CEVA HANDBOOK
OF POULTRY DISEASES

3 REOVIROSIS

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DEFINITION

Reovirus infections are associated with signs of arthritis/tenosynovitis, immunosuppressive states, losses from poor performance in broiler chickens and broiler breeders and some disease symptoms in other fowl species (turkeys, ducks, geese, wild ducks).

HISTORY

In 1957, a research team from West Virginia University, USA, reported the isolation of a pathogenic agent from synovitis lesions in broilers, resistant to furazolidone and oxytetracycline (Olson et al., 1957). Subsequently, the authors reported that the newly discovered agent caused synovitis only in young chicks, whereas such a resistance was unusual for MS. Further research by the same group, led by Dr Olsen, discovered that the synovitis-causing agent was a virus, which they named «viral arthritis agent». Although initially wrongly classified as a poxvirus, subsequent electron microscopic studies have identified it as a reovirus (Walker et al., 1972).

Histological investigations in experimentally-infected chickens have revealed typical tenosynovitis lesions, thus providing convincing evidence that the reovirus is capable of provoking arthritis/tenosynovitis (Olson & Weiss, 1972). The avian reovirus has not caused only viral arthritis/tenosynovitis, but it was repeatedly discovered in association with enteritis in chickens and blue comb disease in turkeys. Experimentally, reoviruses were shown to induce myocarditis and hepatitis in chickens (Van der Heide L., 2000). In the 1970s, so-called «malabsorption syndrome» was reported in broilers, attributed initially to reovirus infection as such an agent was isolated from chickens with clinical signs of the disease (Van der Heide & Horzinek, 1981). But the attempts to reproduce the syndrome with a reovirus were not always successful, and other viruses (enterovirus, parvovirus, calicivirus) and even bacteria were also isolated. It should be noted that reovirus isolates 1733 and 2408 were capable of independently inducing malabsorption syndrome.

At present, these strains are included in some commercial inactivated vaccines.

The vaccination of broiler flocks against reovirus in field conditions improved production, but did not result in complete elimination of malabsorption syndrome symptoms, suggesting that other etiological factors were at work (Van der Heide L., 2000).

CHARACTERISTICS AND CLASSIFICATION OF THE PATHOGEN

The family *Reoviridae* is named after the first three letters of the diseases they cause (Respiratory – Enteric – Orphan). The avian reovirus belongs to the genus Orthoreovirus, and differs from mammalian isolates in that it has no haemagglutination capacity (Glass et al., 1973), and is able to induce cell fusion (Wilcox & Compans, 1982) and natural disease in birds. Furthermore, avian and mammalian viruses do not cross-react in virus neutralisation tests (Spandidos and Graham, 1976).

Viral particles are non-enveloped, with icosahedral symmetry, double stranded RNA (dsRNA), 70–80 nm in size. The genome can bedivided into 3 size classes: L (large), M (medium) or S (small). Class L contains 3 segments (L1, L2 and L3), class M – also 3 segments (M1, M2 and M3) and class S – four segments (S1, S2, S3, S4), (Spandidos and Graham, 1976). The protein coding abilities of all ten genome segments of the S1133 strain have been determined (Varela & Benavente, 1994). Together with mammalian reoviruses, the patterns of electro-phoretic migration of genome segments in some avian reovirus isolates exhibit substantial polymorphism.

The avian reovirus genome expresses at least 12 translation products, 8 of them structural proteins incorporated in progeny virions. The other 4 proteins are non-structural and are expressed in infected cells, but not in mature reoviruses (Martinez-Costas et al., 1997; Varela and Benavente, 1994). Proteins coded by class L genes are designated as lambda (λ), by class M – mu (μ) and by class S – sigma (σ). The structural proteins of each class are labelled in alphabetical order (λA, λB, etc.) according to their electrophoretic mobility, in order to distinguish them from the numeric sequence of respective proteins of mammalian reovirus (λ1, λ2, etc.). The avian reovirion contains at least 10 different structural proteins, 8 of which (λA, λB, λC, μA, μB, σA, σB and σC) being primary translation products of respective coding mRNAs, and the other two (μBN and μBC) originating from post-translational cleavage of precursors (Varela et al., 1996). The M3 and S4 genes express two primary non-structural proteins (μNS and σNS, respectively) which are easily detected in the cytoplasm of infected cells. Furthermore, two

other non-structural proteins coded by the avian reovirus S1 gene – p10 and p17 – have been identified (Benavente & Martynez-Costas, 2007).

