role in OPA.

For many years, the inability to culture JSRV and the lack of antibodies to the virus in affected sheep impeded the confirmation of this virus as the aetiological agent. However, molecular biological techniques provided a key advance, namely, the cloning and sequencing of the 7.5 kb JSRV genome following purification of virions from lung washes of naturally affected sheep (23). JSRV has been designated as a beta-retrovirus because of its genetic organisation and its structural proteins. Although cloned JSRV genes, used as hybridisation probes, have revealed a range of homologous endogenous sequences in the genome of both healthy and OPA-affected sheep (1, 9, 23), JSRV is clearly exogenous and associated exclusively with OPA (13). JSRV is detected constantly in the lung fluid, tumour, peripheral blood mononuclear cells, 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 (6, 15).

The sheep genome contains many copies of endogenous viral sequences that are highly related to JSRV. Although they are not involved in the aetiology of OPA, their expression in the fetus may, by induction of tolerance, account for the apparent lack of immune response of mature animals to exogenous JSRV (14).

a) Nucleic acid recognition methods

Sequencing of JSRV and endogenous sequences in the sheep genome has led to the development of PCRs that specifically detect JSRV (1, 13). Using this sensitive procedure, JSRV has been detected in peripheral blood mononuclear cells of unaffected in-contact sheep from flocks with OPA, as well as experimentally infected lambs (5, 7, 10) and the bronchoalveolar lavage samples from unaffected in-contact sheep (22). Longitudinal studies in OPA-affected flocks have shown that lambs become infected at a very early age. A high proportion of animals in these flocks are infected, yet only a minority develop OPA (2, 16). JSRV has been found in colostrum and milk obtained from sheep in OPA-affected flocks and JSRV can be detected within a few months in the blood of lambs fed artificially with colostrum and milk (De las Heras et al., unpublished observations).

• Control and treatment

b) Animal inoculation

OPA cannot be transmitted to any laboratory animal and can be transmitted to sheep only with material that contains JSRV, such as tumour homogenates, concentrated cell-free lung fluid from natural cases of OPA and virus produced from molecular clones. Following the experimental inoculation of adult sheep, clinical disease develops only after several months or years. In contrast, JSRV infection can be induced in 100% of lambs aged 1–6 months at the time of inoculation and a high proportion of these animals develop clinical signs (62–90%) and lesions (87–100%) of OPA (17).

At this time there is no practical animal inoculation method for the diagnosis of OPA.

c) Virus isolation

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 (11, 18).

d) Clinical signs and pathology

There is no reliable laboratory method for the ante-mortem diagnosis of OPA in individual animals at this time, therefore flock history, clinical signs and post-mortem lesions are the primary method for the diagnosis of the disease. As 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 râles 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 (20).

In some countries, another form of OPA (atypical OPA) occurs, which generally presents as an incidental finding at necropsy or the abattoir (4).

e) Necropsy

OPA lesions 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.

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.

f) Histopathology

Histologically, the lesions are characterised by proliferation of mainly type II pneumocytes, a secretory epithelial cell in the pulmonary alveoli. Nonciliated (Clara) and epithelial cells of the terminal bronchioli 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.

A prominent feature is the accumulation of large numbers of alveolar macrophages in the alveoli adjacent to the neoplastic lesions (21).

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 (4).

For more detailed accounts of the clinical, post-mortem and histopathological aspects of OPA, the reader is referred elsewhere (4, 19).

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 (3, 8).

2. 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 (12, 20).
C. REQUIREMENTS FOR VACCINES AND DIAGNOSTIC BIOLOGICALS

There are no vaccines or diagnostic biologicals available at the present time.

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