UAB
Universitat Autònoma de Barcelona

Pathological findings in pigs affected by inclusion body rhinitis

FACULTAT DE VETERINÀRIA

Student: Núria Isabel Molina
Professors: Jorge Martínez and Joaquim Segalés
Veterinary Final Degree Project Report
June 2025 Submission
Experimental – Retrospective

TABLE OF CONTENTS

1. Introduction 3
2. Hypothesis and objectives 4
3. Materials and methods 4
3.1 Data collection and processing 5
3.2 Clinical and pathological features in selected pigs 6
3.3 Statistical analyses 7
4. Results 7
5. Discussion 9
6. Conclusions 11
7. References 12
8. Appendix 15

1. Introduction

Rhinitis is defined as inflammation of the mucous membrane lining the nasal cavity (Beard, 2014). Most of the scientific swine literature focuses on atrophic rhinitis, as it is the most significant and widely studied form of rhinitis in pigs. Consequently, one of the most studied diseases causing rhinitis is progressive atrophic rhinitis, triggered by toxigenic strains of an important swine pathogen, *Pasteurella multocida* type D (Kloos *et al*., 2015). Also *Bordetella bronchiseptica* has been involved in atrophy of nasal turbinates within the so-called regressive atrophic rhinitis (Z. Wang *et al*., 2020).

Another disease characterized by nasal turbinates inflammation is inclusion body rhinitis (IBR), which is caused by a *Porcine cytomegalovirus* (PCMV). This virus belongs to the *Betaherpesvirinae* subfamily within the *Herpesviridae* family. Infection with PCMV was originally denominated as "inclusion body rhinitis" based on the histopathological changes observed in cytomegalic cells of the nasal mucosa of affected pigs. Affected animals have basophilic intranuclear inclusion bodies (8–12 μm) in cells of the nasal mucosa, mainly in submucosal glands, but inclusion bodies can be also present in other tissues (Basso *et al*., 2017).

PCMV is widespread worldwide and has a high prevalence in swine populations. Even though PCMV is ubiquitous in pig populations (Martín-Valls *et al*., 2022), only severe systemic disease develops in neonates or young individuals in naïve herds. Furthermore, congenital infection can lead to reproductive losses due to foetal mortality (De Maio *et al*., 2021). In immunologically naïve herds, the virus causes foetal and piglet mortality, stunted growth, rhinitis, pneumonia, and occasionally neurological signs, but the most common clinical signs include sneezing, nasal discharge, coughing and dyspnoea (Mettenleiter *et al*., 2019).

PCMV primarily replicates in the nasal mucosa and/or the lachrymal or Harderian glands. Secondary replication varies with age and may involve the nasal glands, lachrymal and Harderian glands, kidney tubules, and, less commonly, the epididymis and oesophageal mucous glands (Fiebig *et al*., 2018). In animals over three weeks of age, viremia occurs between 14-21 days post-infection, and nasal shedding lasts from 10 to 30 days. Moreover, the incubation period ranges from 10 to 20 days (Edington *et al*., 1977).

Natural PCMV infection is restricted to pigs, and the virus does not replicate in other species. The most common mode of transmission is horizontally, via the oronasal route, but congenital transmission is also possible. The virus is shed through nasal and ocular secretions, urine, and cervical fluids (Mettenleiter *et al*., 2019). Most pigs begin shedding PCMV in nasal secretions when they are between 3 and 6 weeks of age and reach a maximum between 5 and 8 weeks (Plowright *et al*., 1976). Congenitally infected pigs may shed the virus lifelong. During viremia, affected animals can show signs of depression and anorexia. The disease tends to be self-limiting, at least in pigs over three weeks of age. There is still no vaccine or treatment available for PCMV infection, making difficult the elimination of the virus from herds (Mettenleiter *et al*., 2019).

As previously mentioned, PCMV is highly prevalent among the worldwide swine population, with herd prevalence exceeding 90% in Europe, North America, Japan and the United Kingdom (Fryer *et al*., 2001; Mettenleiter *et al*., 2019). Some studies are carried out to strengthen this affirmation. One study in China also supported the widespread distribution of PCMV in southwest China (Liu *et al*., 2013). Moreover, one study carried out in Spain assessed the prevalence of this virus and tried to associate the presence of different respiratory virus in nursery farms displaying clinical signs

compatible with swine influenza. The work included 55 cases of respiratory disorders and PCMV was detected in 40 of them. Other detected pathogens in this study were *Porcine reproductive and respiratory syndrome virus* (PRRSV), *Porcine respirator coronavirus* (PRCV), *Swine orthopneumovirus* (SOV), *Porcine circovirus 2* (PCV2) and *Porcine circovirus 3 (PCV3)* (Martín-Valls *et al*., 2022).

One of the most important characteristics of PCMV is its capacity to induce latency in those animals that survive primary infections (Mettenleiter *et al*., 2019). For this reason, this etiological agent is thoroughly investigated in xenotransplantation because of the difficulty of detection in an organ donor swine due to latency. Xenotransplantation is an effective solution to address the scarcity of tissues for human transplantations, however, it also entails certain risks. Owing to the high rate of PCMV infections, this has become a potential threat for those treatments (Liu *et al*., 2016). It has been demonstrated that PCMV has an important impact on transplant survival, highlighting the necessity to eliminate it from donor pigs (Denner *et al*., 2020).