Reovirus strains have been differentiated by cross neutralisation tests in cell culture (Kawamura & Tsubahara, 1966). The American S1133 isolate is found in many commercial vaccines in widespread use worldwide, despite the existence of numerous regional variants. The differentiation of strains is currently performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) (Jones, 2000).

In 1998, a new highly-pathogenic strain as identified in Poland and other European countries, causing high mortality and production losses, even though the parent flocks were vaccinated (Van Loon et al., 2001). The etiological agent responsible was isolated and identified as ERS-1 (Enteric Reovirus Strain). ERS-1 caused 100 % mortality after oral inoculation to one-day- old SPF chickens, 53% after application in 3-week-old birds and 12% – in 9-week-old birds. These results corresponded to other findings indicating increased host resistance to reovirus infection with age.

Avian reoviruses are stable between pH 3 and pH 9. At 56°C, they are inactivated for less than one hour. A survey on the endurance of avian reoviruses on common materials has demonstrated that the virus can survive more than 10 days in feathers, wood shavings, glass, rubber, galvanised metal and 4–10 weeks in water with limited infectivity. A number of avian reoviruses are sensitive to some enzymes such as trypsin etc. (Jones, 2000).

Avian reoviruses are relatively resistant to some disinfectants. Some of the strains survive treatment with 2% formaldehyde at 4°C (Meulemanns & Halen, 1982), while others are only partially inactivated by 2% phenol after 24 h at room temperature. A complete inactivation occurs with 100% phenol (Petek et al, 1967).

Viruses can be cultured in embryonated chick eggs, where 6-day incubation into the yolk sac causes death accompanied by haemorrhages in embryos and appearance of yellow-greenish foci in the liver (McNulty, 1993). Chick embryos and chick cell cultures (fibroblasts, lung, liver and kidney of chick embryo, and chick kidney cells) are sensitive to reoviruses. Among them, the most sensitive for primary isolation are embryonic chick liver cells. The production of syncytia is a typical cytopathic effect of avian reoviruses (Jones, 2000).

The cycle of avian reoviral replication occurs in several consecutive stages in the cytoplasm. During the first stage, adsorption and penetration begin with extracellular attachment and entry into the cells via receptor-mediated endocytosis and acidification of virus-containing endosomes, needed to release the transcription active core into the cytosol. In members of the *Orthoreovirus* genus this occurs via the surface protein σ1. The formed endosome fuses with lysosomes, and some of the proteins are hydrolysed. A subviral particle is formed, which is released by lysosomes into the cytoplasm. After activation of transcriptase, the transcription stage is initiated (Zarkov, 2003).

The fact that avian reoviruses are able to attach and replicate not only in avian, but also in mammalian cells implies that the avian reovirus receptor is a ubiquitous cell surface protein (Robertson and Wilcox, 1986). On the other hand, the observation that mammalian reoviruses are not attached to avian embryo fibroblasts shows that avian and mammalian reoviruses attach to different cell-surface receptors (Barton et al., 2001).

The next stage is the transcription of the subvirus particles onto RNA fragments. This is performed only on the (-) strand of the two-stranded (±) RNA, each fragment being independently transcribed. Synthesized iRNA leave subviral particles from lysed surface proteins. Translation is the next stage. Synthesized early iRNA carry the information for synthesis of core and capsid proteins. All iRNA are responsible for synthesis of structural and non-structural virus-specific proteins.

RNA replication occurs in the subsequent stage via synthesis of two-stranded (±) RNA in the subvirus particle. Single-stranded (+) RNA serves as the template for synthesis of (-) RNA, the complementary chain of daughter (±) RNA.

