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Retroviridae

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Table of Contents

Viral Characteristics

Classification

Alpharetrovirus

Avian Leukosis

Betaretrovirus

Ovine Pulmonary Adenocarcinoma

Enzootic Nasal Tumor

Gammaretrovirus

Feline Leukemia

Feline Sarcoma Virus

Avian Reticuloendotheliosis

Deltaretrovirus

Bovine Leukosis/Leukemia

Lentivirus

Maedi/Visna

Caprine Arthritis/Encephalitis

Equine Infectious Anemia

Feline Immunodeficiency

Bovine Immunodeficiency

Glossary

This is a family of large single-stranded RNA viruses that use the enzyme reverse transcriptase in their replication cycle. A number of oncogenic retroviruses cause animal diseases of major importance. Because of their mode of replication, retroviruses are probably present in all vertebrate genomes.

Viral Characteristics

- These RNA viruses are enveloped, single-stranded RNA with an icosahedral nucleocapsid.
- The envelope has glycoprotein surface spikes (see Fig. 15.1). Retroviruses are unique among viruses in that they bring two identical copies of their genome in virions (are diploid).
- The ssRNA is converted to ssDNA by the enzyme reverse transcriptase. From the ssDNA, dsDNA (called provirus DNA) is made, which is then integrated into the host chromosome. The provirus dsDNA then serves as a template for the production of mRNA and progeny ssDNA genomes.
- The conversion of ssRNA to ssDNA, mediated by the viral enzyme reverse transcriptase, results in a dsDNA molecule longer than that of the original genome. This dsDNA migrates to the nucleus where it is ultimately integrated into the host chromosome by the viral enzyme integrase.
- Once integrated into the host genome, the viral dsDNA is referred to as a provirus. The provirus remains latent until "triggered" into transcription of mRNA by host cell machinery.
- Viral mRNA transcription of the provirus is mediated by cellular RNA polymerase II.
- The new virions are released by budding, which does not always result in cell lysis.
- There is a high mutation rate, as reverse transcription is an error-prone process. Thus, retroviruses usually present a high genetic diversity.
- Many retroviruses carry oncogenes (e.g., Rous sarcoma virus in chickens), while others do not (e.g., human T-cell lymphotropic virus). However, some retroviruses may cause tumors without carrying oncogenes.
- All retroviral genomes consist of two molecules of ssRNA, (+)sense, have 5' cap and 3' poly-(A) (equivalent to mRNA) and four characteristic coding regions (*gag-pro-pol-env*). *Gag* (group specific antigen: matrix protein, nucleoprotein, capsid) genes; *pro* (protease) gene; *pol* (reverse transcriptase and RNase-H); and *env* (envelope, receptor binding) genes (see Fig.15.2). These vary in size from ~8-11 kb. They are the only viruses that are truly diploid. Additionally, there is a specific type of cellular transporter RNA (tRNA) (usually trp, pro or lys) - required for replication that is present in the virion.

- The virions are sensitive to heat, lipid solvents, and detergents but are relatively resistant to ultraviolet light damage.

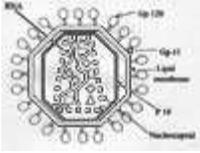


Figure 15-1. Retroviridae (80 - 100 nm). These are enveloped, single-stranded RNA viruses with an icosahedral nucleocapsid. The envelope has characteristic glycoprotein surface spikes. - To view this image in full size go to the IVIS website at www.ivis.org . -

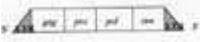


Figure 15-2. Gene arrangement of a typical retrovirus (avian leukemia virus, feline leukemia virus). LTR - lateral terminal repeat; *gag* - genes encoding core and capsid proteins; *pro* - gene encoding protease; *env* - genes encoding envelope glycoproteins. - To view this image in full size go to the IVIS website at www.ivis.org . -

Classification

Currently there are seven genera in the family. All of the genera except Lentivirus and Spumavirus cause neoplastic changes in specific cell types. The genera are, with significant viruses, as follows:

Alpharetrovirus

- Avian leukosis virus
- Avian sarcoma virus
- Avian myeloblastosis virus
- Rous sarcoma virus

Betaretrovirus

- Mouse mammary tumor virus: A much studied important virus of mice.
- Ovine pulmonary adenocarcinoma virus
- Enzootic nasal tumor virus

Gammaretrovirus

- Feline leukemia virus
- Feline sarcoma virus
- Avian reticuloendotheliosis virus

Deltaretrovirus

- Bovine leukemia virus

Epsilonretrovirus

- Fish tumor viruses

Lentivirus These viruses cause immunodeficiency-type diseases.

- Maedi/Visna virus
- Caprine arthritis encephalitis virus
- Equine infectious anemia virus
- Feline immunodeficiency virus
- Bovine immunodeficiency virus
- Human immunodeficiency viruses 1 and 2
- Simian immunodeficiency viruses

Spumavirus Foamy agents (e.g., bovine and simian foamy viruses) that cause persistent but silent infections in several natural hosts. They are occasional contaminants in cell cultures.

The major diseases caused by retroviruses are discussed below under their genera.

Alpharetrovirus

Avian Leukosis

Cause

Avian leukosis virus. The avian leukosis group of viruses (ALGV) is comprised of 10 subgroups, A through J, based on differences in envelope glycoproteins. Subgroups A to E, and J viruses infect chickens. The other subgroup viruses occur in quail, partridges and pheasants.

