

PMWS or Porcine Circovirus Disease (PCVD): An Old Virus in a New Environment or a Complete Misnomer?

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Introduction

A wasting syndrome in Western Canadian pigs, first identified in 1991 in high health Specific Pathogen Free (SPF) herds, was reported in 1996 (Clark 1996, Harding 1996). The authors proposed the term "postweaning multisystemic wasting syndrome" (PMWS) to describe the clinical condition. Porcine circovirus (PCV) nucleic acid and antigen were demonstrated in abundance within the lesions of affected pigs and subsequent isolation and characterization of a "new" porcine circovirus (PCV2) virus from diseased pigs was reported (Ellis et al. 1998). PCV genome was also associated with interstitial pneumonia and lymphadenopathy in a 6 week-old pig in California (Daft et al. 1996) and a PCV2 virus was also recovered from this animal (Allan et al., 1998). In 1996/97, a clinical wasting disease associated with PCV2 was described in France (LeCann et al. 1997) and Spain (Segalés et al. 1997). Since these initial reports of PCV2-associated PMWS, the disease has been reported in almost all pig producing countries around the world.

PMWS histological lesions associated with an abundance of PCV2 antigen has now been retrospectively described in archived tissue samples taken in 1986 from pigs in Spain and the United Kingdom (Rodríguez-Arrijoja et al. 2003, Grierson et al. 2004) and in 1989 in Japan (Mori et al. 2000). Moreover, evidence of PCV2 infection in pigs has been detected as early as 1969 (Sánchez et al. 2001). It is now recognised that PCV2 is not a "new" virus, but a "newly discovered" virus and PMWS is not a new disease, but the expression of this disease syndrome changed in the early to mid 1990s from occasional clinical diseases in a few pigs to epizootic diseases outbreaks of high mortality in pigs world wide.

It has been estimated that PMWS costs around 600 million Euros per year to the European Union (Armstrong and Bishop, 2004). Common rates of morbidity and lethality associated with PMWS seen in affected farms are 4–30% (with exceptional rates over 50-60%) and 70–80%, respectively, with resulting mortality rates on farms between 4-20% (Segalés and Domingo 2002)

PMWS is now recognized as a disease of pigs where PCV2 infection is needed for expression of the clinical condition, however it is also recognized that PCV2 infection, linked to other co-factors, is necessary for the consistent development of full clinical disease in pigs.

Consistent and repeatable PMWS disease models have been obtained using infectious (Allan et al. 1999, 2003, Krakowka et al. 2000) and non-infectious (Krakowka et al. 2001) co-factors. The reproduction of full clinical disease has been reported in a high percentage of colostrum deprived (CD) and gnotobiotic (germ free) pigs co-inoculated with PCV2 and porcine parvovirus (PPV), porcine respiratory and reproductive syndrome virus (PRRSV), mycoplasma hyopneumonia (Mhy) or inoculated with a potent immunostimulant.

Clinical signs

PMWS most commonly affects pigs of 2 to 4 months of age, although the disease has been described in 1 to 6 month-old pigs and outbreaks of PMWS/PCVD are now being increasingly reported in fattening pigs (J Wadelove, personal communication).

The major clinical sign of PMWS is wasting but it is usually seen concomitantly with other signs such as pallor of the skin, respiratory distress, and diarrhea and, occasionally, icterus (Harding and Clark 1997). A relatively striking feature of pigs in the early clinical phases of PMWS is the increase in size of subcutaneous lymph nodes (mainly inguinal superficial lymph node), although it is not always seen (Segalés et al. 2004).

Other infections or diseases are more commonly found on PMWS-affected farms, when compared to non-affected farms (Ellis et al. 2004) and it has been suggested that the final clinical outcome observed on farms affected with PMWS is the sum of the effects of various management factors and concurrent diseases.

Lesions

The main lesions of PMWS occur in lymphoid tissues, although inflammatory infiltrates associated to PCV2 infection have been detected in a wide range of tissues from affected pigs.