Next follows the formation of virions and their release from the cell. Newly formed subvirus particles are an intermediate stage of virion formation. The final stage consists in binding of the polypeptide from the virion surface with the endoplasmic reticulum. The process takes anywhere from 15 to 52 hours. The virions leave the cell either solely or in aggregates (Zarkov, 2003).

The interaction between the virus and the cells results in apoptosis. Similarly to many other viruses, the avian reovirus infection elicits intracellular apoptosis, manifested through DNA fragmentation in the cytoplasm. Avian-reovirus induced apoptosis occurs in the early stage of virus replication

(Labrada et al., 2002). Proteolytic and conformational changes are resulting from reovirus apoptosis. A recombinant avian reovirus protein σC is reported to activate apoptosis, suggesting that apoptosis in infected cells is triggered by various mechanisms of viral gene expression (Benavente & Martynez-Costas, 2007).

Avian reoviruses are among the few enveloped viruses capable of inducing cell–cell fusion (Duncan et al., 2004). Unlike enveloped fusogenic viruses, avian reoviruses induce the formation of syncytia on the inner side of the infected cell, so it could be hypothesized that fusion triggers the synthesis of new viral products, and thus that it is not a part of virus penetration. The formation of syncytium in infected cells by avian reoviruses is obviously regulated by non-efficient synthesis and rapid degradation of p10 protein. The cell-cell transmission of the virus is followed by apoptosis-mediated destruction of the syncytium, causing enhanced release of the virus and extensive spread of infection (Salsman et al., 2005).

It is generally acknowledged that virus-induced syncytium formation contributes to the cytopathic effect. Apoptosis is established in tissues with extensive syncytium after infection with avian reovirus, suggesting a correlation between virus replication and apoptosis. A direct correlation between cytopathogenesis and apoptosis has been demonstrated in vivo (Finkel et al., 1995; Shen & Shenk, 1995).

Tissues in avian reovirus-induced tenosynovitis and myocarditis infections have also been shown to exhibit apoptosis. The mechanism leading to arthritis is not completely understood. During in vivo apoptosis, apoptotic bodies are phagocytised by adjacent cells, leading to intracellularbreakdown without provoking inflammation. There are, however, examples of tissue damage caused by viral infection where apoptosis and necrosis are both present, and where there is no clear distinction between the contribution of each to cell death (Lin et al., 2007).

Penetration through the cell membrane may occur in the early or late infection stage, after virus gene expression has started. Early membrane permeability causes reversible structural and functional changes of membranes followed by passages of small and large molecules together with viral particles. Late damage is related to enhanced permeability of ions and small molecules but not of macro molecules (Gonzalez and Carrasco, 2003).

EPIDEMIOLOGY

Avian reoviruses are omnipresent in poultry farming regions, although the infections they cause are mostly asymptomatic.

The susceptibility of birds to reovirus infections is largely dependent on their age. As they develop, birds become more resistant to infection and lesion development. It has been established that experimentally-infected one-day-old chicks are more sensitive to tenosynovitis compared to 2-week-old exposed birds. Articular lesions in one-day-old infected chicks are significantly more severe compared to those seen in older birds. The reovirus pathology is mainly associated with joint lesions, but may be enhanced by the involvement of other infectious agents such as Mycoplasma synoviae or Staphylococcus aureus. Although the disease is mainly prevalent among meat-type birds, arthritis has also been reported in egg-laying chickens (Schwartz et al., 1976). Evidence of the higher susceptibility to reovirus arthritis of broiler chickens compared to White Leghorns was provided by Jones et al. (1984).

The persistence of avian reoviruses in tissues of infected chickens is long-term. Reovirus has been isolated from the spleen of a chicken 285 days after infection, as well as from an arthritic joint 13 weeks after experimental infection. It is believed that the virus within the joint could be reactivated at the point of sexual maturity or other biological triggering events. This might explain the occasional reisolation of the virus from the joints of broiler breeders, given that adult birds are normally infection-resistant (Jones, 2000).

