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PMWS etiology: Agent interactions

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Post-weaning multisystemic wasting syndrome (PMWS) was described in 1996 (Harding et al.1996) and since this first description it has been reported in most pig-producing countries in the world (Allan et al. 2000a). PMWS is characterized by weight loss, paleness of the skin, respiratory signs, and, less frequently, jaundice and diarrhea in late nursery-early fattening pigs. At necropsy, generalized lymphadenopathy and non-collapsed lungs are the most common findings, and kidneys with white spots and a small yellowish liver can also be observed (Harding et al. 1996, Rosell et al. 1999). These clinical signs and macroscopic lesions are not specific for PMWS and are frequently observed in other diseases. In contrast, microscopic lesions observed in lymphoid tissues, consistent of lymphoid depletion and histiocytic infiltration, are highly specific for this disease.

The role of porcine circovirus type 2

Porcine circovirus type 2 (PCV2) is consistently found in high amounts within the PMWS characteristic microscopic lesions by immunohistochemistry or in situ hybridization (Rosell et al. 1999). In fact, this association is so strong that the current case definition for PMWS includes detection of PCV2 in characteristic lesions. The other two requirements that a case needs to fulfill to be diagnosed as PMWS are the following:

- The presence of compatible clinical signs
- The presence of characteristic microscopic lesions in lymphoid tissues (Sorden 2000)

PCV2 is a ubiquitous virus in swine, and subclinical infection is common in commercial farms. Therefore, PCV2 is present in all PMWS cases, but not all pigs infected by PCV2 develop PMWS. Moreover, PMWS has only been reproduced by inoculation of PCV2, alone or in combination with other agents. However, the disease is not easily reproduced by inoculation of pigs with PCV2 alone, and more success has been achieved by coinoculation with other agents (Allan et al. 1999, Harms et al. 2001, Rovira et al. 2002). For these reasons, PCV2 should be considered a necessary but not sufficient cause of PMWS.

Coinfection with porcine parvovirus

Several studies have been done in order to identify the factors that trigger PMWS. In the first successful experimental reproduction of PMWS, the PCV2 inoculum used to inoculate the experimental pigs was found to be contaminated by porcine parvovirus (PPV). After this finding, the inoculation of PCV2 in combination with PPV has been used as an effective method to reproduce PMWS (Allan et al. 1999). However, it is not clear if this interaction is responsible for the PMWS field cases. PPV is ubiquitous among swine around the world, being present in almost all swine farms. However, PPV infection in pigs usually occurs after PMWS onset because maternal immunity to PPV lasts three to six months (Mengeling 1999). In a Korean and a Canadian study, only 25% and 13% of PMWS affected pigs were found to be coinfected by PPV, respectively (Kim et al. 2002, Ellis et al. 2000). This percentage was even lower in a case-control study performed at the Iowa State University (Pogranichniy et al. 2002). Interestingly, in this study the percentage of PPV infected pigs was similar for control and PMWS cases, showing that PPV infection is not necessarily a risk factor for PMWS in field cases. In summary, although PPV has been demonstrated to trigger PMWS in experimental conditions, this virus does not seem to play an important role in field conditions.

Coinfection with porcine reproductive and respiratory syndrome virus

Coinfection with porcine reproductive and respiratory syndrome virus (PRRSV) and PCV2 has been investigated. This interaction is more likely to play an important role in PMWS field cases because PRRSV infection occurs before PCV2 infection in natural conditions. Moreover, PRRSV infection is very common in modern swine industry. This coinfection has been detected in 60 to 20% of PMWS affected pigs in the US, Spain, Korea, and Western Canada (Sirinarumitr et al. 2001, Segales et al. 2002, Pogranichniy et al. 2002, Allan et al. 2000a, Kim et al. 2002). This relatively high percentage of coinfected pigs is not surprising, considering that the prevalence of PRRSV in these countries is high. Interestingly, the abovementioned case-control study (Pogranichniy et al. 2002)

found that the risk for PMWS is much higher in PRRSV-infected pigs than in PRRSV-negative pigs.

