

UPDATE ON SYNDROMES AND CLINICAL PROBLEMS ASSOCIATED WITH PORCINE CIRCOVIRUS TYPE 2 INFECTION (A REVIEW)

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SUMMARY: Porcine circovirus type 2 is considered as one of the most important pathogens of swine. The identification and correlation of PCV2 with PMWS, was followed by an increasing isolation of the virus from pigs suffering from various syndromes and disease problems. Infection by PCV2 has been associated with systemic disease, porcine dermatitis and nephropathy syndrome, porcine respiratory disease complex and reproductive disorders. Moreover, PCV2 has been associated with congenital muscular tremor type AII, proliferative and necrotizing pneumonia, acute pulmonary edema, granulomatous enteritis and necrotizing lymphadenitis. Despite the evidence of PCV2 association with all these syndromes and disorders, still there is a lack of knowledge concerning the relative pathogenic mechanisms.

Key words: porcine circovirus type 2, syndromes, clinical problems.

PORCINE CIRCOVIRUS TYPE 2 (PCV2) AND ASSOCIATED DISEASES

Porcine circoviruses (PCV), members of the genera Circovirus, family Circoviridae, are small non-enveloped viruses that contain a single-stranded circular DNA of about 1.76kb. Two types of circoviruses have been isolated and identified, PCV type 1 and PCV type 2 (Meehan et al., 1998). Initially PCV1 was a common finding in porcine kidney PK-15 cell lines (Tischer et al. 1974). PCV1 is considered as non pathogenic to pig (Allan et al., 1995, Tischer et al. 1986). However, Saha et al (2011) demonstrated that under experimental infection of porcine foetuses inoculated at 55 days of foetal life with PCV1, the virus can replicate and produce pathology in the lungs of foetuses. Still, more research is needed on this area. Regarding PCV2, the virus was initially associated with Postweaning Multisystemic Wasting Syndrome (PMWS) (Harding and Clark,

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1997, Ellis et al., 1998) and shortly, more scientific works followed revealing a link between PCV2 and other clinical features and disease forms differentiated from PMWS. Under this scope, Allan et al. (2002) proposed as a new terminology able to describe the new situation replacement of PMWS Porcine Circovirus Disease (PCVD). Respectively, on March 2006 the Board of American Association of Swine Veterinarians (AASV) adopted the term Porcine Circovirus–Associated Disease (PCVAD).

PCVD attract the relevant research interest worldwide, resulting in a continuous flow of new information. As a consequence, several terminologies referring to PCVD have been proposed. Thus, according to AASV (2006), PCVD may be subclinical or include one or more of the following clinical manifestations: Multisystemic disease with weight loss (formerly known as PMWS), high mortality, respiratory signs including pneumonia, Porcine Dermatitis and Nephropathy Syndrome (PDNS), enteric signs, reproductive disorders. Likewise, the Veterinary Diagnostic Laboratory at Iowa State University, Ames, Iowa, USA, summarizes PCVAD as follows: Severe Systemic PCV2 Infection (former PMWS), PCV2-Associated Pneumonia, PCV2-Associated Lymphoid Depletion, PCV2-Associated Abortions and Reproductive Failure, PCV2-Associated Myocarditis and Vasculitis in Growing Pigs, PDNS, PCV2-Associated Enteritis, PCV2-Associated Hepatitis, PCV2-Associated CNS Disease, PCV2-Associated Exudative Epidermitis.

The most recent proposed change in current terminology derives by Joakim Segales (2012) and in accordance with, PCVD includes: PCV2 subclinical infection (PCV2-SI), PCV2 systemic disease (PCV2-SD) (former PMWS), PCV2 lung disease (PCV2-LD) instead of PCV2-associated respiratory disease and proliferative and necrotizing pneumonia, PCV2 enteric disease (PCV2-ED) instead of PCV2-associated enteritis, PCV2 reproductive disease (PCV2-RD) instead of PCV2-associated reproductive failure and PDNS.