Most birds are apparently infected via the faecal-oral route, although evidence of respiratory infection or transmission through the eggs has been found. Egg-based transmission was confirmed after experimental infection, but it is unlikely in natural conditions (Al-Mufarrej et al., 1996). It is believed that newly-hatched infected chickens could spread the infection to other chicks in the hatchery via the faecal-oral route. Another possible entrance door for reoviruses is the damaged skin of the foot pad (Al-Afaleq & Jones, 1990). Reoviruses can persist in infected birds for more than 40 weeks.

Economic losses related to reovirus infections often result from increased mortality, high slaughterhouse culling rates and poor production traits including weight loss and high feed conversion ratios.

CLINICAL SIGNS AND PATHOLOGY

Avian reoviruses are associated with a variety of disease states in chickens, including respiratory diseases, enteritis, hepatitis, myocarditis and the so-called stunting/malabsorption syndrome, although a direct virus-disease relationship was convincingly shown only in the viral arthritis/ tenosynovitis syndrome, characterised by swelling of the tibiotarsal joints and lesions of the gastrocnemius tendons (Benavente & Martynez-Costas, 2007).

Arthritis/tenosynovitis.

The typical reoviral arthritis/tenosynovitis is clinically manifested with lameness and swelling of the tibiotarsal joints in particular and, less frequently, of the tarsometatarsal joints. In the early stage, this joint swelling is mild and the necropsy reveals affected synovial membranes and adjacent tissues, with increased amounts of transparent fluid within the joint capsule which may be opaque in case of secondary infection with mycoplasmae or bacteria. As the disease progresses, petechiae with small erosions on the articular cartilage are detected. The adhesions between tendons and fibrous tissue ingrowth may provoke swelling of the drumstick and impaired locomotion.

Fig.1

Arthritis/tenosynovitis. Clinically manifested by lameness and swellings primarily affecting the tarsometatarsal joints and feet.

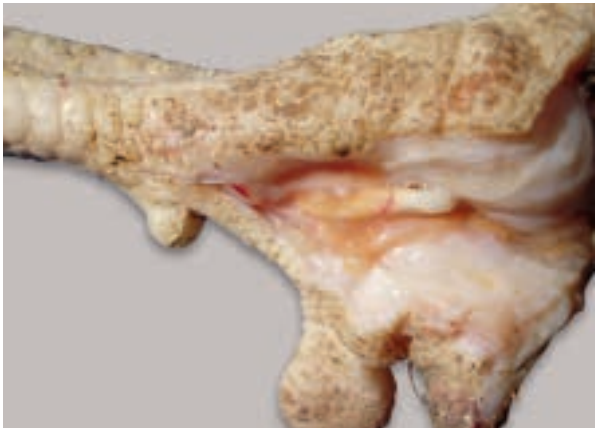

Fig.2

In some cases, joint cavities or tendon sheaths contain a small amount of straw-yellow exudate whereas in other – the exudate is haemorrhagic or fibrinous.

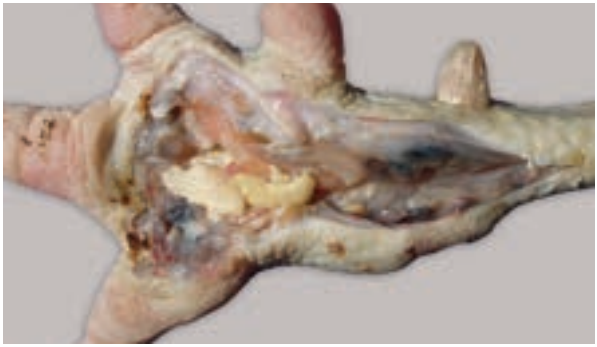

Fig.3

Fibrinous tenosynovitis. The inflammation of the tendon progresses to a Chronic-type lesion characterised by tissue fibrosis in the affected area.