The ALGV group contains both replication-competent and replication-defective viruses. The defective viruses are not important as causes of leukosis.

Subgroup A viruses cause most outbreaks of avian leukosis that manifest as a lymphoid leukosis, a B cell lymphoma. This is the most important and common neoplasm associated with the disease.

Viruses of subgroup J have been associated with myeloid leukosis in broilers.

Most of the viruses causing avian leukosis are exogenous. Endogenous ALGVs, which mostly belong to subgroup E and occur commonly in chickens and other avian species, are of little or no pathogenicity. These proviral DNA sequences are integrated into germ line cells and are thus transmitted vertically.

Occurrence

Avian leukosis viruses occur commonly in chickens, quail, partridges and pheasants worldwide and the disease is of great economic importance.

Transmission

Although transmission may occur by contact, as virus is present in feces and saliva, the principal means of transmission is via the egg. Blood-sucking parasites are potential vectors. Endogenous viruses, which are common in the chicken but not important as causes of leukosis, are also transmitted genetically in the germ line from parent to offspring.

Pathogenesis, Clinical and Pathologic Features

All avian leukemia group viruses are oncogenic, except those belonging to subgroup E. The mechanisms involved in the development of neoplasia by viruses, that is, oncogenesis, are described in Chapter 4. Such factors as genetics (autosomally transmitted susceptibility or resistant avian cells) and the age and sex of the host can also be important in the development of tumors.

The incubation period is variable and may be as long as months or years. After infection the virus is disseminated to tissues throughout the body where it replicates.

Within B-cells, the provirus induces neoplasia by integrating closely to the host *c-myc* oncogene. As a result, the cell is stimulated to divide when the viral genes are being transcribed. In erythroblastosis, integration is near the *c-erbB* gene, with a similar outcome.

With those viruses that are considered fast-transforming, their genome has been found to contain the *c-onc* proto-oncogene. Multiple copies of the *c-onc* gene result in overproduction of the protein, which stimulates cellular transformation. The oncoproteins produced may act as hormones, growth factor receptors, transcription regulation factors, or kinases associated with cellular signaling mechanisms.

Viruses of subgroups A through D are associated with a variety of neoplastic conditions in chickens, including lymphoid leukosis, erythroblastosis, myeloblastosis, myelocytoblastosis, osteopetrosis, nephroblastomas, hemangiomas, and sarcomas. The more common forms are as follows:

- *Lymphoid leukosis* is by far the most prevalent form of avian leukosis / sarcoma. The disease is most often seen in chickens at least 16 weeks of age and occurs more commonly in females. Clinical signs may be absent or birds may appear thrifty with pale combs. The abdomen may be enlarged because of massive tumor growth in the liver.
- *Osteopetrosis* is a sporadic disease that occurs primarily in males. The shafts of the long bones are thickened, often resulting in a stilted gait. Affected birds may be anemic and also have lesions of lymphoid leukosis.
- *Erythroblastosis* may be manifested in one of two forms, anemic or proliferative, with the latter form being the more common. Clinical signs are similar for both forms. Chickens become depressed, emaciated, and dehydrated. With the anemic form, there are few circulating erythroblasts and chickens appear pale, as opposed to cyanotic with the proliferative form in which circulating erythroblasts are present in large numbers.
- *Myeloblastosis* is similar clinically to erythroblastosis. There is an abnormal proliferation of myeloblasts resulting in severe leukemia.

Diagnosis

- Clinical specimens: whole birds in extremis.
- Diagnosis of the neoplastic conditions caused by avian leukosis / sarcoma viruses is usually based on clinical signs and gross and histopathologic lesions, but lymphoid leukosis may be confused with the acute form of Marek's disease in older birds.
- Differential features, which are summarized in Fig. 15.3, include: nodular tumors in the bursa of Fabricius as opposed to diffuse enlargement with Marek's disease; intrafollicular cell proliferation in the bursa of Fabricius as opposed to interfollicular cell proliferation with Marek's disease; and the cytologic appearance of lymphoid cells that are uniformly "blast" cells with lymphoid leukosis but a mixture of mature and immature pleomorphic cells with Marek's disease.
- Isolation of the virus or the demonstration of antibody is not considered to be of value in diagnosis because avian leukosis group viruses are ubiquitous in chickens.



Figure 15-3. Differential features of Marek's Disease (MD) and Lymphoid Leukosis (LL). - To view this image in full size go to the IVIS website at www.ivis.org . -

Prevention

- There is no vaccine available and eradication is the preferred method of control. Since the viruses are primarily transmitted via the egg, virus infected breeders are detected by testing the egg albumin for viral antigen by an ELISA method. Positive birds are eliminated.
- ELISA and immunofluorescence assays are used to detect antibodies in serum and egg yolk.

- Most commercial flocks of chickens are now free of exogenous ALG viruses.
- Some birds are genetically more resistant to fowl leukosis; they have decreased numbers of specific cell surface viral receptors.
- Incubators should be clean and adequately disinfected.
- Control blood-sucking parasites.