This virus has also an immunosuppressive effect, and affected animals are easily co-infected with other pathogens (Liu *et al*., 2013). However, the mechanisms by which immunosuppression occurs are not completely understood (Cibulski *et al*., 2015).

So, as PCMV is an important virus that can be found worldwide and sometimes is underestimated by the presence of other agents, the aim of this experimental – retrospective study was to obtain information about inclusion body rhinitis through the review of all porcine necropsies carried out by the Veterinary Pathology Diagnostic Service of the Autonomous University of Barcelona (UAB) between the years 2010 and 2022. These necropsies were analysed using the UAB database called Diagnet, which contains all the information from performed necropsies.

2. Hypothesis and objectives

PCMV is a well-known pathogen of swine but its impact on the industry is not well-determined. Despite its potential relevance, this virus may interact with other pathogens and lesions observed at necropsy are usually underestimated. Therefore, the objective of this study was to assess the relationship of IBR in pigs with other findings observed in necropsies. Consequently, two different control groups were required. Emphasis was focused on the prevalence of IBR and its concomitance with other lesions and pathogens.

The hypothesis of this study is that animals with IBR are more likely to display non-nasal specific lesions at necropsy and may interact with other well-established pathogens of swine (e.g., PRRSV and PCV2).

3. Materials and methods

The study was carried out through a retrospective analysis of all porcine necropsies performed between 2010 and 2022 by the Veterinary Pathology Diagnostic Service of the Autonomous University of Barcelona. During this period, a total of 1,621 necropsies were undertaken by different professionals, and each necropsy report was individually reviewed in detail for the purposes of this study.

3.1 Data collection and processing

To this end, three study groups were established.

1. Group 1: Animals diagnosed as suffering from IBR (it included pigs with intranuclear inclusion bodies in submucosal glands and non-suppurative inflammation of the nasal turbinates). As shown in Figure 1.
2. Group 2: Animals that had non-suppurative rhinitis without inclusion bodies in the nasal turbinates.
3. Group 3: Animals without rhinitis nor intranuclear inclusion bodies in the nasal turbinates.

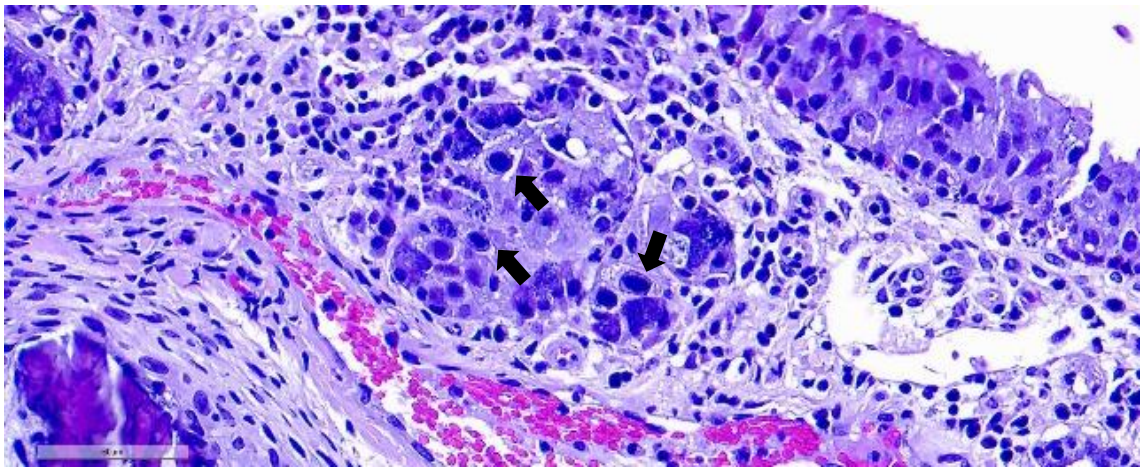

Figure 1. Nasal mucosa from a PCMV affected pig. Large intranuclear inclusions (arrows) are abundant in the nasal mucous glands. Lymphoplasmacytic inflammation is also observed in the lamina propria.

For the purpose of establishing these three groups, all necropsies included in the analysis were initially examined to determine which animals had rhinitis and which did not. Subsequently, a second screening was conducted on the animals that exhibited rhinitis during the initial review to determine which of them also presented PCMV inclusion bodies in the nasal turbinates.

From this initial review, we concluded that out of the 1,621 necropsies examined, 594 animals exhibited rhinitis, and only 38 of these 594 had also inclusion bodies and were, therefore, diagnosed as IBR affected pigs.

At this stage, we had already defined the first group of study; however, additional revisions were necessary to establish the other two groups. As previously mentioned, the animals belonging to the second group exhibited non-suppurative rhinitis. Therefore, this group consisted of 556 necropsied pigs that suffered from rhinitis without inclusion bodies in the nasal turbinates. To select the animals for this group, we subsequently chose those animals between 14 and 60 days of age, and only one animal per farm. The same criteria were applied to the third group that was composed by 1,027 necropsied pigs in which no rhinitis was observed.