Malabsorption syndrome (MAS) or runting-stunting syndrome is a major and highly prevalent problem in the broiler chicken industry. Birds are usually susceptible to MAS during the first two weeks after hatching. It is mainly characterised by gastrointestinal lesions, which result in weight loss and depression. Gastrointestinal lesions include proventriculitis and enteritis with cell infiltration, villous and cystic crypt atrophy. It is suggested that the reovirus is a primary agent of early intestinal lesion development in MAS (Songserm et al., 2003). Having experimentally reproduced infection with field avian reovirus strains in broiler and white leghorn chickens, the authors established vacuolar degeneration and enterocyte desquamation in the small intestine, more pronounced in broilers.

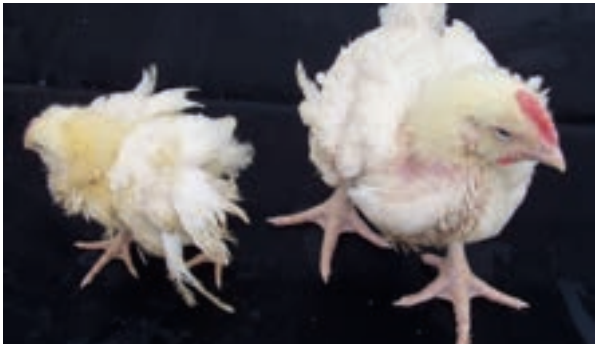

Fig.4

Malabsorption syndrome in broiler chickens. Results in considerably reduced live weight in affected birds and a various degree of heterogeneity in the flock, varying from 5-10% to 40-50%, usually seen after the age of 14 days.

Fig.5

MAS, broiler chicken. The growing primary wing feathers are abnormally big for chickens with retarded growth, they protrude at various angles, so the disease is termed "helicopter disease".

Fig.6

MAS, broiler chicken. Usually, a high-degree of atrophy of the pancreas is observed.

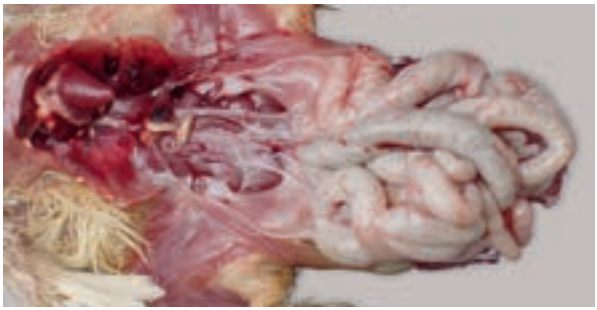

Fig.7

MAS, broiler chicken. The small intestine is pale, dilated, often intertwined as a ball in the caudal part of the pleuroperitoneal cavity.

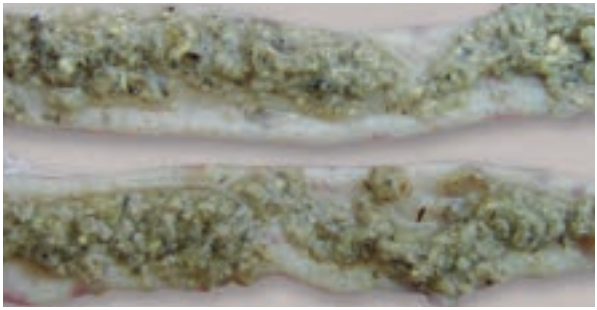

Fig.8

MAS, broiler chicken. The intestinal content is indigested feed.

Reoviruses and adenoviruses have been isolated in broiler chickens with alimentary disorders. Distinguishing features were the gizzard findings in adenoviral infections (erosions and basophilic intranuclear inclusions), (Lenz et al., 1998).