Rous Sarcoma Virus and other Alpharetroviruses

The Rous sarcoma virus (RSV), avian myeloblastosis virus and avian erythroblastosis virus are frequently defective and require a helper ALGV for replication. These viruses can become rapid transforming viruses (experimentally) when a cellular oncogene is incorporated into their genome. They are not thought to be transmitted naturally. The RSV was the first virus, shown in 1911 by Peyton Rous, to cause a solid malignant tumor. Subsequently it was found that there were a number of RSVs that produce tumors in various mammals.

The defective avian sarcoma virus carries the transduced oncogene *v-crk*, whose product binds to several cellular proteins resulting in in vitro cell transformation. Figure 15.4 is a diagrammatic representation of the genome. This and the previously mentioned defective viruses are mainly of research interest.

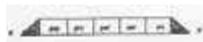


Figure 15-4. Gene arrangement of the Rous sarcoma virus. LTR - lateral terminal repeat; *gag* - genes encoding core and capsid proteins; *pro* - gene encoding protease; *env* - genes encoding envelope glycoproteins; *src* - sarcoma gene. - To view this image in full size go to the IVIS website at www.ivis.org . -

Betaretrovirus

Ovine Pulmonary Adenocarcinoma

(Jaagsiekt, Pulmonary adenomatosis)

Cause

Ovine pulmonary adenocarcinoma virus. As many as 15 - 20 copies of endogenous virus per cell are present in the genome of sheep; however, disease is caused by exogenous virus.

An oncogene has not been found in the genome and the mechanism of transformation has not been elucidated.

Occurrence

The disease occurs in sheep worldwide except for Australia. It rarely affects goats.

Transmission

By airborne respiratory droplets and also by vertical transmission.

Clinical and Pathologic Features

The virus replicates in alveolar and bronchial cells and tumors arise from these cells.

Pulmonary adenomatosis is a chronic slowly progressive, eventually fatal pneumonia of sheep characterized by adenomatous proliferation of viral infected alveolar and bronchiolar epithelium. The resulting adenocarcinomas may metastasize. Mannheimia or Pasteurella bacteria may be involved in a secondary pneumonia, which may be terminal. There is coughing, nasal discharge, and difficulty breathing, leading eventually to emaciation and death. The incubation period may be as long as several years.

The disease can be confused clinically with ovine progressive pneumonia (discussed below - Maedi/Visna), but lung lesions are distinctly different. Grossly, there are widespread nodular growths throughout the lung that are microscopically adenomas or adenocarcinomas.

Diagnosis

- Clinical specimens: Formalin-fixed lung tissue with lesions.
- Diagnosis is usually based on gross and microscopic lung lesions.
- Attempts to cultivate the virus in cell cultures have not been successful.
- ELISA and PCR have been used to detect virus in pulmonary exudates.
- The absence of detectable specific antibodies precludes the use of serological tests.

Prevention

- Vaccines are not available.
- Clinically affected sheep should be removed from the flock. The disease was eradicated from Iceland by depopulation measures.

Enzootic Nasal Tumor

The enzootic nasal tumor virus of sheep and goats is closely related to the virus causing ovine pulmonary adenocarcinoma. The genomes of sheep and goats have copies of endogenous betavirus sequences that are closely related.

The disease is characterized clinically by serous to mucopurulent nasal discharge and open-mouthed breathing. The tumor

or tumors originate from the mucosa of the nares and may be unilateral or bilateral. The nasal passages may become completely occluded, and the tumorous growths may extend into the sinus, cranial cavity, and pharynx. Diagnosis is based on gross and microscopic lesions. Confirmation requires demonstration of the virus.

Gammaretrovirus

Feline Leukemia (FeL)

Cause

Feline leukemia virus (FeLV).

- There are three subgroups of the virus, A, B and C based on differences in the gp70 envelope glycoprotein.
- Subgroup A viruses grow exclusively in feline cells; B and C viruses also grow in human, canine and mink cells. The viruses can be propagated for long periods in feline fibroblast cells; replication does not result in observable CPE.
- FeLV-A can be recovered from all cats naturally infected with viral feline leukemia. FeLV-A tends to be less pathogenic than the other two subgroups.
- FeLV-B arises as a result of recombination between *env* genes of FeLV-A and proviral DNA of endogenous FeLV. FeLV-B can be isolated from about 50% cats with FeL.
- FeLV-B is only transmitted with FeLV-A. FeLV-B is frequently lost in cats with FeL.
- Infection with both subgroups A and B viruses is more serious than with only subgroup A. For example, neoplastic disease incidence increases with A and B coinfection over that of A alone. Among those chronically infected with subtypes A and B, 30% are diagnosed with lymphoma.
- FeLV-C arises in FeLV-A infected cats as a result of mutations in the FeLV-A *env* gene.
- FeLV-C causes a fatal anemia and thus is rarely transmitted.
- Frequent recombination of FeLV with host cell genes yields replication defective recombinant feline sarcoma viruses. The latter viruses can be isolated from fibrosarcomas in young cats.
- FeLV possess the characteristic retrovirus gene arrangement (see Fig. 15.2), where LTR stands for lateral terminal repeats.
- FeLV has been associated with a variety of different malignancies. The mechanisms of oncogenesis include: possession of viral oncogenes, such as *v-myc* (see Chapter 4); transduction of a proto-oncogene to an active state; disruption of a tumor suppressor gene; or insertional mutagenesis (insertion of proviral DNA disrupts the structure or function of another gene, generally involved in cell cycle regulation).