Many research efforts focus towards understanding the pathogenic mechanisms and identification of factors needed for PCVD modulation. Probably more than one factor involve in PCVD etiology and these can be viral dependent, host dependent, factors that can cause immunomodulation and coinfections (Opriessnig et al., 2007, 2011).

PCV2 SUBCLINICAL INFECTION

PCV2 infection is ubiquitous, while the prevalence of PCVD is not commensurate regarding to PCV2 worldwide distribution. Thus it can be postulated that the most common form of PCV2 infection is the subclinical one (Segales, 2012). In this form, PCV2 infection may be limited to some lymph nodes with no clinical disease (Gillespie 2009). In these cases a necrotizing lymphadenitis may be revealed in clinically healthy pigs (Opriessnig et al 2007). On the other hand, there are field evidences that PCV2 subclinical infection may have a negative impact on vaccine efficacy (Opriessnig et al 2006), while there is indication that PCV2 vaccination may have a positive impact in improving productive parameters (average daily gain, percentage of runts, body condition and carcass weight) in PCV2 subclinical infected pigs (Young et al. 2011).

PCV2 SYSTEMIC DISEASE (PCV2-SD)

PCV2-SD is a relative recent described syndrome having a significant economic impact on global pig industry (Allan and Ellis 2000; Clark, 1997; Segales et al., 1997). PCV2 is considered as the main causative agent of the disease (Allan and Ellis 2000; Allan et al., 1998; Ellis et al., 1998; Hamel et al., 1998; Meehan et al., 1998). PCV2-SD has been reproduced experimentally by inoculation of PCV2 alone and in combination with other pathogens, such as porcine parvovirus or Reproductive and Respiratory Syndrome (PRRS) virus. The combined experimental infection with parvovirus and PCV2 found to lead to increased replication of PCV2, possibly due to synergistic mechanisms, while large PCV2 antigen quantities and little or no antigens of parvovirus were detected at lesions. Additionally, simultaneous infection with PCV2 and PRRS virus is common in farm level and according to Allan et al. (2000) in these cases replication of PCV2 is reinforced. Therefore, PRRS virus probably plays an important role at PCV2-SD pathogenesis not only under experimental conditions but also in field. Furthermore, simultaneous infection by *Mycoplasma hyopneumoniae*, a frequent finding in PCV2-SD cases probably increases the incidence and severity of disease (Opriessnig et al., 2004; Kim et al., 2003a; Stockhoff-Zurwieden et al., 2003; Rovira et al., 2002; Bolin et al., 2001<, Harms et al., 2001; Kennedy et al., 2000; Krakowka et al., 2000; Allan et al., 2000; Choi and Chae, 2000). Studies with experimental PCV2 infections of pigs indicate that there is a long incubation period and the impact of various stress factors is needed for PCV2-SD manifestation to be expressed (Wellenberg et al., 2004; Fenaux et al., 2002; Krakowka et al., 2001; Allan et al., 2000).

The syndrome is characterized by low morbidity while mortality varies from 1-2% up to more than 40% and most often affects animals aged 5-12 weeks. Clinical manifestations are progressive weight loss, dyspnea, lymphadenopathy, muscle weakness, lethargy, dark-colored diarrhea, paleness and sometimes jaundice. Moreover, findings such as cough, pyrexia, gastric ulcer, meningitis and sudden death may be present (Gillespie, 2009; Segales and Domingo, 2002; Allan and Ellis, 2000; Harding and Clark, 1997).

At postmortem examination, lymph nodes, especially mesenteric, inguinal and submandibular, are usually finding enlarged. Lungs are discolored, spleen is swollen and proliferative, while kidneys may be swollen and discolored. Wasting, pale skin, jaundice maybe reveals. However, these findings are not characteristic (Segales et al., 2004; Allan and Ellis, 2000; Rosell et al., 1999; Harding and Clark, 1997).

The main histopathological findings include lymphoid depletion together with histiocyte replacement in lymphoid tissues, and intracytoplasmic inclusion bodies (Segales et al., 2004; Chianini et al., 2003; Kennedy et al., 2000; Krakowka et al., 2000; Rosell et al., 1999; Allan et al., 1998; Harding and Clark, 1997). In the lungs, liver, kidney, heart and intestines it is possible to have granulomatous lesions (Opriessnig et al., 2007).