Finally, for the purpose of overall analyses, we included in the study 38 animals with IBR (Group 1), as well as 47 animals with rhinitis (Group 2) and 48 animals without rhinitis nor intranuclear inclusion bodies in the nasal turbinates (Group 3).

3.2 Clinical and pathological features in selected pigs

The same clinical and pathological findings (designated as "variables" from now on) were studied for the three groups. For each necropsy, we noted the animal age, sex, weight, origin (if available), and eventual complementary tests. For this study it was only required the results of the immunohistochemistry (IHC) and/or RT-qPCR (retrotranscriptase quantitative polymerase chain reaction) for PRRSV and PCV2 carried out in the selected cases.

Age (in days) and weight (in kilograms) were studied as continuous variables. Categorical variables included farm, sex, PRRSV infection, PCV2 infection and a wide range of pathological findings; those latter ones are presented in Table 1.

Table 1. Summary of the pathological findings observed during the study, categorized by systems.

System	Pathological findings
Respiratory	Bronchopneumonia, interstitial pneumonia, pulmonary sequestration/abscesses, lung interstitial edema, pulmonary/alveolar edema, nasal turbinate atrophy, fibrinous pleuritis
Cardiovascular	Pericarditis, serous atrophy of subepicardial fat
Hepatic	Hepatic lipidosis, hepatitis, hepatic glycogenosis, jaundice
Gastrointestinal	Gastritis, nodular lymphoid hyperplasia in colon, enteritis, atrophy and fusion of intestinal villi, enterocolitis, colitis, erosion/ulcer of the esophageal portion of the stomach, typhlocolitis
Immunological	Thymic atrophy, lymphadenitis and lymphocyte depletion, tonsillitis
Nervous	Meningitis, meningoencephalitis
Musculoskeletal	Tenosynovitis, polyarthritis
Urinary	Nephritis
Skin/subcutis	Subcutaneous abscesses, palpebral edema
Systemic/General	Growth retardation, sepsis, emaciation, peritonitis

PRRSV is one of the most important pathogens in swine industry because of its impact on swine health and the great economic losses (H. Wang *et al*., 2021). PCV2 is also considered one of the most economically important pathogens for the industry and is ubiquitous in most pig farms (Sagrera *et al*., 2024). In contrast, PCMV does not usually cause serious diseases on its own, but it can reactivate in situations of immunosuppression. For those reasons, it can be speculated that some indirect relation between these three porcine viruses might exist, despite the lack of strong scientific evidence.

In addition, for the present study, pivot tables were created in Excel using all the information gathered from the necropsies of the three studied groups. These tables were created with the purpose of showing the different percentages that each group had for the different variables studied. The use of Excel pivot tables allowed establishing relations among all studied variables. These tables are provided in the Appendix.

3.3 Statistical analyses

All data analyses carried out in this study were conducted using R Commander (Rcmdr). Those tests were carried out to determine if there was any relation between the variables studied.

The Chi-square ($\chi 2$) test was selected at first to conduct this study because of its suitability to analyse categorical datasets. But, as the Chi-square test has some limitations like small sample size, the Fisher's exact test was applied due to low expected frequencies (Kishore & Jaswal, 2023). These two different tests were applied to all the categorical variables. A significance level of 0.05 was selected and p-values <0.05 ($p < 0.05$) were considered statistically significant.

Once those tests were conducted, if Fisher's exact test showed a p-value less than 0.05, a pair-wise Fisher's exact test was applied. This post hoc named pairwise performs comparisons between proportions, following a significant Fisher's exact test of homogeneity.

Furthermore, for the continuous variables, normality was first assessed using the Shapiro-Wilk test (significance level set at $p < 0.05$). If the data did not follow a normal distribution, the non-parametric Kruskal-Wallis test was applied to evaluate differences between groups.

4. Results

The final data collection comprised 41 different variables. Overall results are summarized in the Appendix, which includes the frequency of the different variables analyzed for each study group.

As tables of Appendix show, the most observed lesions in Group 1 were: interstitial pneumonia, bronchopneumonia, serous atrophy of subepicardial fat, gastritis, and atrophy and fusion of villi, which are indicated for all the three groups in Figure 2.