Occurrence

The disease, which occurs worldwide, is a major, frequent malady of domestic cats and some other Felidae including wild cats and jungle cats.

Colostrum appears to protect kittens for the first month of life. Older kittens are particularly susceptible with their susceptibility decreasing with age. It is estimated that only about 1 in 5 cats exposed at 10 weeks of age will develop persistent infection.

Kittens of persistently infected queens usually become infected.

Transmission

The virus is present in respiratory and oral secretions and in urine and feces. Infection is by ingestion and spread is by direct and indirect contact and transplacentally. Saliva is particularly infectious and biting and mutual grooming are common means of spread.

Pathogenesis

The main stages in the progression of FeLV infection are as follows:

- Initial infection
Virus replicating in surrounding lymphatic tissues
- Primary or transient viremia
Replication in systemic lymphatic tissues, bone marrow and other tissues
(May be elimination of the virus or latent infection.)
- Secondary or persistent viremia (May be elimination of the virus)
Extensive involvement of the bone marrow, stomach, pharynx, esophagus, salivary glands, bladder, and respiratory tract leading to one of the following:
Virus elimination / Latent infection / Active infection
- With active infection, virus is excreted in saliva, feces, urine, and respiratory secretions.
- Clinical disease develops and is manifested in various forms.

Clinical and Pathologic Features

Most cats when infected with FeLV mount an effective immune response and recover completely without evidence of any clinical signs. A small percentage is viremic for a variable period but are asymptomatic and eventually eliminate the virus. Those whose immune response is insufficient (about 2%) remain persistently infected and may go on to develop one of a number of neoplastic or non-neoplastic forms of the disease.

Approximately 80% of cats harboring the virus die within three years.

Clinical signs vary with the different forms of the disease and are related to the nature, extent and location of lesions. The forms are as follows:

Neoplastic forms:

Approximately 20% of persistently infected cats develop one of the following lymphosarcoma forms: alimentary, multicentric, thymic, or lymphoid leukemic. Clinical signs vary with the different forms of tumors. General signs are lethargy, anorexia and weight loss.

Some important features of the various forms of lymphosarcoma are as follows:

Alimentary form: The cat may display anorexia, vomiting and diarrhea. Abdominal masses involve the small intestine, cecum and colon; associated mesenteric lymph nodes may be affected.

Multicentric form: Generalized lymphadenopathy, renal lymphosarcoma, splenomegaly, and hepatomegaly may be found. This form is usually seen in young cats.

Thymic form: Dysphagia, and dyspnea are common signs, and cyanosis may be present in advanced cases. Pleural fluid may contain neoplastic cells.

Lymphoid leukemic form: The bone marrow is primarily involved and cancerous lymphocytes circulate in the blood. Jaundice, fever anemia and pallor of mucous membranes are frequent, and lymphadenopathy, splenomegaly, and hepatomegaly may be present. Varying degrees of fever, anorexia and weakness are evident.

Myeloid leukemia: The primary lesion of this non-lymphosarcoma form is in the bone marrow with secondary involvement in the liver, spleen and lymph nodes. This form of leukemia is named according to which hematopoietic cell line is affected, e.g., myelogenous leukemia, erythroleukemia, and lymphoblastic leukemia. Signs include progressive anemia, recurring fever and weight loss.

It should be kept in mind that not all cats with the above referred to forms of FeLV infection will be serologically positive for FeLV antigen. This may complicate the diagnosis.

Non-neoplastic forms:

Immunosuppression

The mechanism responsible for FeLV induced immunosuppression is not well understood. It is thought that the envelope protein p15E may be involved.

The immunosuppression increases susceptibility to bacterial, fungal, protozoan, and viral agents. Some of the manifestations are as follows:

- There may be chronic recurring rhinitis and sinusitis, sores around claws, and periodontal disease. However, these may also be seen as a result of feline immunodeficiency disease. The healing of infectious processes, including abscesses, may be delayed in cats with FeLV infection.
- Cats infected with FeLV are particularly susceptible to bacterial, fungal, and viral respiratory and enteric pathogens. In the chronic infections that ensue there is persistent fever with a progressive loss of weight and condition.
- FeLV infection may predispose to feline infectious peritonitis and *Haemobartonella felis* infection (feline infectious anemia).
- A panleukopenia-like syndrome has been associated with FeLV infection. It has occurred in cats immunized against feline panleukopenia and is invariably fatal.

Reproductive Disorders

- FeLV infection may result in fetal death (fetal resorption), abortion (late gestation) and infertility. Fetal death is thought to be due to endometritis and placentitis. It is estimated that about 75% of infected queens abort.
- Fetuses that survive to term are persistently infected and the resulting kittens are weak and sickly. FeLV infection is considered a cause of what is called fading kitten syndrome.

Glomerulonephritis

This may be present in cats with persistent FeLV infection. It is thought to be due to the deposition of antigen-antibody complexes in the kidney. There is evidence that this immune complex-mediated glomerular nephritis is an important cause of death in FeLV infection.

