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Acute interlobular edema and pleural effusion associated with circovirus in apparently immunized pigs – clinical and pathologic evaluations

S. Henry¹; L. Tokach¹; R. Hesse²; J. Nietfeld²; M. Potter²; D. Madson³

¹Abilene Animal Hospital PA, Abilene, Kansas; ²Diagnostic Medicine/Pathobiology, Kansas State University, Manhattan, Kansas; ³Veterinary Diagnostic and Production Animal Medicine, Iowa State University, Ames, Iowa

A clinical presentation involving porcine circovirus type 2 (PCV2) occurred September through December, 2009, that had striking clinical differences compared to outbreaks before the advent of vaccine. Pigs in good body condition 7 to 14 weeks of age died acutely with marked interlobular pulmonary edema. The affected animals in this case were vaccinated with product and protocol that had proven most effective in the past, yet pigs suffered severe disease and death. The possibilities of an altered circovirus isolate, vaccination protocol non-compliance, pre-immunization infection, a high environmental load of infectious virus or confounding other diseases were all considered in diagnostic efforts.

Clinical circovirus disease first appeared in 11 separate groups of pigs over a 6 week period beginning the first of September, 2009. Groups affected ranged from 7 to 14 weeks of age at onset of clinical signs. Mortality associated with the acute outbreaks ranged from 4%-17% with additional losses due to ill-thrift animals following the initial losses. Mortality in these flows averaged 4% or less prior to the acute outbreaks.

All groups demonstrated a pattern of acute onset accompanied by the rather specific gross lesion of pulmonary interlobular edema and copious yellow to slightly serosanguineous transudate in the thoracic cavity. All pigs had been immunized at 4 and 7 weeks of age with Circumvent PCV vaccine (Intervet Schering-Plough Animal Health). The protocol employed for vaccination had remained unchanged on these farms since the introduction of circovirus vaccines in 2007 and had been highly efficacious as no circovirus disease has been detected in over 2 years. This expression of circovirus disease appeared clinically unique in three aspects:

- Appearance of clinical signs across several different age groups from separate production flows during the same short 6 week time frame.
- Absence of clinical signs in same-source, same-age pigs from these sow farms at other grow-out sites. These non-affected pigs were vaccinated with the same protocol and product.

- Consistent gross pathology lesions of severe interlobular pulmonary edema along with pleural fluid accumulation in nearly all animals examined. Affected pigs were in good body condition, not wasting and rarely presented appreciable lymphadenopathy clinically.

Weaned pigs from two separate breed-to-wean sow farms go to one of 18 separate production facilities either as stand-alone nurseries or nursery-finishing sites. Approximately 2,200 pigs per week and 1,000 pigs per week are weaned from these farms respectively. Both sow farms produce reproductive and respiratory syndrome virus (PRRS) negative pigs and have done so for over 2 consecutive years. Growing pig sites varied from a few miles distant to over 100 miles from the source sow farms. Pigs in 9 of the 18 facilities remained PRRS negative through the entire growing period. PRRS infection and seroconversion occurred in the other 9 sites at 8–10 weeks of age in most cases. Of the 11 affected lots, most but not all were co-infected with PRRS.

Diagnostic confirmation in affected sites and groups was based on clinical signs, gross necropsy lesions, demonstration of lymphoid depletion and other histopathologic changes suggestive of circovirus associated pathology. PCV virus was demonstrated in tissues with immunohistochemistry and PCR. Viremia was consistently demonstrated in affected pigs and clinically. PCV virus sequencing and serum antibody testing by IFA was used to characterize the virus and the immune status of animals in affected and unaffected groups. PCV2 Differential ELISA and the Tween 20 mycoplasma hyopneumoniae ELISA were used to assess vaccine administration compliance. Additionally, PRRS virus status was assessed by PCR, ELISA, virus isolation and viral sequencing. Testing was conducted at Kansas State and Iowa State Veterinary Diagnostic Laboratories.

Laboratory evaluations and results

- On the basis of viral genome sequencing the circovirus present is very similar to those known historically to this region.

