Postweaning Multisystemic Wasting Syndrome

Background: An unusual disease syndrome of weaned (6-12 week old) piglets was identified in several "high health" herds in 1991 in western Canada and was first reported to the swine community in 1997 and 1998. The syndrome, now known by the acronym of porcine postweaning multisystemic wasting syndrome (PMWS), is characterized by a constellation of clinical signs including progressive weight loss, jaundice and mortality rates of 10-40%. Initially, the syndrome was attributed to PRRS virus infection but all attempts to recover PRRS from these herds were unsuccessful and affected pigs were seronegative to known PRRS antigens. Gross manifestations of PMWS such as generalized lymphadenopathy, hepatitis, nephritis and pneumonia were most severe in weanling pigs. Any, all or none of these signs can be present in individual pigs within an age-matched group of affected animals. Histologically, the hallmark changes are systemic angiocentric granulomatous inflammation with syncytial giant cells and prominent, intracytoplasmic basophilic inclusion bodies in phagocytic cells. The etiologic agent has been identified as a porcine circovirus (PCV) with two known variants, an avirulent PCV-1 and a virulent PCV-2.

Agent: The Circoviridae are unusual nonenveloped viruses consisting of two avian agents (chicken anemia virus and psittacine beak and feather disease) and the two porcine agents. Firstly, they are the smallest viruses yet identified. Secondly, in spite of the morphologic similarities, circoviruses do not share common antigenic determinants. Thirdly, the genome of roughly 1,800 (1,759 for PCV-2) bases is a single circular stranded DNA molecule, reminiscent of the structure of a bacterial plasmid (virus) rather than a typical virus of animals. Finally, because of their small size and lack of envelope, the PCVs are very resistant to ordinary disinfectants, treatment with lipid solvents such as chloroform and ether and drying or desiccation.

Pathogenesis: Virtually nothing is known about either the viral determinant(s) of virulence nor the actual means of spread between pigs and within infected pigs. Both field data and limited experimental evidence suggest that phagocytic cells (macrophages and monocytes) are the primary cellular targets for this virus. Viral antigen and DNA is concentrated primarily in lymphoid tissues. Virus infected macrophages swell, proliferate and frequently form syncytial giant cells. In fulminant PMWS, the defining histologic lesion is disseminated angiocentric granulomatous inflammation. Granulomas are frequently accompanied by a variable but occasionally prominent neutrophilic and eosinophilic components and can occur anywhere including the liver, kidney, pancreas, myocardium and the muscular layers of the gastrointestinal tract. Perforated gastric and duodenal mucosal ulcers associated with granulomatous vasculitis have been encountered in PMWS. Viral antigen is usually abundant in these affected organs.

Experimental reproduction of the infection as well as PMWS has been accomplished by inoculation of both conventional "barrier raised" and gnotobiotic neonatal piglets. In both cases, potentiation of PCV-2 and resultant PMWS was accomplished when another porcine viral agent, porcine parvovirus (PPV) was included in the inoculum. While not obligatory for full disease expression, PPV (and likely other viruses such as PRRSV as well) clearly accentuate development of clinical disease. Aside from the well known effects of PPV on developing fetuses, PPV is not associated with significant postnatal clinical disease, even when inoculated into PPV-susceptible neonatal conventional or gnotobiotic swine. This observation is likely very important to the eventual understanding of the host-virus relationship in that it appears that PCV-2 may need "assistance" from other concurrent unrelated viruses, other infectious agents or even unusual environmental conditions to express its full disease potential in pigs.

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Experimentally, dually infected piglets seroconvert to both viruses after infection. Serum antibodies to PCV-2 are often very high and antibody to both the structural and replicative proteins have been identified. In spite of this, viral DNA is readily detected in peripheral blood leukocyte extracts and also in feces, oronasal and ocular secretions, even in piglets inoculated with PCV-2 alone. These data suggest that the infection persists (and is shed into the environment) for many weeks after infection.

In young animals, liver failure has emerged as the proximate cause of death in PCV-2/PPV-infected piglets. In these animals, Kupffer cells and infiltrating macrophages contain large quantities of virus. Hepatocyte degeneration and necrosis is widespread; this feature accounts for the icterus, submucosal edema and elevated serum hepatic enzymes which are features of experimental PMWS. Bilateral kidney damage is a frequent finding in field cases of PMWS; hydrenephrosis and multifocal to diffuse granulomatous nephritis have been seen in gnotobiotic pigs infected with PCV-2 and PPV.

**Epidemiologic Features and Clinical Signs of PMWS:** Even though reliable qualitative epidemiologic data are lacking, it appears that the incidence of PCV-2 infection (by serology) may be quite high. It is likely that every operation of any size where new additions have entered the herd are seropositive for PCV-2. That said however, the actual incidence of clinical disease or PMWS apparently varies greatly within endemic areas and many PCV-2-positive pigs are clinically asymptomatic. The reason(s) for this are unclear. There appears to be a greater problem with PMWS in "high health" operations rather than in routine farrow-to-finish facilities. Recently, PCV-2 infection has been linked to abortions and stillbirths suggesting that the infection can be acquired in utero. If confirmed experimentally, this mode of transmission would explain the development of PMWS in young pigs born to seropositive sows. The role(s) of co-factors, infectious and otherwise in potentiation of the disease remain to be determined. One of the reasons that PMWS has been described as a "syndrome" rather than an infection is that full expression of disease seems to require more than just infection by PCV-2.

Clinical presentation and pathologic features of PMWS vary greatly between affected pigs such that a complete picture of the disease is best appreciated by examining several infected animals. Generalized lymphadenopathy appears to be a regular feature of PMWS. This finding plus evidence of wasting and failure to thrive strongly suggest infection with PCV-2. Liver damage, manifest as icterus and edema is a common clinical sign. Some PMWS-affected pigs may only show uremia and other evidence of renal failure whereas in others respiratory involvement predominates.

**Diagnosis:** A presumptive diagnosis can be made based upon the clinical presentation, multiple piglets affected with some/all clinical signs and necropsy findings of generalized lymphadenopathy, icterus and histologic evidence for granulomatous inflammation in the liver, kidney and gastrointestinal tract. Demonstration of viral antigen in acetone-fixed impression smears, cryostat (frozen) tissue sections or formalin-fixed tissue samples using PCV-2-specific monoclonal antibody or viral DNA by in situ hybridization confirms the diagnosis. The PCR reaction using probes specific for PCV-2 is also used to demonstrate viral DNA in fresh or formalin-fixed tissues. However, the PCR reaction, when performed alone, may produce false positive results. For this reason, it is recommended that PCR be combined with virus isolation, immunohistochemistry for viral antigen or in situ hybridizations for viral DNA in tissue sections for diagnostic purposes.

**Treatment and Prevention:** There is no effective treatment for PMWS-affected animals. It is likely that infection in both clinically affected and asymptomatic individuals persists for long periods (perhaps as a life long infection) and that intermittent or continuous shedding of infectious virus into the environment and to other swine is a common event. Although hard data is lacking, it is likely that decontamination of infected premises will be problematic since this virus is so resistant to ordinary disinfectants. Since PPV is similarly resistant to ordinary methods of disinfection, it is probably useful to view control measures for PCV-2 in the same light as PPV. At the moment (spring 1999), neither the determinants of viral virulence nor the components of an effective immune response are known. While work is progressing on vaccine development, experimental vaccine formulations have not yet been tested for efficacy and nothing is currently available. It is difficult at this point to identify a specific strategy for an infected farm which might limit the effects of PMWS upon production. No doubt these will be developed as more is learned about this virus and its effects upon swine production.