Diagnosis

- Clinical specimens: Blood smears, tumors, bone marrow, and serum.
- A number of diagnostic procedures can be used including histopathologic examination of biopsies, bone marrow examinations, and cytology of thoracic and abdominal fluids. However, the most practical and reliable way to diagnose FeLV infection is with the ELISA and IFA procedures referred to below. All three subgroups are detected by the commonly used FeLV diagnostic tests, but they cannot distinguish between the various subtypes.
- An indirect fluorescence antibody procedure (IFA) on blood smears and the ELISA procedure on serum are the procedures most commonly used for the detection of antigen (the major capsid protein, p27). This antigen can be

found in large amounts in the cytoplasm of infected leukocytes and in platelets. The soluble form is found in the plasma and serum of infected cats. At least three blood smears are recommended for the IFA. A positive test indicates the presence of virus.

- The results of the IFA test and ELISA compare favorably.
- Commercial reagents are available to diagnostic laboratories for the ELISA and the IFA tests. Commercial ELISA kits are available for practitioners.
- The virus can be readily propagated in cell cultures, but virus isolation as a diagnostic tool is expensive and time consuming.
- PCR can be used to detect the virus genome.

Treatment

- Supportive therapy.
- Chemotherapy and irradiation may prolong life in cats with neoplasia.
- Antiviral agents (including human recombinant INF- α and AZT) may delay the onset of clinical signs but are not curative.

Prevention

- The FeLV is labile and quickly loses its infectivity in the environment. It is easily inactivated by commonly used disinfectants.
- The disease can be eradicated from colonies by periodic serologic testing with the removal of positive cats, and disinfection of potentially contaminated areas. New additions should be quarantined and tested before admission to the main colony. Cats in the main colony are retested at yearly intervals or less.
- There should be an interval of at least 1 month before introducing negative cats to a formerly infected environment.
- Some owners will elect to keep FeLV-positive cats that are asymptomatic. Such cats are a threat to negative cats and thus should be kept indoors and isolated from negative cats. They may later develop feline leukemia virus-related disease.
- Subunit and killed virus vaccines are available and administered from nine weeks of age. They do not eliminate pre-existing infections. The vaccines don't interfere with tests for viral antigen.
- Evaluation with ELISA or IFA is recommended prior to vaccination.

Feline Sarcoma Virus

Feline leukemia viruses often undergo recombination with host cell genes resulting in replication-defective recombinant sarcoma viruses (FeSV). They are unable to replicate without the aid of wild-type FeLV. In each of these recombinant viruses one of seven oncogenes has been transduced by FeLV. For example, the Gardner-Arsstein-GA-FeSV has the (*c-fas*) oncogene. More than ten different feline sarcoma viruses have been identified.

Feline sarcoma viruses have been isolated from rare multicentric fibrosarcomas in younger cats. FeSV is confined to the tumor and there is no evidence of cat-to-cat transmission of these viruses.

Definitive diagnosis depends on extensive laboratory procedures.

Avian Reticuloendotheliosis

This term comprises several disease syndromes. The causes are reticuloendotheliosis (RE) viruses (Gammaretrovirus) mainly comprising three closely related serologic subtypes that are distinctly different from the leukosis/sarcoma group of retroviruses.

These viruses are widespread and may cause various serious neoplasia in chickens and turkeys, and also in ducks, geese, pheasants and Japanese quail. Some outbreaks have been attributed to vaccines contaminated with reticuloendotheliosis virus.

Virus spread occurs through contact and via the egg. Infections are frequently subclinical. Viral antigen in serum can be detected with an agar gel precipitin test. ELISA (commercially available) and other serological procedures are used to detect antibody. The viruses can be cultivated in a variety of avian cells but often replicate without discernible cytopathic effect.

Given the nature of disease control measures are not feasible.

Deltaretrovirus

Bovine Leukosis

(Bovine leukemia, enzootic bovine leukosis)

Cause

Bovine leukemia virus (BLV). Only one antigenic type has been found. Only a small percentage of animals infected with BLV develop B cell lymphosarcoma. Most infected animals develop a persistent lymphocytosis without any apparent clinical features.

The virus produces syncytia in cell cultures and immune serum prevents syncytia formation. This is used as an assay for

virus or antibody.

Occurrence

The bovine leukemia virus (BLV) is distributed worldwide and occurs particularly frequently in dairy cattle. Most infections are unapparent and as many as 80% of a dairy herd may be infected. The disease has been eradicated from some countries; others are in process of eradication.

Transmission

Cattle are infected by direct contact with blood from an infected animal during blood sampling, clinical examinations, castration and dehorning. Mechanical transmission by biting insects may play a role, particularly in tropical regions. Approximately 10 to 15% of calves born to infected cows are infected.

Pathogenesis

B lymphocytes are the primary target cells and there follows an unapparent infection or a B-cell lymphoma. The virus does not contain an oncogene. Instead two regulatory gene proteins, Tax and Rex, are key in the progression of neoplasia. In particular, the Tax protein associates with host cell transcription factors leading to the transcription of the BLV provirus. Most infected animals are asymptomatic; around 30% develop a persistent lymphocytosis and less than 2% eventually develop lymphosarcoma.

Clinical and Pathologic Features

Although non-immune cattle of all breeds can be infected at any age with bovine leukemia virus (BLV), most infections occur in dairy cattle more than two years of age. The fact that disease is seldom seen in younger animals is related to the presence of protective maternal antibody (for 5 - 6 months) and the separation of younger animals from the remaining herd until they reach sexual maturity.