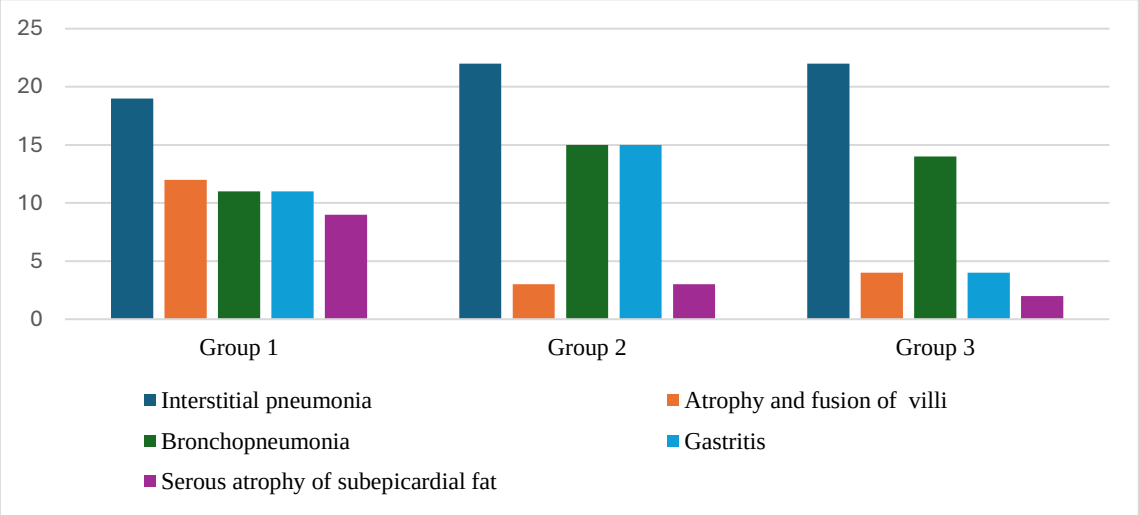

Figure 2. Proportion of cases in which each lesion: pneumonia, bronchopneumonia, serous atrophy of subepicardial fat, gastritis, and atrophy and fusion of villi, was identified in each group. The numbers in the Y-axis indicate the number of cases in which each lesion was observed.

As depicted in Figure 2, the most common lesion was interstitial pneumonia accompanied by bronchopneumonia with similar percentages among groups; these lesions did not stand out due to their relatively homogeneous distribution across the groups. Interestingly, gastritis was especially prevalent in Groups 1 and 2. Serous atrophy of subepicardial fat and atrophy and fusion of intestinal villi was observed at a higher percentage in pigs from Group 1. Other lesions had much lower frequencies of presentation.

Of all variables studied, statistically significant differences were found only in a few of them, namely atrophy and fusion of intestinal villi, serous atrophy of subepicardial fat, and gastritis (Table 2). Since the first statistical approach did not specify where the statistical significance lay, post hoc tests were required to identify the differences among specific groups.

Table 2. Results of the Chi-square ($\chi 2$) and the Fisher's exact test. The results indicate that the variables serous atrophy of subepicardial fat, atrophy and fusion of intestinal villi, and gastritis were statistically significant, as $p < 0.05$.

		Serous atrophy of subepicardial fat		**Atrophy and fusion of intestinal villi**		**Gastritis**	
		Yes	No	Yes	No	Yes	No
Groups	**1**	9	29	12	26	11	27
	2	3	44	3	44	15	32
	3	2	46	4	44	4	44
		$X^2 = 9.903$, $p = 0.0071$		$X^2 = 13.067$, $p = 0.0015$		$X^2 = 8.804$, $p = 0.0123$	
		Fisher's exact test, $p = 0.0103$		Fisher's exact test, $p = 0.0030$		Fisher's exact test, $p = 0.0085$	

Nine animals with IBR exhibited serous atrophy of subepicardial fat, which represented 64.29% (9/14) of all studied cases in the three groups displaying this lesion. A similar pattern was found for atrophy and fusion of intestinal villi. In this case, twelve animals with IBR showed this lesion, accounting for 63.15% (12/19) of the total number of cases with this lesion. In contrast, gastritis was found in a 36.67% (11/30) and 50 % (15/30) in Groups 1 and 2, but only in 9% (4/44) in Group 3. Detailed results and values are provided in the Appendix.

Pairwise Fisher's exact tests were conducted to assess the distribution of specific lesions among the diagnostic groups, including serous atrophy of subepicardial fat. After adjusting for multiple comparisons with the Holm method, for serous atrophy of subepicardial fat the only statistically significant difference was observed between Group 1 and Group 3 ($p.adj = 0.0283$). No significant differences were observed between Group 1 and Group 2 or between Group 2 and Group 3. Detailed results and values are provided in Table 3.

Moreover, pairwise Fisher's exact tests were conducted to assess differences in the prevalence of intestinal villous atrophy and fusion, as well as gastritis, among the three groups. Regarding villous atrophy and fusion, comparisons between Group 1 and Group 2 and between Group 1 and Group 3 yielded statistically significant differences ($p.adj$ =

0.0107 and *p.adj = 0.021*, respectively). By contrast, the comparison between Groups 2 and 3 was not significant, indicating a similar prevalence of intestinal atrophy and fusion in those two groups. These results indicate that the prevalence of villous atrophy and fusion was markedly higher in Group 1 than in Groups 2 and 3.

In case of gastritis, the comparison between Group 1 and Group 2 was not significant, suggesting a similar prevalence of gastritis in these groups. However, comparisons between Group 1 and Group 3 and between Group 2 and Group 3 were statistically significant (*p.adj = 0.0406* and *p.adj = 0.0145*, respectively). These findings indicate that animals in Groups 1 and 2 exhibited a significantly higher prevalence of gastritis than those in Group 3.

Table 3. Pairwise Fisher's exact test results for serous atrophy of subepicardial fat, gastritis, and intestinal villous atrophy and fusion.