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- Concentrations of circovirus detected in tissue and serum were considered extremely high in most cases with cycle threshold (Ct) < 10 for many tissues and Ct < 20 for serum pools.
- Co-infection of affected lots of pigs with PRRS virus was confirmed in most but not all of the acute circovirus-affected groups.
- PRRS genome sequencing demonstrated virus known to have been present in these production flows in the past, and it is known that PRRS infection occurred in these sites/flows in the past 2 years.
- IFA antibody levels of weaned pigs were at levels suggesting they are not likely to interfere due to passive maternal antibody. Accordingly, the pigs appeared to be “vaccinatable”, meaning that under normal circumstances it is expected these pigs would mount an immune response post-vaccination.
- Compliance antibody evaluations initially revealed poor responses to vaccination although groups evaluated later exhibited excellent responses to vaccination. Several groups that exhibited disease appeared to have been well vaccinated based on compliance tests performed prior to the onset of disease. The negative results initially, in older pigs, were possibly a result of too long of intervals between the second vaccination and sample collection. Other, less likely reasons include administration non-compliance or profound immune suppression (caused by an unknown agent) resulting in failure to produce measurable antibody levels to both PCV2 and mycoplasma vaccination.
- Antigen (vaccine) failure was explored directly through company review of product. Nine different serial lots were employed in vaccination of both affected and unaffected lots of pigs with no relationship discovered relative to administered product.
- Post-vaccination IFA titers were stimulated as expected with most individuals $\geq 1:5120$ prior to clinical disease in the groups in which sampling preceded detection of illness. Post-vaccination antibody titer was as predicted in unaffected groups of pigs. However, it was difficult to distinguish between titers induced by vaccination versus those induced by infection.
- No other agents except for PCV2 and PRRSV have been isolated or identified thus far in the investigation. We have demonstrated torque teno virus (TTV) genotypes 1 and 2 in some of the pigs, but the significance is unknown and the pathogenesis of TTV has not been elucidated. Porcine cytomegalovirus (PCMV) was also detected in several pigs.
- Vaccination did not eliminate the virus from the environment. Environmental sampling was conducted in an affected nursery between groups at multiple steps along the cleaning and disinfection cycle. Viral genetic material was detected at all stages by PCR; whether this represented infectious virus or not was not determined.
- Viremia, detected prior to the second immunization, was observed in some samples of some groups. This indication of active viral infection prior to immunization led to altered timing of immunization. Further evaluation of maternal antibody levels indicated that pigs at younger ages would be “vaccinateable.”
- Vaccination timing was altered with initial vaccination at 3 weeks of age and the second vaccination 3 weeks later. Mycoplasma and circovirus vaccinations were concurrent. Sampling pigs vaccinated on this earlier time schedule was conducted at 3 week intervals with final sampling when pigs were 18 weeks of age.
- Immunization on this schedule resulted in a strong, and persistent, antibody response to circovirus demonstrated with IFA titers remaining $\geq 1:5140$.
- No evidence of circovirus viremia was detected through 18 weeks of age.
- No cases of porcine circovirus associated disease-acute pulmonary edema (PCVAD-APE) appeared in the pigs vaccinated on this younger protocol.
- Most important, mortality for all reasons declined in finisher to levels that were lower than had been achieved prior to September 2009. Mortality in finisher flow is $\sim 2\%$ at present. In addition, ADG in groups vaccinated on the younger age schedule has shown a 9% improvement to date.
- A possible negative consequence of vaccination at weaning appears to be inordinate stress for the pigs at a most vulnerable transition.

Discussion

Immunologic management of circovirus infection and disease in production settings is complex, certainly not the simple “vaccinate and disease disappears” result as it initially appeared when vaccines became available. The inter-relationship between pathogen, environmental load, host immunity and possibly virus variant combine in a way that recommends vigilant assessment of vaccine response. The environmental persistence and exposure is a constant risk of infection. This is mitigated only if nearly all the population is actively immunized, unlike successful immunization controls for other diseases in which just

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tilting the balance to prevent inter-animal transmission constitutes success. The first critical indicator in failure to immunize is demonstration of viremia in vaccinated, and presumed immunized, animals. In this case and in others our clinical observation is that viremia with PCV2b is predictive of suboptimal growth and elevated mortality.

A second clinical method of value is demonstration of the accomplishment of immunization with a strong post-vaccination antibody response. Rather than presuming vaccination efficacy and population coverage, evaluating vaccinated populations for viremia as a routine part of clinical workup is justified.