Most animals infected with BLV remain clinically normal. Those that develop disease (approximately 2%) ultimately die after a long (weeks to months) clinical course. Initial clinical signs are often those of weight loss and reduced milk production, but may be quite varied depending on the site of tumor development.

The disease is a B-cell lymphoma. The organs most commonly affected are the lymph nodes, heart, abomasum, uterus, and spleen. When the superficial lymph nodes are involved they may be swollen and appear as lumps under the skin usually in the neck and rear flank region.

Diagnosis

- Clinical specimens: Affected tissues (formalin-fixed) and serum.
- Presumptive diagnosis of BL is often based on the finding of tumors in the locations mentioned above upon clinical and gross necropsy examination. Microscopic examination of affected tissues is required to confirm the disease. It must be kept in mind that there are sporadic forms of non-viral bovine leukosis (thymic, multicentric); they usually affect younger animals.
- Specific antibody may be detected in the serum of infected cattle by different serological tests including ELISA, radioimmunoassay and the agar gel immunodiffusion test (AGID). The latter is most commonly used for diagnosis and epidemiological studies. Many cattle have antibodies to BLV but most never develop disease.
- The virus can be isolated and cultivated in blood lymphocytes but this is not practicable for diagnosis.
- Although not practicable for diagnosis PCR can be used to detect virus in lymphocytes.
- Blood lymphocyte counts, which were once used in diagnosis, are no longer used as not all infected animals have a lymphocytosis.

Prevention

- Vaccines to prevent BL are not available.
- Eradication is accomplished by testing and removal of serologically positive animals and only admitting to the herd serologically negative cattle.
- Care must be taken to prevent spread of the virus during blood sampling, clinical examinations, castration, dehorning, etc. Insect control may be advisable in affected areas.
- In heavily infected herds eradication may not be feasible. Negative animals should be separated from the serologically positive and efforts directed to preventing spread. By taking adequate precautions it is possible to maintain herds with a few seropositive animals, without spread to other animals.

Lentivirus

Maedi/Visna

(Ovine progressive pneumonia)

Cause

Maedi/visna (MV) virus, a species in the genus *Lentivirus* ovine/caprine lentivirus group. The virus has a dense core and the RNA genome is related to that of the virus of caprine arthritis encephalitis. There are homologies of 60% in the *env* gene

and about 75% in the *gag* and *pol* genes. Antigenic changes take place that are thought to be due to selection of strains expressing alternative antigens.

Occurrence

The disease occurs widely in sheep throughout the world with the exception of Australia, New Zealand, and Iceland from which it was eradicated.

Transmission

The virus of MV is shed in nasal secretions and in the milk of infected ewes.

Pathogenesis

The incubation period varies from several months to years. Following initial infection, most animals are viremic. This allows for the development of an immune response, both humoral and CMI. However, this is insufficient for elimination of the infection and facilitates the development of characteristic immunopathology.

Infection results in a chronic, progressive inflammation, which is characterized by the presence of macrophages and lymphoproliferation mainly in the lungs and mammary glands. Lesions also occur in synovial membranes and the brain. These lesions are the result of immunopathology in response to the presence of persistent viral antigens.

Activation of latent provirus occurs in monocytes, triggered by monocytes maturation into macrophages in response to inflammatory signals. Therefore, infected monocytes are a source of persistent antigen – only expressing viral antigen whenever they mature into macrophages.

In addition to the persistence associated with latent virus-infected monocytes, the replication of ssRNA for progeny genomes is error-prone. As a result, many variants of the virus exist within an individual. The immune system then needs to respond to the various viral variants, as this takes time the variants become a source of persistent antigen.

Clinical and Pathologic Features

Maedi/Visna is a slowly progressive, eventually fatal disease in a small percentage of adult sheep. It is manifested in two different forms, the respiratory syndrome (with arthritis and mastitis) and the infrequent nervous syndrome. The Icelandic words "maedi" and "visna" mean dyspnea and wasting, respectively.

Although sheep remain infected for life, few develop clinical disease. In those that do, there is a protracted incubation period of a year or longer. The various disease manifestations, which progress over a period of months, are most often seen in sheep more than two years of age.

The pulmonary form is characterized by a slow and progressive weight loss and dyspnea upon exertion.

Sheep with the CNS demyelinating form develop ataxia of the hind quarters and ultimately paralysis.

Chronic active inflammation is noted histologically in affected tissues. Lung lesions are those of interstitial pneumonitis and lymphoid hyperplasia. Leukoencephalomyelitis with focal demyelination and lymphocytic perivascular cuffing are observed in the brain. Affected mammary glands are fibrotic with lymphocytic infiltrates, and affected joints are characterized by proliferative changes in the synovial membrane.

Diagnosis

- Clinical specimens: Serum and live clinically ill sheep.
- Diagnosis is usually based on clinical signs and histopathologic lesions with supporting serologic evidence of exposure as determined by the agar gel immunodiffusion (AGID) test, ELISA or Western blotting.
- The virus of MV is closely related antigenically to the virus of caprine arthritis encephalitis and the current AGID test kits will detect antibodies to both viruses.
- Virus isolation is not practicable for routine diagnosis.

Prevention

- No vaccines are currently available.
- Prevention is best accomplished by maintaining closed serologically negative flocks. All replacement stock should be serologically negative.
- Control of MV within a flock requires periodic serologic testing and subsequent removal of seropositive animals. Lambs should not be allowed to suckle seropositive ewes.