Enlargement of lymph nodes is the most prominent feature of early clinical phases of PMWS (Clark 1997, Rosell et al. 1999). And the microscopic lymphoid lesions observed in PMWS-affected pigs are unique (Clark 1997, Rosell et al. 1999).

Lungs may be enlarged, non-collapsed and rubbery in consistency, following a diffuse or patchy distribution. These findings correspond microscopically to interstitial pneumonia.

In the majority of PMWS affected pigs, liver may appear unchanged or slightly pale but in a few cases, the liver is enlarged, pale, and firm in consistence, with a fine granular surface (Rosell et al. 2000).

Some PMWS-affected pigs show white spots in the kidney cortex (non-purulent interstitial nephritis), a lesion which, at this age, is almost only found in PMWS cases.

Distribution

PCV2 is now considered a ubiquitous virus, both in countries where PMWS has or has not been detected (Allan and Ellis 2000, Segalés et al. 2004) and PMWS has been diagnosed in a wide range of countries. Notable exceptions where PCV2 infection is present and PMWS has not been diagnosed include Australia and Finland. It is also of note that only 1 confirmed outbreak of PMWS has been reported in Norway and very few outbreaks of the disease have been reported in Belgium, when compared to neighboring countries such as France, The Netherlands, Germany and Denmark.

Diagnosis

The diagnostic criteria for PMWS (not PCVD) in single animals are now well established (Sorden 2000; Segalés et al. 2002). Classically, a pig or a group of pigs suffer from PMWS if they fulfill the following criteria (Sorden 2000):

- Clinical signs including growth retardation and wasting, frequently with dyspnea and enlargement of inguinal lymph nodes, and occasionally with jaundice;

- Presence of characteristic histopathological lesions in lymphoid tissues (lymphocyte depletion together with granulomatous inflammation, and presence of inclusion bodies in a proportion of affected pigs; and
- Detection of moderate to high amounts of PCV2 within the lesions in lymphoid and other tissues of affected pigs.

A herd case definition for PMWS should include the occurrence of a clinical process, characterized mainly by wasting and mortality, significantly in excess of the expected and/or historical level for each farm, and the establishment of individual diagnoses of the disease in a number of pigs (Segalés et al. 2003).

Prevention and control

Among PCVD, PMWS is the disease scenario with the major economic impact on swine production. To date, effective control measures to date for PMWS, without the control of PCV2 infection, have focused on the understanding of the co-factors and triggers involved on individual farms and the control or eradication of these triggers.

Prospective studies carried out in France from 1998 (Madec et al., 2000) and more recently in Sweden (Per Wallgren et al., 2005) have clearly shown that management deviations occurred in severely PMWS affected farms. As a result of these studies it was suggested that several environmental conditions might be necessary in association with PCV2 infection to lead to the clinical expression of the disease. The implementation of what is today known as the Madec's 20-point plan significantly decreased the percentage of mortality in severely affected farms (Madec et al., 2001). In studies (Allan et al. 2002, Calsamiglia et al. 2004), reported that PCV2 infection or low serological titres to PCV2 in sows at farrowing had a significant effect on the overall mortality of its offspring due to PMWS. Conversely, more recent studies in Denmark and the United Kingdom have shown that high levels of antibody to PCV2 in sows and gilts does not relate to protection from PMWS in the piglets derived from these animals (Hassing et al. 2004, Allan et al. 2005). However, the protective effect of maternal passive immunity on PMWS development is supported by the fact that disease occurs once these titres have declined (Rodríguez-Arrijoja et al., 2002; Larochelle et al., 2003; Sibila et al., 2004). Therefore, measures that increase maternal immunity and decrease sow viremia at farrowing may diminish PMWS impact on piglet mortality.

