

Clinical and Pathological Perspectives of Jembrana Disease Virus Infection: A Review

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Jembrana disease virus (JDV) is a viral pathogen that causes Jembrana disease in Bali cattle (*Bos javanicus*). Jembrana disease poses the major concern in Bali cattle industry as it gives rise to significant economic detriment due to mortality of cattle. During the first outbreaks, mortality of approximately 60000 cattles in a year was observed due to JDV infection. The pathology of JDV is unusual for a lentivirus infection as it is associated with an clinically acute, often lethal disease syndrome, and a short incubation period in Bali cattle. Studies of Bali cattle experimentally infected with JDV have provided insights into haematological change, cytopathological response, and immune response in naturally occurring infection. The localization of JDV in various tissues or organs were also had been reported. This review discusses the progression of clinical symptoms and the pathological changes during the development of Jembrana disease.

Keywords: Jembrana disease; virus distribution;
Cytopathology; immunopathology, clinical progression.

Jembrana disease is a bovine disease that affects Bali cattle (*Bos javanicus*). In 1964, it was first identified as an acute and contagious disease in the Jembrana district of Bali island (Indonesia). In consequence, the ethiological agent is called Jembrana disease virus (JDV), a lentivirus member of the family Retroviridae¹. The pathology of JDV infection is unusual for a lentivirus infection as it

is associated with a severe, often lethal disease syndrome, and a short incubation period in Bali cattle. Fatal issues occur only one to two weeks post-infection. These characteristics of Jembrana disease are in contrast to the chronic and progressive diseases over a long incubation periods typically associated with lentiviral infections^{2,3}. For example, the human immunodeficiency virus type 1 (HIV-1) that causes immunodeficiency, may lead to death of infected patients several years after infection⁴.

The most genetically and antigenically closely related BIV, only induces a subclinical disease in experimentally infected taurine cattle (*Bos taurus*), with mild clinical and pathological

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changes. The clinical and pathological manifestations include a temporary lymphocytosis, and possibly a lymphadenopathy in relation with follicular hyperplasia⁵. The JDV pathological syndrome is nevertheless not unprecedented as the acute, severe nature of Jembrana disease, with no recurrence in recovered animals. It is shared by a lethal variant of simian immunodeficiency virus (SIV) which also induces an acute, severe disease syndrome in pig-tailed macaques^{6,7}.

Clinical Progression

It is hard to accurately establish the progression of clinical symptoms and the pathological changes during the development of Jembrana disease in naturally occurring infections. This can only be correctly achieved by performing experimental infections by using defined conditions and by controlling possible influencing factors. Infections were carried out by inoculation of Bali cattle with blood from a case of Jembrana disease^{8,9}. After a short incubation period of 5 to 12 days, affected animals showed various clinical signs, i.e. elevated rectal body temperature equal or more than 39.3°C and persisting for 7 days, lethargy, anorexia, enlargement of the superficial lymph nodes, a mild ocular and nasal discharge, diarrhoea with blood in the faeces and pallor in the mucus membrane^{8,9}. Not all these clinical symptoms are shared by all infected animals^{10,11}.

During the febrile phase, viruses are found in the plasma fraction of the blood and exhibiting a high titre of up to 10^8 ID₅₀/ml, equaling to 10^{10} to 10^{11} viral genome copies/ml of plasma^{8,12}. During the acute stage, viruses are also detected in secreted fluids, i.e. saliva, milk, and nasal discharge. Several studies showed that direct transmission happens in close contact with acutely infected animals to susceptible cattle^{10,13,14}. It occurs probably by virus contained in secreted fluids, by the conjunctival, intranasal and oral routes¹⁰. It has been suggested that, due to the high viral titre in the blood, the virus is possibly transmitted mechanically by haematophagous arthropods^{13,14}. This aspect has nevertheless been demonstrated.

In experimentally JDV-infected Bali cattle, the mortality rate was quite high, approximately 17%⁸. This is consistent with data obtained in several observational field studies^{11,14,15}. In fatal infections, death, occurring within only 1 to 2 weeks

post-infection, was attributed to multisystem dysfunction^{2,3}. In animals that survive, lesions regressed about 35 days post-infection and there is no recurrence of disease¹⁴. The recovered cattle are resistant to further development of clinical disease upon challenge^{10,16}. This suggests that most probably vaccination, using denatured or attenuated viral particles, can be performed to limit the disease spread.

During the first observed outbreaks of Jembrana disease, the clinical disease was not reported in other types of cattle and this led to belief that the disease is unique to Bali cattle.^[3,14] Experimental infections have however shown that JDV was able to infect other cattle types, including the most commonly farmed cattle, i.e. Friesian cattle (*Bos taurus*) and Ongole cattle (*Bos indicus*) and also buffaloes (*Bubalus bubalis*), pigs, sheep and goats.^[10] Except for sheep and goats, all these animals developed a mild febrile response but not other overt clinical signs of disease^{2,10}. The clinical symptoms would so be difficult to detect in field conditions.

Haematological Changes and Cytopathological Response

JDV infections caused a well defined pathological condition in experimentally infected Bali cattle.^[8,9,10,14,17] The disease was generalized, except for the central nervous system.^[9] The observed main haematological changes comprised normocytic normochronic anaemia, a mild thrombocytopenia, leucopenia, a slight neutropenia, eosinopenia lymphopenia, reduced total plasma protein, and an elevated blood urea concentrations⁸. These haematological changes suggest a systemic abnormal function of the haematopoietic system^{8,18}.