Caprine Arthritis Encephalitis

(Leukoencephalomyelitis of goats, caprine encephalomyelitis)

Cause

Caprine arthritis encephalitis virus; a non-oncogenic retrovirus of the genus Lentivirus. As mentioned earlier, this virus is closely related antigenically to the virus causing Maedi/Visna.

Occurrence

Caprine arthritis-encephalitis (CAE) virus is widely distributed in goats of all ages and breeds throughout the world. The

disease is seen most frequently in dairy goats.

Transmission

Young kids are most commonly infected through the ingestion of milk from infected does. Horizontal transmission is thought to occur by direct contact with secretions and excretions from infected goats and through coitus.

Pathogenesis

The pathogenesis of the disease is similar to Maedi/Visna. It is characterized by chronic persistent inflammation, which is not resolved in spite of a vigorous CMI response to viral antigen. Infected monocytes are a source of persistent antigen and a large number of viral variants generated during viral replication; this combination contributes to the inability of the host to resolve the infection. Immunopathologic mechanisms are thought to be responsible for the development of most lesions.

Clinical and Pathologic Features

The development of the disease is similar to Maedi/Visna. Virus replicates in macrophages and CMI responses contribute to the lesions. Chronic connective tissue disease affects the joints of mature goats; a leukoencephalomyelitis is seen in young goats and less commonly there is mastitis or pneumonia in older goats.

The arthritic form is characterized by a proliferative synovitis of the carpal, fetlock, hock, and stifle joints. Joints are enlarged, especially the carpal joints, and common histological lesions are those of synovial cell proliferation and inflammatory cell infiltration (lymphocytes, plasma cells, and macrophages). The arthritis may remain static or become progressively worse with development of fibrinous concretion, necrosis, and mineralization.

Central nervous system (CNS) disease is principally seen in young kids 2 - 4 months of age and is characterized by a progressive ascending paralysis. Microscopically, the CNS lesions resemble those of Visna in sheep and include lymphocytic cell infiltration and demyelination of the white matter.

Some infected goats may develop an interstitial pneumonitis and some infected does may develop swollen, fibrotic mammary glands.

Diagnosis

- Clinical specimens: Serum and affected sheep.
- Diagnosis of CAE associated disease is usually made on the basis of clinical signs and serologic evidence of exposure. The serologic tests most often used are the agar gel immunodiffusion procedure and ELISA.
- The virus can be propagated in caprine cell cultures derived from synovial membranes, but isolation is time consuming and rarely attempted. The virus induces syncytia in cultured cells although it may take weeks for them to become observable.

Prevention

- Goats infected with CAB virus remain infected for life.
- Prevention is best accomplished by maintaining closed herds.
- All replacement animals should be isolated and tested serologically (ELISA or AGID).
- Control of CAE in herds in which the virus is enzootic is difficult. If economically feasible, test and removal is the preferred method. Alternatively, serologically positive animals should be segregated from negative animals. Young kids should be removed from positive does at birth.
- Milk from infected does should not be fed unless it has been pasteurized.

Equine Infectious Anemia

(Swamp fever)

Cause

Equine infectious anemia virus (EIAV). Strains have a common CF antigen but can be differentiated by virus neutralization. EIAV is capable of infecting all members of equidae, including horses, mules and donkeys. It was also the first retrovirus observed to be transmitted mechanically by insects (tabanids). Infected animals remain infected for life.

Occurrence

Equine infectious anemia (EIA) is a disease of Equidae that occurs frequently in many countries. It is particularly prevalent in low-lying swampy regions. Incidence of the disease has been greatly reduced in some countries as a result of control measures.

Transmission

This occurs mechanically when blood from an infected horse is introduced into a susceptible horse via hematophagous insects (tabanids), hypodermic needles, and surgical instruments. The virus may be present in milk, saliva, semen and urine and thus direct and indirect transmission is thought to be possible.

Pathogenesis

EIA virus infects monocytes/macrophages and Kupffer cells, whereby the integrated provirus can be transported

throughout the body. In spite of a vigorous immune response to viral antigen, the virus persists as provirus within infected cells.

As with other retroviruses, many variants of the virus are produced due to the error-prone replication process. In the case of EIA, release of these variants can be traced to intermittent febrile periods.

The humoral response to the presence of the viral antigen stimulates the production of non-neutralizing antibodies. These antibodies bind viral antigen, resulting in the formation of immune complexes. Once formed, the immune complexes trigger the classical complement cascade (see Chapter 4), which in turn leads to fever production, anemia, thrombocytopenia, and glomerulonephritis.

The anemia is the result of the combined effects of hemolysis, phagocytosis of erythrocytes, and a decrease in the production of the blood cells of the erythropoietic lineage.

Clinical and Pathologic Features

The incubation period following exposure to EIA virus is generally 2 - 6 weeks. The resulting disease may be acute or chronic.

The acute form is characterized by sudden onset of fever, depression, anorexia, thirst, progressive weakness, petechial hemorrhages, ventral edema, and death in 2 - 4 weeks.