Although PCV2 is omnipresent in pig populations, the prevalence of PCV2-SD is not relevant. Thus, Sorden (2000) proposed that diagnosis of PCV2-SD should be based on certain criteria: 1) relevant clinical symptoms, such as wasting, weight loss, and respiratory disease, 2) presence of PCV2-associated microscopic lesions (lymphoid depletion and/or histiocytic replacement of follicles in lymphoid tissues), and 3) detection of PCV2 antigen or nucleic acids in microscopic lesions using immunohistochemistry or *in situ* hybridization. According to Segales (2012) these diagnostic criteria should be: 1) Weight loss and paleness of skin (respiratory and/or digestive clinical signs may

be present as well) 2) Moderate to severe lymphocyte depletion with granulomatous inflammation of lymphoid tissues (plus granulomatous inflammation in a number of other tissues) 3) Moderate to high amount of PCV2 in damaged tissue (Segales et al., 2012). Moreover, Opriessnig et al. (2007) proposed that in order to put PCV2-SD diagnosis, PCV2 antigen must be revealed in more than 1 lymphoid tissue (lymph node, tonsil, spleen) or in 1 lymphoid tissue (lymph node, tonsil, spleen) and at least 1 other organ system (i.e., lung, liver, kidney, intestines) or in 2 two organ systems such as lung, liver, kidney, intestines. In case that PCV2 antigen is associated with only 1 specific organ system, diagnosis should be referred to another PCVD, while existence of severe lesions with a limited amount of PCV2 antigen present is consistent with severe chronic PCVAD.

DERMATITIS AND NEPHROPATHY SYNDROME (PDNS)

PDNS was firstly reported in 1993 in Great Britain while the association of this syndrome with PCV2 infection was suggested at 2000 (Rosell et al., 2000; Smith et al., 1993). The syndrome occurs at weaning, growing and adult pigs as well (Drolet et al., 1999). Affected animals are lethargic with little or no pyrexia, but the most characteristic symptom is the appearance of raised red to purple skin lesions, most prominent on the hind limbs and perineal area, although these lesions might be extended also in other body areas. With time, lesions covered by dark crusts, cutaneous lesions gradually fade, sometimes leaving scars (Drolet et al., 1999; Chae, 2005; Segales et al., 2004). Although, morbidity is low (~ 1%), the syndrome is often fatal, especially in pigs aged more than 3 months old, while in younger animals mortality rates decrease (Chae, 2005; Done et al., 2001; Duran et al., 1997; Ramos-Vara et al., 1997). Pigs that survive will recover and gain weight within 7 to 10 days (Segalés et al., 1998).

Gross lesions, apart these of skin, include enlarged, tan and waxy kidneys with petechial hemorrhages (Segales et al., 2004; Harding, 2004; Ramos-Vara et al., 1997). Histopathology examination reveals systemic necrotizing vasculitis (particularly in skin, kidney, lymph nodes, stomach, spleen and liver) and fibrino-necrotizing glomerulonephritis, while there is an absence or just a mild depletion of lymphocyte with mild granulomatous inflammation of lymphoid tissue. (Segales, 2012; Segales et al., 2004; Duran et al., 1997; Ramos-Vara et al., 1997; Thibault et al., 1998). Kidney lesions are suggestive of a type 3 hypersensitivity reaction, which is characterized by deposition of antigen-antibody aggregates or immune complexes (Rosell et al., 2000; Thibault et al., 1998), although the pathogenesis of the syndrome has not yet been fully elucidated.

Coinfections with other pathogens, eg *Pasteurela multocida* (Lainson et al., 2002; Thomson et al., 2001) or combinations of pathogens such as PCV2 and PRRS virus (Rosell et al., 2000b; Thibault et al., 1998) supported that are involved in PDNS pathogenesis. Moreover, Krakowka et al. (2008) was experimentally reproduced PDNS with PRRSV and terqa teno virus in PCV2-free pigs, assuming that PDNS is not always associated with PCV2.