The ERS-1 strain provokes a high death rate in affected chickens and induces lesions as well as a congested and enlarged spleen, liver and thymus, pericarditis and whitish foci (liver necroses). ERS infection has been detected in 21 broiler flocks, and in 10 out of them, a bacterial co-infection with E.coli and/or O.rhinotracheale was also present. Macroscopically, in ERS infected flocks with concurrent bacterial infection, polyserosites were observed. Chickens from ERS-positive flocks without co-infection, exhibited an enlarged liver with petechiae, pale and small-sized pancreas, hydropericardium, watery content of the proventriculus, small intestine and caeca. Also, unilateral swelling of the gastrocnemius tendon was observed in 3 of the affected farms, whereas femoral head necrosis occurred in 7 farms (De Herdt et al., 2008).

DIAGNOSIS

Tentative diagnosis is easy, based on clinical signs and lesions. To prove the reovirusetiology in infected birds, some diagnostic tests were developed. In cell cultures, cytopathic effects may be observed 72 h after the challenge infection. The serum neutralisation (SN) test is a routine serological technique for detection of antibodies, but it requires a live virus and cell culture (Giambrone & Solano, 1988).

ELISA is also suitable for detection of reovirus in multiple samples. ELISA results are closely correlated to SN test results. The monoclonal capture ELISA test is a variant of the assay (Pai et al., 2003; Chen et al., 2004). This technique is more sensitive than the conventional ELISA due to its capability to detect viral RNA. The expressed σproteins (σB and σC) are used as surface antigens to induce neutralisation of anti-reovirus antibodies. The main component of the outer capsid is the σB protein, while σC is attached to the cell, i.e. an apparent specificity exists (Macalintal, 2004).

Molecular techniques such as in situ hybridization (ISH) and reverse transcriptase in situ polymerase chain reaction (RT -in situ-PCR) have also been developed. RT -in situ-PCR is faster and more sensitive than ISH for the purposes of avian reovirus detection (Liu et al., 1999).

DIFFERENTIAL DIAGNOSIS

Viral arthritis should be differentiated from *M. synoviae-induced*, staphylococcal arthritic conditions and the spontaneous rupture of the tendon of the gastrocnemius muscle. According to some researchers, the histological lesions induced by the reovirus consist in diffuse lymphocytic inflammation, while those caused by staphylococci appear as a focal purulent synovitis (Hill et al, 1989).

With regard to MAS, other etiological factors may also play a role in etiogenesis. The pathology caused by ERS-1 strain is of asepticaemic nature, and a bacterial co-infection is often involved.

PREVENTION AND CONTROL

Although avian reoviruses are ubiquitous, their presence does not necessarily indicate infection. An infectious condition is present when the host responds to pathogen-induced alterations. To prevent reovirus infection, poultry producers should implement strict biosecurity measures, beginning with cleansing, washing and disinfection of houses after each production cycle. Bearing in mind that the avian reovirus can survive at least 10 days in feathers, eggshells and wood shavings, such materials should be removed from chicken houses (and indeed the farm) prior to cleansing and disinfection.

Vaccination is among the most important disease prevention tools. Live and inactivated vaccines have been developed and are in widespread use (Van der Heide, et al., 1983). The aim is to ensure the direct immunity of the flock via active immunisation of breeders at a young age, which would pass antibodies to the progeny via breeder eggs. The passive immunity obtained through maternal vaccination facilitates the transfer mainly of immunoglobulin G (IgG) antibodies through the eggs. From maternal blood, IgGs are transferred to yolk mass and may pass into the embryonic circulation through the embryonic yolk sac membrane. As such, the vaccination of breeders may block egg-transmitted disease, including that caused by reoviruses (Van Loon et al., 2001). Experimental reovirus challenge has been used to demonstrate that the vaccination of breeders against tenosynovitis results in immunity of the progeny of the experimental test when compared to a non-vaccinated group (Van der Heide et al., 1976).

During the last decade, the in ovo application of antibody-complex vaccine was investigated (Guo et al., 2003). This method offered at least 70% protection if applied on the 8th day of incubation and, apparently, did not affect hatchability.

Analysing breeder flock vaccination programmes, Giambrone (1986) concluded that the one-day-old progeny of a hyperimmunised flock which received 1 dose live and 2 doses inactivated reovirus vaccine provided the highest possible antibody titer and the best resistance to clinical infection after experimental challenge infection.

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