The chronic form of EIA is the most common. Affected horses are intermittently febrile and anemic. They experience weight loss and often have edema of the limbs and abdomen. Some affected horses may exhibit ataxia, and on rare occasions ataxia may be the only clinical sign. Remissions are common and may last for years with the animal appearing essentially normal. Viremia may be present for years and even during remissions, however, the disease is usually fatal.

Diagnosis

- Clinical specimens: Serum, cerebrospinal fluid from ataxic horses.
- Since EIA infection is persistent, the demonstration of specific antibody (to the core virus protein p26) is routinely used for diagnosis. This is accomplished most reliably by the agar gel immunodiffusion test (AGID) usually referred to as the Coggins test.
- A competitive ELISA is also used but results should be confirmed with the Coggins test.
- The virus can be isolated and cultivated in equine leukocyte culture; there is no noticeable CPE.
- Proviral DNA can be detected by PCR. Additionally, viral RNA can be detected by reverse transcriptase (RT)-PCR. In RT-PCR, the RNA template is copied into cDNA by the enzyme reverse transcriptase (isolated from a retroviral source), using primers specific to the genome of the virus.

Prevention

- Vaccines are not currently available.
- All horses on the premises should be serologically tested. Positive horse should be destroyed or confined to vector proof quarters, or segregated from other horses at pasture by at least 200 yards to prevent mechanical spread by biting insects.
- Many countries and states will only allow entrance of sero-negative animals.

Feline Immunodeficiency Virus Infection

Cause

Feline immunodeficiency virus. Five subtypes of FIV have been identified based on differences in the envelope amino acid sequences.

Occurrence

Feline immunodeficiency virus (FIV) occurs frequently in cats throughout the world. Similar viruses have been recovered from wild and zoo felids. Male free-roaming cats have the highest incidence of infection.

Transmission

This is mainly by bites.

Pathogenesis

The pathogenesis of FIV infection is similar to that observed with HIV, and thus FIV infection is sometimes referred to as feline AIDS. FIV replicates primarily in CD4⁺ (helper) T lymphocytes, but also in macrophages, astrocytes, and microglial cells.

Once infected, a chronic viremia ensues that peaks at 7 - 8 weeks then declines. However, viremia increases in the terminal stages of the illness.

The humoral response is normal. However, there is progressive decrease in the function of the CMI due to decreases in CD4⁺ cells. As a result of the CD4⁺ decrease, an increase in the numbers of opportunistic infections associated with clinical immunodeficiency is observed.

There is also an increase in the number of variants, due to error-prone replication.

Clinical and Pathologic Features

The disease is seen in three stages, as follows:

- *Acute stage*: Clinical signs appear 1 - 2 months following infection and consist of depression, fever, and a generalized lymphadenopathy.
- *Subclinical stage*: Signs of illness disappear after a few weeks or months but cats remain viremic for life. A period of relative normalcy may last for several months to years.
- *Chronic stage*: Infected cats eventually succumb to various chronic opportunistic infections because of an impaired immune system. Chronic infections may result in stomatitis, gingivitis, rhinitis, conjunctivitis, pneumonitis, enteritis, and dermatitis. There may be clinical signs of neurologic dysfunction and concurrent FeLV infection may aggravate the disease and result in neoplasia.

Diagnosis

- Clinical specimen: serum.
- Since cats infected with FIV remain infected for life. The detection of antibody to FIV is considered to be the most reliable and convenient means of diagnosis. Antibody may be detected by an immunofluorescence assay or by an ELISA. ELISA test kits are available commercially and are considered to be highly sensitive and specific.

Treatment

- Supportive care and antimicrobials for secondary infections.
- Vaccination for diseases other than rabies is not recommended.
- Reverse transcriptase inhibitors like those used in the treatment of HIV, e.g., azothiouridine, are claimed to reduce the severity of the disease. Interferon- α has also been used.

Prevention

- A killed vaccine prepared from two isolates of FIV is commercially available in the USA. Cats receiving the vaccine become serologically positive. Efficacy of the vaccine is under current evaluation.
- Prevention is best accomplished by keeping cats indoors. Avoid contact with feral and free-roaming cats.
- Only admit serologically negative cats to the household.

Bovine Immunodeficiency Virus Infection

Cause

Bovine immunodeficiency virus. The first isolation of bovine immunodeficiency virus (BIV) was in 1972 from a dairy cow with persistent lymphocytosis in Louisiana.

Morphologically, the virus resembles the human immunodeficiency virus-1.

Additional isolations indicate that the virus is widespread in cattle; however, its pathogenicity has not yet been demonstrated unequivocally, although there is some evidence that it may be involved in predisposing cattle to other infections/diseases. Experimentally infected cattle have exhibited lymphoid proliferation and decreased cell-mediated cytotoxicity.

Jembrana Disease

The virus of this disease (Jembrana disease virus) resembles the bovine immunodeficiency virus. The disease, which has only been reported as affecting Balinese cattle (Bali, Indonesia), is characterized by a short course with fever, enlarged lymph nodes and sometimes death. Cattle (*Bos javanicus*) that recover are viremic and thus carriers.

Glossary

Oncogene: A gene that encodes a protein whose expression leads to cell transformation and malignancy (changes in the cell including loss of contact inhibition, which leads to neoplastic potential).

Transduction: Transfer of host DNA genetic material from one cell to another by a virus such as a retrovirus or a bacteriophage. A specialized form of transduction is the introduction of oncogenes into cells by retroviruses.

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