	Group 1	Group 2	n	p-value	p-value adjusted	significance
Serous atrophy of subepicardial fat	Group 1	Group 2	85	0.0299	**0.0598**	**ns**
	Group 1	Group 3	86	0.00942	**0.0283**	*
	Group 2	Group 3	95	0.677	**0.677**	**ns**
Intestinal villous atrophy and fusion	Group 1	Group 2	85	0.00356	**0.0107**	*
	Group 1	Group 3	86	0.0105	**0.021**	*
	Group 2	Group 3	95	1	**1**	**ns**
Gastritis	Group 1	Group 2	85	0.816	**0.816**	**ns**
	Group 1	Group 3	86	0.0203	**0.0406**	*
	Group 2	Group 3	95	0.00482	**0.0145**	*

- **n**: The number of subjects in each comparison.
- **p-value**: The raw p-value from the Fisher's Exact Test for each pairwise comparison.
- **p-value adjusted**: The adjusted p-value using the Holm correction method to account for multiple comparisons.
- **Significance**: Indicates whether the result is statistically significant:
  - **"*"** indicates statistical significance (p-value < 0.05).
  - **"ns"** indicates "not significant" (p-value ≥ 0.05).

In addition, no statistically significant differences were found between the different groups of study and the presence of PCV2 and PRRSV. The same happened with the other variables mentioned above and with the continuous variables.

5. Discussion

PCMV has been studied for years, but its interactions with other viruses are not as well-known as others. In addition, as it is not a virus that causes high mortalities or severe disease, its infection is not usually reported. However, this virus is characterized by expressing reduced body condition, apathy and anorexy (Basso *et al*., 2017).

PCMV has been associated with concomitant infections and its potential role as an immunosuppressive agent has been discussed. Specifically, it has been demonstrated that PCMV is able to infect and propagate in monocytes, and it has been shown that such infection reduces the expression of IL-8 and TNF-α, pro-inflammatory cytokines, and increases IL-10, a cytokine with anti-inflammatory/regulatory functions. These data can

reinforce the hypothesis that animals affected by PCMV are more sensitive to coinfections (Kavanová *et al*., 2018)**.** That was the reason for studying potential coinfection with two of the most important swine viral pathogens, PRRSV and PCV2. However, the frequency of coinfection was not different from that of animals showing non-IBR rhinitis and those without rhinitis.

Obtained results suggest an indirect relationship between PCMV and the atrophy and fusion of intestinal villi in studied pigs. In fact, a previous study reported that PCMV infection was associated with severe diarrhoea and atrophy and fusion of villi caused by *Cystoisospora suis* (Basso *et al*., 2017). In this report, PCMV was considered to suppress cellular immunity, facilitating the proliferation of this enteric pathogen and exacerbating the intestinal lesions, including the atrophy and fusion of villi. The anorexia in this case was a clinical sign of affected pigs, but the atrophy and fusion of villi were attributed to the coccidia (Basso *et al*., 2017). However, this parasite was not observed in any of our cases. In contrast, statistically significant differences support a potential association between IBR and intestinal mucosal damage.

In porcine periweaning failure to thrive syndrome (PFTS) investigations, PCMV was detected in pigs with atrophy and fusion of villi and thymus atrophy, but without any direct statistical correlation with the syndrome (Pallarés & Ramis, 2019). Some studies indicate that post-weaning anorexia could have some influence on the villi structure and, therefore, it is expectable to find this lesion in PFTS cases (Huang *et al*., 2012; Moeser *et al*., 2012; Huang & Huang, 2015). However, it must be emphasized that PFTS cases are diagnosed by ruling out infectious, management and nutritional causes, and the eventual presence of PCMV would, in consequence, discard PFTS.

Atrophy and fusion of intestinal villi and serous atrophy of subepicardial fat are different lesions, but they can be connected by a common pathological mechanism such as malnutrition or anorexia. It is documented that malnutrition is associated with a reduction in height and atrophy of the intestinal villi (Shaw *et al*., 2012). Studies in humans have shown that undernourished individuals are more likely to develop villous atrophy (Hossain *et al*., 2021).

Serous atrophy of subepicardial fat is characterized by the loss of fat reserves surrounding the heart, turning gelatinous and translucent. This is a classic sign when animals are suffering anorexia or malnutrition, and eventual cachexia, due to the mobilization of energetic reserves. This finding is usually present in chronic diseases or in some processes that can complicate the correct ingestion or absorption of nutrients (Soto *et al*., 2022). For this reason, it can be possible to suspect a link between this pathological finding and the anorexia expressed by PCMV. One study in reindeers concluded that prolonged malnutrition could exacerbate serous atrophy of subepicardial and bone marrow fat, considering a significant indication of lack of energy as the immediate cause of death (Josefsen *et al*., 2007).