Partial control of epizootic PMWS has been achieved on some farms in the United Kingdom by changes in the diet of affected pigs (Donadeu et al., 2003). These changes included the increase of nutrient density of young pig diets and addition of commercial feed additives, most of them with anti-oxidant effects. However, these results have not been confirmed by other workers. On the other hand, a recent study has shown that conjugated linoleic acid (CLA) ameliorates PCV2 experimental infection (Bassaganya-Riera et al., 2003). Finally, it has been suggested that the addition of vitamin E and/or selenium in the feed may be of benefit in those farms with PMWS (Boebko et al., 2004). Overall, although some preliminary field and experimental data on nutrition suggest that certain nutritional factors might favour a decrease in PMWS outcome, there is not enough scientific information available to establish the real effect of nutrition in this particular disease.

The use of autogenous vaccine preparations has also been reported as advantageous in the control of PMWS in several countries, including the UK. This procedure involves the homogenization of lymphoid material from diseased pigs on specific farms, followed by

inactivation and ajuventing and administration to sows, gilts and young piglets on the same farm.

An inactivated, ajuvanted commercial PCV2 vaccine for use in sows and gilts is now available in some countries under emergency licence. This vaccine has been shown experimentally and in field trials to reduce the incidence of PMWS on affected farms (Reynaud et al. 2004a,b), presumably due to increased levels of serum antibodies to PCV2 following vaccination and the transfer of these protective antibodies to piglets in colostrum. The efficacy of this vaccine in controlling PMWS under field conditions remains to be fully elucidated, but early reports are very favorable.

Experimental PCV2 vaccine prototypes, including inactivated, recombinant and DNA vaccines have shown a significant protection when evaluated by evolution of body weight and rectal temperatures after PCV2 challenge (Blanchard et al. 2003, Pogranichnyy et al. 2004). A chimeric infectious DNA clone containing the immunogenic ORF2 capsid gene of PCV2 cloned into the non-pathogenic PCV1 genetic backbone induced antibody response to PCV2 capsid when inoculated in pigs and was shown to be attenuated compared to the PCV2 virus (Fenaux et al., 2003). This vaccine also appears to be protective against development of PCV2-associated lesions in an experimental model.

Field observations from farmers and veterinarians have suggested that certain genetic lines of pigs, specifically in relation to boar lines, are more or less susceptible to PMWS. This observation has been supported by recent experimental studies where Landrace pigs were experimentally shown to be more susceptible to develop PMWS lesions than Duroc and Large White pigs (Oppriessnig et al. 2004). Other studies have shown contradictory results with the use of Pietrain boar line; while the use of this genetic line did not seem to have any effect on the offspring in one study (Rose et al. 2003), another study showed lower general postweaning and PMWS associated mortalities (López-Soria et al. 2005).

The role of an unknown agent in causing the expression of PMWS: The New Zealand and Swiss scenario

In New Zealand PMWS was diagnosed for the first time on a farm on the North Island in October 2003. Since this initial diagnosis the Ministry of Agriculture and Forestry has carried out an extensive epidemiological survey in this country to document the incidence of the disease and attempt to identify a new "exotic infectious agent" responsible for PMWS in New Zealand. PMWS in New Zealand has been treated as an "exotic disease" with the relevant movement restrictions etc being put in place. As of 12 August 2004 it appears that there are a total of 16 PMWS-affected farms on the North Island of New Zealand and no PMWS-affected farms have been seen on the South Island. The 16 affected farms are, in general, located in a very limited geographical are of the North Island and are generally hobby or part-time farms. As of August 2004, no main-stream pig farms in New Zealand have been affected by PMWS. The determination of the temporal aspects of the outbreak and spread mechanisms of PMWS in New Zealand has, by the admission of the New Zealand authorities "proven problematic". Even though there was a reliance on farmer recall of morbidity and mortality, it appears from the studies carried out to date that, in some places in New Zealand PMWS outbreaks with mortalities in excess of 30% may have occurred as early as 2000, or perhaps even earlier. It is difficult to understand why outbreaks of disease with mortalities in excess of 30% remained unreported and undiagnosed for nearly 4 years in the New Zealand pig industry and, because of this a