PCV2 LUNG DISEASE (PCV2-LD)

Porcine Respiratory Disease Complex (PRDC) has an important impact on health and productivity of pigs aged 6-22 weeks. Clinically, PRDC is characterized by decreased growth, increased feed conversion ratio, lethargy, anorexia, cough, fever and dyspnea. The intensity of symptoms and the mortality rate of the syndrome vary and depend on the combinations of pathogens involved each time (Segales et al., 2004; Kim et al., 2003b; Thacker, 2001). Several viruses and bacteria can be involved in the etiology of PRDC such as PRRSv, influenza virus, *Mycoplasma hyopneumoniae*, *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* (Thacker, 2001).

Ellis et al. (1999) after the detection of PCV2 in pigs suffering from proliferative necrotizing pneumonia, speculated that PCV2 may be also involved in the PRDC etiology. This aspect was supported by Kim et al. (2003b) following the increased frequency of PCV2 detection in PRDC cases. This specific role of PCV2 is possibly related to interaction or synergy with other viral respiratory pathogens, such as PRRS virus, which has been found to increase the activity of PCV2 (Harms et al., 2001; Allan et al., 2000; Ellis et al., 1999). Indeed, experimental studies have shown that mixed infection of pigs with both viruses respiratory symptoms and lung lesions were particularly severe (Chae, 2005; Harms et al., 2001). Simultaneous infection with PCV2 and bacteria has also been reported in cases of PRDC (Kim et al. 2003b), while of Oppriessnig et al. (2004) indicated that infection by *M. hyopneumoniae* increases the severity of lung lesions caused by PCV2.

Symptoms of PCV2-LD and PCV2-SD are quite similar, thus differential diagnosis is important, which is based mainly on histopathological findings. Microscopic lesions include granulomatous bronchointerstitial pneumonia with mild to severe necrotizing and ulcerative bronchiolitis and bronchiolar fibrosis, while there is an absence of PCV2-SD lesions in lymphoid tissues. However, lesions of bronchiolitis should be differentiate from these that can be caused by swine influenza or porcine respiratory coronavirus infections (Oppriessnig et al, 2007; Gillespie et al, 2009; Segales, 2012). According to Chae (2005) four diagnostic criteria should be satisfied in PCV2-RD cases: (a) existence of respiratory symptoms such as severe breathing, not responding to antibiotic treatment, (b) presence of microscopic lung lesions compatible with infection with PCV2, (c) detection of PCV2 in these lesions and (d) absence of the characteristic microscopic lesions in other tissues, particularly lymphoid.

PCV2 REPRODUCTIVE DISEASE (PCV2-RD)

In international literature several reports associate PCV2 infection with reproductive disorders. PCV2-RD main clinical manifestations are abortions, stillbirths, mummified fetuses and increased preweaning mortality (Pensaert et al., 2004; Kim et al., 2004a; Farnham et al., 2003; Sanford, 2002; Meehan et al., 2001). Histopathologic lesions include non-suppurative to necrotizing or fibrosing myocarditis in stillborn and neonatal pigs, chronic, passive, hepatic congestion and mild pneumonia in fetuses (West et al., 1999; Segales et al., 2012). These lesions are not typical in order to establish an accurate diagnosis (Chae, 2005).

Johnson et al. (2002) experimentally infected embryos of different ages with PCV2 and noted that the virus can affect late-term fetuses causing reproductive failure,

while the time of infection determines the clinical course of the disease (Gillespie et al., 2009). It should be noticed that field cases of PCV2-RD are quite rare, presuming that old adult animals are immune due to high seroprevalence (Pensaert et al., 2004; Oppriessnig et al., 2007). Thus, gilts, breeding populations with a high proportion of gilts or naive herds are susceptible for PCV2-RD. However, there are still several unanswered questions regarding the impact of PCV2 infection on sows and their embryos and further research is needed.