Gastritis was significantly less prevalent in animals from Group 3 compared to those in Groups 1 and 2. This finding suggests that the presence of rhinitis is associated with a higher frequency of gastritis compared to animals without rhinitis. No significant association was found between the presence of rhinitis with inclusion bodies and gastritis, as statistical analysis showed no meaningful differences between Groups 1 and 2. These results suggested that rhinitis may be a contributing factor to an increased risk of gastric lesions or they have an unknown etiology in common. As previously mentioned, the most common lesions observed in PFTS affected pigs were villous atrophy of the small

intestine and gastritis, among others. It is possible that those gastrointestinal lesions presented in those pigs were secondary to anorexia. Notably, the same study that identified these lesions as the most common in PFTS also occasionally reported intranuclear inclusion bodies contained in the nasal glandular cells in affected animals (Huang *et al*., 2012; Huang & Huang, 2015).

Ultimately, the concomitance of IBR with these lesions could be associated with PFTS. Nevertheless, the true aetiopathogenesis of PFTS remains unresolved, and the involvement of an unknown pathogen cannot be completely ruled out (Franzo *et al*., 2019).

6. Conclusions

The present retrospective study confirmed that serous atrophy of subepicardial fat and atrophy and fusion of intestinal villi were significantly more common in pigs with PCMV infections than in both control groups. In contrast, gastritis was significantly more frequent in Group 1 and Group 2 compared to Group 3.

Those findings demonstrate a strong statistical link between IBR and systemic signs of wasting like serous fat atrophy and villous atrophy. These results suggest that PCMV is not always causing a subclinical infection in pigs without further consequences, but may contribute to multisystemic wasting under field conditions.

Obtained results emphasize the importance of performing routine histopathological evaluations and statistical analyses to investigate concurrent lesions in swine populations. Additional studies with larger sample sizes would be necessary to further elucidate causal relations and to evaluate their implications for herd health, productivity, and disease management strategies.

7. References

Basso, W., Marti, H., Hilbe, M., Sydler, T., Stahel, A., Bürgi, E., & Sidler, X. (2017). Clinical cystoisosporosis associated to porcine cytomegalovirus (PCMV, Suid herpesvirus 2) infection in fattening pigs. *Parasitology International*, *66*(6), 806–809. https://doi.org/10.1016/j.parint.2017.09.007

Beard, S. (2014). Rhinitis. *Primary Care: Clinics in Office Practice, 41*(1), 33–46. https://doi.org/10.1016/j.pop.2013.10.005

Cibulski, S. P., Pasqualim, G., Teixeira, T. F., Varela, A. P. M., Dezen, D., Holz, C. L., Franco, A. C., & Roehe, P. M. (2015). Porcine cytomegalovirus infection is not associated to the occurrence of post-weaning multisystemic wasting syndrome. *Veterinary Medicine and Science*, *1*(1), 23–29. https://doi.org/10.1002/vms3.5

De Maio, F. A., Winter, M., Abate, S., Birochio, D., Iglesias, N. G., Barrio, D. A., & Bellusci, C. P. (2021). Molecular detection of Porcine cytomegalovirus (PCMV) in wild boars from Northeastern Patagonia, Argentina. *Revista Argentina de Microbiologia*, *53*(4), 325–332. https://doi.org/10.1016/j.ram.2020.12.003

Denner, J., Längin, M., Reichart, B., Krüger, L., Fiebig, U., Mokelke, M., Radan, J., Mayr, T., Milusev, A., Luther, F., Sorvillo, N., Rieben, R., Brenner, P., Walz, C., Wolf, E., Roshani, B., Stahl-Hennig, C., & Abicht, J. M. (2020). Impact of porcine cytomegalovirus on long-term orthotopic cardiac xenotransplant survival. *Scientific reports*, *10*(1), 17531. https://doi.org/10.1038/s41598-020-73150-9

Edington, N., Watt, R. G., & Plowright, W. (1977). Experimental transplacental transmission of porcine cytomegalovirus. *The Journal of hygiene*, *78*(2), 243–251. https://doi.org/10.1017/s0022172400056138

Fiebig, U., Abicht, J. M., Mayr, T., Längin, M., Bähr, A., Guethoff, S., Falkenau, A., Wolf, E., Reichart, B., Shibahara, T., & Denner, J. (2018). Distribution of Porcine Cytomegalovirus in Infected Donor Pigs and in Baboon Recipients of Pig Heart Transplantation. *Viruses*, *10*(2), 66. https://doi.org/10.3390/v10020066

Franzo, G., Kekarainen, T., Llorens, A., Correa-Fiz, F., & Segalés, J. (2019). Exploratory metagenomic analyses of periweaning failure-to-thrive syndrome-affected pigs. *The Veterinary record*, *184*(1), 25. https://doi.org/10.1136/vr.105125

Fryer, J. F. L., Griffiths, P. D., Fishman, J. A., Emery, V. C., & Clark, D. A. (2001). Quantitation of porcine cytomegalovirus in pig tissues by PCR. *Journal of Clinical Microbiology*, *39*(3), 1155–1156. https://doi.org/10.1128/JCM.39.3.1155-1156.2001

Hossain, M. S., Begum, S. M. K. N., Rahman, M. M., Mazumder, R. N., Parvez, M., Gazi, M. A., Hasan, M. M., Fahim, S. M., Das, S., Mahfuz, M., Sarker, S. A., & Ahmed, T. (2021). Alterations in the histological features of the intestinal mucosa in malnourished adults of Bangladesh. *Scientific reports*, *11*(1), 2355. https://doi.org/10.1038/s41598-021-82079-6