Three inoculation experiments confirm that PRRSV infection potentiates PCV2 replication. In the first experiment (Allan et al. 2000b), inoculation of pigs with PCV2 and PRRSV resulted in a subclinical infection for both viruses. However, PCV2 load and tissue distribution was enhanced by coinfection with PRRSV.

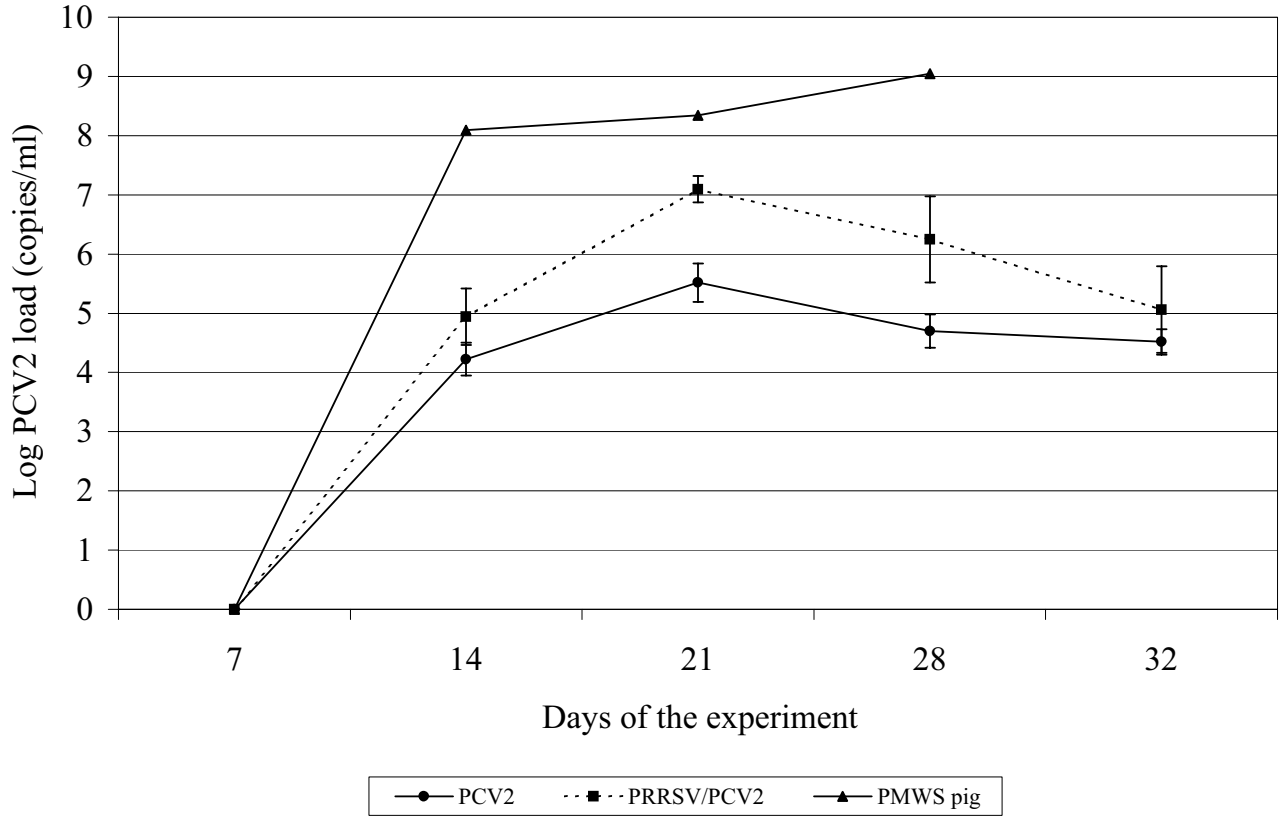
In the second experiment (Harms et al. 2001), severe disease was produced in all pigs inoculated with PCV2 and PRRSV. In this experiment, PMWS was also reproduced in a number of pigs inoculated with PCV2 alone. However, percentage of affected pigs, severity of clinical signs, intensity of microscopic lesions, and amount of PCV2 in tissues were enhanced by coinfection with PRRSV. On the other hand, pneumonia was more severe in coinfected pigs than in pigs infected with PRRSV alone.