complete understanding of the temporal progression of PMWS prior to the initial formal diagnosis in 2003 and the actual means of spread in each case may remain elusive. It has been hypothesised by the New Zealand authorities that an agent X (exotic to New Zealand) entered New Zealand in about 1999 in imported pig meat, which was fed to pigs with insufficient processing. One of the New Zealand herds was infected directly from this source and developed PMWS. Secondary spread has occurred to other like-minded farmers with whom infected herds have had frequent contact. This hypothesis is, to date, unproven date, unproven and is based on farmer interviews, retrospective analysis of farmers' records and kill numbers. A number of important questions regarding the epidemiology of PMWS in New Zealand require further examination. Central to this hypothesis on Agent X and PMWS is whether or not the farms in question in 1999 actually developed PMWS. There appears to be no data to support this, except clinical signs of wasting in pigs. It is well documented that ill-thrift and/or wasting in pigs can be caused by a number of conditions. Because of this, and the numerous inaccurate reports from veterinarians of outbreaks of PMWS in pigs based on clinical signs only, the international scientific community has agreed a common standard for laboratory based diagnosis of this condition. This must include clinical condition and typical gross and histological lesions and an abundance of PCV2 antigen associated with these lesions.

It is interesting to note the recent finding by Swiss researchers regarding this topic. In a recent study in Switzerland it has been shown that only 4 of 72 piglets selected from 26 farms with more than 10% clinically wasting piglets were actually diagnosed as having PMWS using the internationally accepted criteria.

PCVD/PMWS and the global pig industry

It is acknowledged that the global pig industry is, in many respects an ever changing environment. The genetics of commercially farmed pigs are continually being “upgraded” to accommodate consumer demand for leaner meat. Indeed, it could be argued that the commercial pig that is farmed today is a genetically diverse animal from the pig that was farmed 10 years ago. In addition husbandry practices have changed, and the contents of pig feed and the vaccines and biologicals used in pig production have also changed extensively. Vaccination of young piglets is a concept introduced in the early to mid 1990s. It is noteworthy that the first outbreak of PMWS in Sweden was on a “test station” set up and managed outside the traditional “welfare friendly” Swedish system and incorporated early weaning and vaccination of piglets and multiple movement and mixing of piglets. To date, all the outbreaks of PMWS in Sweden have been strongly associated with management malfunctions. In a recent review article on this topic (Visscher et al., 2002) the authors state that "disease of the host is not the evolutionary goal of the pathogen. Sub-clinical infections are common, they are the rule, diseases are the exception". This would appear to have been the situation with PMWS/PCVD until recently. In the same article the authors go on to make the following important observation: "the interplay between microbes and host should not necessarily be seen as an ongoing battle but a co evolution of species". Is it possible that accelerated breeding by "natural selection" for leaner traits, increased prolificacy and/or disease resistance in combination with changes in pig farming practices and nutrition has resulted in an unforeseen modulation of the PCV2-host co-evolution?

In conclusion, it would appear that two distinct theories to explain the pathogenesis and epidemiology of PMWS and PCVD are emerging. The initial scientific literature that outlined the importance of PCV2 in this disease scenario and the experimental reproduction of PMWS using PCV2 as inoculum is now being challenged by retrospective epidemiological data from New Zealand, Denmark and the UK that suggests that PCV2 is not the causal agent of PMWS. However, contemporary epidemiological studies in Sweden and Northern Ireland to date, do not support the hypothesis of an "exotic incursion" into the Swedish or Northern Ireland pig herd but do support the hypothesis that changes in the Swedish industry precipitated an explosion of PCV2-associated disease.

Further studies are ongoing in Ireland, other EU countries and New Zealand in an attempt to identify and characterise a "new" common infectious agent that may be responsible for the global explosion of disease. To date no such agent has been reported and the predominance of scientific evidence still supports the hypothesis that PCV2 is the causal agent of PMWS/PCVD and that control of PCV2 infections by vaccination at a herd level will eventually control the global epidemic of PMWS.

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