Huang, Y., Gauvreau, H., & Harding, J. (2012). Diagnostic investigation of porcine periweaning failure-to-thrive syndrome: Lack of compelling evidence linking to common porcine pathogens. *Journal of Veterinary Diagnostic Investigation*, *24*(1), 96–106. https://doi.org/10.1177/1040638711425939

Huang, Y., & Huang, Y. (2015). Pathological Features and Proposed Diagnostic Criteria of Porcine Periweaning Failure-to-Thrive Syndrome. *Veterinary Pathology*, *52*(3), 489–496. https://doi.org/10.1177/0300985814542810

Josefsen, T. D., Sørensen, K. K., Mørk, T., Mathiesen, S. D., & Ryeng, K. A. (2007). Fatal inanition in reindeer (Rangifer tarandus tarandus): pathological findings in completely emaciated carcasses. *Acta veterinaria Scandinavica*, *49*(1), 27. https://doi.org/10.1186/1751-0147-49-27

Kavanová, L., Moutelíková, R., Prodělalová, J., Faldyna, M., Toman, M., & Salát, J. (2018). Monocyte derived macrophages as an appropriate model for porcine cytomegalovirus immunobiology studies. *Veterinary Immunology and Immunopathology*, *197*, 58–62. https://doi.org/10.1016/j.vetimm.2018.01.008

Kishore, K., & Jaswal, V. (2023). Statistics Corner: Chi-squared Test. *Journal of Postgraduate Medicine, Education and Research*, *57*(1), 40–44. https://doi.org/10.5005/jp-journals-10028-1618

Kloos, B., Chakraborty, S., Lindner, S. G., Noack, K., Harre, U., Schett, G., Krämer, O. H., & Kubatzky, K. F. (2015). Pasteurella multocida toxin- induced osteoclastogenesis requires mTOR activation. *Cell Communication and Signaling*, *13*(1), 40. https://doi.org/10.1186/s12964-015-0117-7

Liu, X., Liao, S., Xu, Z., Zhu, L., Yang, F., & Guo, W. (2016). Identification and Analysis of the Porcine MicroRNA in Porcine Cytomegalovirus-Infected Macrophages Using Deep Sequencing. *PloS one*, *11*(3), e0150971. https://doi.org/10.1371/journal.pone.0150971

Liu, X., Liao, S., Zhu, L., Xu, Z., & Zhou, Y. (2013). Molecular epidemiology of porcine Cytomegalovirus (PCMV) in Sichuan Province, China: 2010-2012. *PloS one*, *8*(6), e64648. https://doi.org/10.1371/journal.pone.0064648

Martín-Valls, G. E., Li, Y., Díaz, I., Cano, E., Sosa-Portugal, S., & Mateu, E. (2022). Diversity of respiratory viruses present in nasal swabs under influenza suspicion in respiratory disease cases of weaned pigs. *Frontiers in veterinary science*, *9*, 1014475. https://doi.org/10.3389/fvets.2022.1014475

Mettenleiter, T. C., Ehlers, B., Müller, T., Yoon, K. J., & Teifke, J. P. (2019). Herpesviruses. In J. J. Zimmerman, L. A. Karriker, A. Ramirez, K. J. Schwartz, G. W. Stevenson, & J. Zhang (Eds.), *Diseases of swine* (11th ed., pp. 548–575). Wiley-Blackwell. https://doi.org/10.1002/9781119350927.ch35

Moeser, A. J., Borst, L. B., Overman, B. L., & Pittman, J. S. (2012). Defects in small intestinal epithelial barrier function and morphology associated with peri-weaning failure to thrive syndrome (PFTS) in swine. *Research in Veterinary Science*, *93*(2), 975–982. https://doi.org/10.1016/j.rvsc.2012.01.003

Pallarés, F. J., & Ramis, G. (2019, 16 de marzo). *Actualización sobre el síndrome de fallo de desarrollo peridestete (PFTS)*. *Artículo científico*, 1-5. Facultad de Veterinaria, Universidad de Murcia. https://portalinvestigacion.um.es/documentos/63c0b35d3df4c204fbb03501

Plowright, W., Edington, N., & Watt, R. G. (1976). The behaviour of porcine cytomegalovirus in commercial pig herds. *The Journal of hygiene*, *76*(1), 125–135. https://doi.org/10.1017/s0022172400055017

Sagrera, M., Garza-Moreno, L., Sibila, M., Oliver-Ferrando, S., Cárceles, S., Casanovas, C., Prieto, P., García-Flores, A., Espigares, D., & Segalés, J. (2024). Frequency of PCV-2 viremia in nursery piglets from a Spanish swine integration system in 2020 and 2022 considering PRRSV infection status. *Porcine health management*, *10*(1), 4. https://doi.org/10.1186/s40813-024-00354-0

Shaw, D., Gohil, K., Basson, M. D., & Osawa, J. S. (2012). Intestinal mucosal atrophy and adaptation. *World Journal of Gastroenterology, 18*(44), 6357–6375. https://doi.org/10.3748/wjg.v18.i44