In the third experiment (Rovira et al. 2002), seven conventional pigs were inoculated with PCV2 alone, five with PRRSV, seven with PRRSV and PCV2, and five were sham inoculated. Only one pig, inoculated with PRRSV and PCV2, developed PMWS. The rest of the pigs were subclinically infected by the viruses they were inoculated with. However, important differences were observed between the PCV2-inoculated and the PRRSV+PCV2-inoculated groups:

- Microscopic lesions were more intense in coinfected pigs than in pigs infected with PCV2 alone.
- PCV2 nucleic acid (detected by in situ hybridization) was more abundant in lymphoid tissues from PRRSV+PCV2-inoculated pigs than in lymphoid tissues from pigs inoculated with PCV2 alone.
- PCV2 was found in an higher number of tissues in coinfected pigs, compared to PCV2-infected pigs.
- PCV2 load in serum (measured by TaqMan PCR) was significantly higher in PRRSV+PCV2-inoculated pigs than in PCV2-inoculated pigs (see **Figure 1**).

It is interesting to note that the PCV2 load was much higher in the PMWS-affected pig than in the rest of PRRSV+PCV2-inoculated pigs. This is in agreement with the intense PCV2 labeling found by in situ hybridization in tissues from this pig and also in tissues from PMWS field cases. Furthermore, a previous study showed significantly increased levels of PCV2 in serum of naturally PMWS affected pigs, compared to healthy PCV2-infected pigs (Liu et al. 2000). It seems that a certain amount of PCV2 is required to develop PMWS. In this study, PRRSV was shown to increase PCV2 replication, resulting in higher loads of PCV2 in all coinfected pigs and in reproduction of PMWS in one out of seven coinfected pigs.

FIgure 1



Therefore, PRRSV is one of the factors that trigger PMWS, even though it is not present in all PMWS cases.

Other coinfections

PCV2 infection is usually seen in combination with other viral and bacterial pathogens in PMWS field cases such as the following:

- PRRSV
- Swine influenza virus
- Pseudorabies virus
- *Mycoplasma hyopneumoniae*
- Bacterial pneumonia
- Bacterial septicemia

In fact, PCV2 was found alone only in 2% and 15% of PMWS cases in the US and Korea, respectively (Pallares et al. 2002, Kim et al. 2002). Many times it is not clear if those coinfections are triggering factors for PMWS or are the result of secondary infections.

There is some evidence that systemic immunostimulation plays an important role in promoting PMWS. Following this theory, any systemic infection would potentiate PCV2 replication and would increase the risk for PMWS. However, up-to-date inoculation experiments with PCV2 and immunostimulation have reported contradictory results (Krakowka et al. 2001, Ladekjaer-Mikkelsen et al. 2002). On the other hand, lymphoid depletion, changes in lymphoid tissue and blood mononuclear cells subpopulations, and increased bacterial infections suggest an immunosuppressed status in PMWS-affected pigs (Domingo et al. 2001). Nevertheless, this hypothesis has not been demonstrated experimentally.

In conclusion, PMWS is a multifactorial disease in which PCV2 infection is necessary, but other factors are also involved. Besides management factors, coinfections with other pathogens such as PRRSV are known to promote the expression of PMWS. Moreover, immunosupression in affected pigs may be responsible for the increased secondary infections observed in PMWS outbreaks. However, further work is needed in order to fully understand the role of PCV2, other agents, and the interactions among them in the pathogenesis of PMWS.

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Figure 1: PCV2 load in serum samples measured by TaqMan PCR for pigs inoculated with PCV2 alone, pigs inoculated with PRRSV (day 0 of the experiment) and PCV2 (day 7 of the experiment) that did not develop PMWS, and the PRRSV+PCV2 inoculated pig that developed PMWS.