PCV2 ENTERIC DISEASE (PCV2-ED)

PCV2-ED is considered as another PCVD with increasing trend of prevalence (Oppriessnig et al., 2007). On farms facing this PCV2 clinical manifestation 10-20% morbidity and mortality up to 50-60% have been reported. Usually, it occurs in pigs aged 8-16 weeks and the main clinical symptoms are diarrhea and growth retardation (Chae, 2005; Kim et al., 2004b; Oppressing et al., 2007). Both clinical expression and gross lesions (thickened intestinal mucosa and enlargement of mesenteric lymph nodes) are quite similar with these of ileitis due to *Lawsonia intracellularis*. However, histopathology is instructive since PCV2-ED is characterized by granulomatous enteritis and the appearance of lesions at Peyer's patches compatible with PCV2 infection, while there are not lesions in other organs (Chae, 2005; Kim et al., 2004b). However, it is essential to differentiate PCV2-ED from PCV2-SD. According Oppressing et al. (2007) diagnosis of PCV2-ED should be relied on the diarrhoea presence, together with the existence of characteristic lesions in Peyer patches but not in other lymph nodes, while PCV2 antigen or nucleic acids should be present within the lesions.

OTHER POSSIBLE PCVD

The continued association of PCV2 with various diseases and pathologic conditions has expanded the list of PCVD, although, further research is needed in order to explore the possible impact of the virus on the relative diseases.

PCV2-Associated Neuropathy: The first association of circovirus with congenital tremor type A2 was done by Hines and Lukert (1994), and later this aspect supported by Stevenson et al. (2001) after finding PCV2 nucleic acid in the brain and spinal cord of infected piglets, while Kennedy et al. (2003) reached on different conclusions.

More recently, Correa et al. (2007) associated PCV2 infection with cerebellar lymphohistiocytic vasculitis combined with hemorrhages or with lymphohistiocytic meningitis. Moreover, PCV2 antigen was found in the lesions of brain tissue. At the same year, Seeliger et al described a neurologic disease characterized by opisthotonus, nystagmus, and convulsions in pigs 6 - 8 weeks of age in which cerebellar vasculitis was also present, which they associated it with PCV2 infection. Still, it is unclear the potential role of PCV2 in the pathogenesis of this disease and further research is needed.

PCV2-Associated acute pulmonary oedema: Recently, a new PCV2 disease syndrome in herds vaccinated against PCV2, under the name acute pulmonary edema (APE). APE has a peracute onset affecting nursery and younger finisher pigs (Cino-Ozuna et al., 2011). Mortality can reach 20%, while main clinical signs are the rapid onset of respiratory distress followed rapidly by death. PCV2 involvement was speculated

since it was the only pathogen detected in the examined tissues. Although, authors mentioned a possible explanation regarding pathogenesis, since there is only one relevant report confirmation is needed.

CONCLUSIONS

Several reports associate PCV2 with various syndromes and disease problems of pigs. However, even though PCV2 is widespread in pigs, there is not indubitable proofs that PCV2 really induce all these problems, while too many questions exist concerning the contributing factors that involve in PCVD pathogenesis. Thus, the continuation of relative research effort is imperative in order to be able to proceed to effective control and prevention of PCVD.

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DOKAZIVANJE SINDROMA I KLINIČKIH PROBLEMA POVEZANIH SA CIRKOVIRUS TIP 2 INFEKCIJOM

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Izvod

Svinjski cirkovirus tip 2 je jedan od vrlo važnih patogena kod svinja. Identifikacija i korelacija PCV2 sa PMWS je praćena sa povećanjem broja izolacija kod svinja obolelih od različitih sindroma i bolesti. Infekcija sa PCV2 je povezana sa sistemskim obolenjem, svinjskim dermatitisom, sindromom nefropatije, kompleksom respiratornih obolenja svinja i poremećajima reprodukcije. Šta više, PCV2 uzrokuje i kongenitalni tremor mišića tip AII, proliferativnom i nektotičnom pneumonijom, akutnim pulmarnim edemom, granulomatoznim enteritisom, i nekrotičnim lifadenitisom. Uprkos dokazanoj povezanosti PCV2 sa navedenim obolenjima i poremećajima, još uvek nije potpuno razjašnjen patogeni mehanizam ove infekcije.

Ključne reči: svinjski cirkovirus tip 2, sindrom, klinički problemi.

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