Soto, M. E., Pérez-Torres, I., Rubio-Ruiz, M. E., Manzano-Pech, L., & Guarner-Lans, V. (2022). Interconnection between cardiac cachexia and heart failure—Protective role of cardiac obesity. *Cells, 11*(6), 1039. https://doi.org/10.3390/cells11061039

Wang, H., Xu, Y., & Feng, W. (2021). Porcine reproductive and respiratory syndrome virus: Immune escape and application of reverse genetics in attenuated live vaccine development. *Vaccines, 9*(5), 480. https://doi.org/10.3390/vaccines9050480

Wang, Z., Zhang, Y., Wang, L., Wei, J., Liu, K., Shao, D., Li, B., Liu, L., Widén, F., Ma, Z., & Qiu, Y. (2020). Comparative genomic analysis of Bordetella bronchiseptica isolates from the lungs of pigs with porcine respiratory disease complex (PRDC). *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*, *81*, 104258. https://doi.org/10.1016/j.meegid.2020.104258

8. Appendix

Table 4. Prevalence of pathological lesions observed in study groups.

	Group 1	Group 2	Group 3
Bronchopneumonia	11/38 (27.5%)	15/47 (37.5%)	14/48 (35%)
Interstitial pneumonia	19/38 (30.16%)	22/47 (34.92%)	22/48 (34.92%)
Serous atrophy of subepicardial fat	9/38 (64.29%)	3/47 (21.42%)	2/48 (14.29%)
Hepatic lipidosis	1/38 (16.7%)	3/47 (50%)	2/48 (33.3%)
Gastritis	11/38 (36.67%)	15/47 (50%)	4/48 (13.33%)
Enteritis	4/38 (28.57%)	6/47 (42.86%)	4/48 (28.57%)
Atrophy and fusion of intestinal villi	12/38 (63.15%)	3/47 (15.79%)	4/48 (21.06%)
Hepatitis	2/38 (33.33%)	4/47 (66.67%)	0/48 (0%)
Subcutaneous abscesses	1/38 (100%)	0/47 (0%)	0/48 (0%)
Enterocolitis	3/38 (27.27%)	4/47 (36.36%)	4/48 (36.36%)
Pericarditis	2/38 (33.33%)	2/47 (33.33%)	2/48 (33.33%)
Fibrinous pleuritis	4/38 (36.36%)	3/47 (27.27%)	4/48 (36.36%)
Septicemia	1/38 (50%)	0/47 (0%)	1/48 (50%)
Pulmonar abscesses	1/38 (100%)	0/47 (0%)	0/48 (0%)
Colitis	5/38 (27.78%)	5/47 (27.78%)	8/48 (44.44%)
Hepatic glycogenosis	2/38 (50%)	2/47 (50%)	0/48 (0%)
Erosion of the esophageal portion of the stomach	1/38 (11.11%)	4/47 (44.44%)	4/48 (44.44%)
Nasal turbinate atrophy	2/38 (20%)	7/47 (70%)	1/48 (10%)
Meningitis	4/38 (44.44%)	4/47 (44.44%)	1/48 (11.11%)
Jaundice	1/38 (50%)	1/47 (50%)	0/48 (0%)
Palpebral edema	1/38 (50%)	0/47 (0%)	1/48 (50%)
Typhlocolitis	1/38 (20%)	3/47 (60%)	1/48 (20%)
Tenosynovitis	1/38 (100%)	0/47 (0%)	0/48 (0%)
Peritonitis	1/38 (20%)	3/47 (60%)	1/48 (20%)
Tonsillitis	1/38 (33.33%)	1/47 (33.33%)	1/48 (33.33%)
Interstitial edema	1/38 (50%)	1/47 (50%)	0/48 (0%)
Pulmonary edema	1/38 (20%)	2/47 (40%)	2/48 (40%)

Nephritis	1/38 (33.33%)	1/47 (33.33%)	1/48 (33.33%)
Meningoencephalitis	1/38 (25%)	2/47 (50%)	1/48 (25%)
Polyarthritis	1/38 (25%)	0/47 (0%)	3/48 (75%)
Nodular lymphoid hyperplasia in colon	3/38 (100%)	0/47 (0%)	0/48 (0%)
Thymic atrophy	2/38 (33.33%)	3/47 (50%)	1/48 (16.67%)
Lymphadenitis	2/38 (40%)	2/47 (40%)	1/48 (20%)
Lymphoid depletion	4/38 (16%)	10/47 (40%)	11/48 (44%)
Growth retardation	6/38 (23.08%)	12/47 (46.15%)	8/48 (30.77%)
Emaciation	26/38 (33.77%)	25/47 (32.46%)	26/48 (33.77%)
PRRSV	11/38 (35.48%)	11/47 (35.48%)	9/48 (29.03%)
PCV2	4/38 (25%)	5/47 (31.25%)	7/48 (43.75%)
Sex	0 (males):29 (76.32%) 1 (females):9 (23.68%)	0 (males):39 (82.98%) 1 (females):8 (17.02%)	0 (males):39 (81.25%) 1 (females):9 (18.75%)