The cytopathological response was complex and occurred in progressive steps.^[9] In the first stage, a general lymphoreticular reactions occurs in lymphoid organs. Study showed that it was characterized by the main process of intense non-follicular proliferative response by lymphoblastoid cells and reticulum cells (dendritic cells). It was hypothesized that a major role of T lymphocytic reaction occurs during the proliferative changes in lymphoid system in the acute stage. In the second stage, it took place and spread in liver, kidney, adrenal medulla, pulmonary organ and elsewhere. In kidney,

glomerular hypercellular swelling was occurred. Then lesions regressed but were still observed up to 60 days post-infection. In pulmonary organ, strong reaction to infection occurred in pulmonary alveolar cells by swelling and proliferation, particularly in the anterior lobes. Mononuclear cell infiltration was also accompanied this process⁹. Morphologic examinations of lungs showed severe vascular lesions¹⁷. They represented pulmonary granulomatous appearance, disseminated in entire the lung. Excluding the rest of blood cellular components, a high number of intravascular macrophages occupied the lumina of the pulmonary vessels with diameter of 20 to 200 microns (both in arteries and veins). Concentric layers of perithelial cells, comprised with macrophages and plasma cells, were also sometimes found around arteries and veins. Destruction or necrosis of tissues or blood vessels rarely occurred¹⁷. Intracytoplasmic inclusions and pleomorphic basophilic took place in all affected tissues. The processes particularly occurred for the second week until about the fifth week of infection, but persistently could be found in small numbers for more than eight weeks. Both minute basophilic granular forms and large intravacuolar inclusions were structure which constantly detected in reticular cells, macrophages (Kupffer cells), pulmonary alveolar cells, lymphoblasts and occasionally vascular endothelium⁹. As lesions are typical to JDV infection, they can be used in post-mortem diagnosis of Jembrana disease¹⁷.

Immune response

Immunohistochemical studies on experimentally JDV-inoculated Bali cattle showed that the proportion of IgG-containing cells in the lymphoid organs became significantly raised during healing stage (convalescence) but fall off during the acute stage^{19,20}. This finding was conforming with studies by ELISA (enzyme-linked immunosorbent assay) and AGID (agar gel immunodiffusion) which showed a slowed antibody response. JDV-specific antibodies were remained undetected until 11 weeks post-infection in most infected cattle. This antibody response was maximal at 23-33 weeks post-infection and was still detectable at 59 weeks post-infection¹⁶. The transient immunosuppression occurring during the acute stage was proved by a decrease of IgG-containing cells in the lymphoid organs and of the

ratio of bovine CD4/bovine CD8 lymphocytes in lymph nodes follicles^{19,20}.

Virus Distribution in Tissues and Organs

During the acute stage of infection, a high virus load in plasma of infected Bali cattle was evidenced equaling up to 10^{10} to 10^{11} viral genome copies/ml.^[12] The inoculated buffaloes, sheep, Ongole and Friesian cattle also showed a continuing firmly viraemia.^[11] Particularly in buffaloes, JDV persisted in blood or spleen for at least 9 months. For the other species, the virus persisted for less than 9 month, a shorter period. In inoculated crossbred cattle, the animal was viraemic for 3 months.^[11] The resistant (survived or recovered) animals are however persistently viraemic for at least 25 months after recovery although the virus titre dramatically drops to 10^1 infectious units/ml of plasma.^[10,14] It was hypothesized that the humoral immune response is not the major factor in the resolution of the acute disease as antibody is only produced several weeks after infection^{10,16}.

During the acute stage, viruses are also detected in secreted fluids, i.e. saliva, milk, nasal discharge. The virus is no more detectable in secretions after 60 days of recovery^{9,10}. The localization of JDV in various tissues or organs was explored by *in situ* hybridization using as probe DIG (digoxigenin)-labeled cDNA derived from *pol* gene. Numerous infected-cells were existed in many tissues early in the disease course during the febrile phase as the high circulating viraemia detected^{15,8}. The highest number of infected-cells were observed in the spleen and also high number of infected-cells were also found in lymph nodes, lungs, bone marrow, liver, kidney, cells in the general circulation and within intravascular lesions in lung^{9,15,17}. The existence of infected-cells in these various tissues explains well the pathological changes observed in different tissues and organs, as described above.

Concluding Remarks

The acute, severe nature of JDV infections, with a short incubation period and no recurrence of disease in recovered animals, is not emblematic to most lentiviral infections. The pathological changes which result from JDV infections, reflect an intense lymphoproliferative disorder affecting most organ systems except for the central nervous system⁹. The proliferative

changes in lymphoid system indicates that a predominantly T lymphocytic reaction takes place during the acute stage that may be associated with transient immunosuppression⁹.

The delayed and temporarily suppressed humoral response provides an explanation for the common occurrence of secondary infections which may lead to fatal issues in affected cattle^{9,18}. Only one example of lentivirus infection, i.e. infection of a lethal variant of simian immunodeficiency virus (SIV), is known to produce effects strikingly similar to JDV infection in pig-tailed macaques^{6,7}. Both viruses induce severe lymphopenia, followed by a rapid and intense lymphoproliferative disorder. These pathological process resulting in substantial increase of blastic lymphocytes in parafollicular regions of lymph nodes, spleen and lymphoid tissues of other organs. In both cases, there are high levels of infectious virus in the plasma and there is no recurrence of clinical signs in animals recovering from viral infections^{6,9}. JDV-recovered cattle resist to further infections for at least 22 months. However, as the recovered cattle developed a delayed humoral response several weeks after infection, it was hypothesized that antibody is not the major factor in the resolution of the acute disease process¹⁶.

Evolutionarily speaking, it is remarkable that such a radically different pathogenesis emerges from a group of viruses that are usually associated with chronic and progressive diseases over a long incubation periods. Such a radical change of *in vivo* pathogenicity should have their origin in multiple genetic determinants that allow higher viral expression level and consequently greater fitness in viral replication and *in vivo* pathogenicity¹.

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