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Clinical and pathological aspects of an outbreak of *Streptococcus suis* serotype 9 infection in pigs[1]

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ABSTRACT.- Hammerschmitt M.E., Schwertz C.I., Lopes B.C., Pereira P.R., Frandoloso R. & Driemeier D. 2022. **Clinical and pathological aspects of an outbreak of *Streptococcus suis* serotype 9 infection in pigs.** *Pesquisa Veterinária Brasileira 42:e07004, 2022.* Setor de Patologia Veterinária, Departamento de Patologia Clínica Veterinária, Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves 9090, Prédio 42505, Porto Alegre, RS 91540-000, Brazil. E-mail: marciahammer@hotmail.com

Streptococcus suis is a Gram-positive pathogen that inhabits the upper respiratory tract and can cause severe systemic inflammatory disease in pigs, mainly during the nursery phase. *Streptococcus suis* is a reemergent pathogen, and outbreaks of its inducing disease represent significant economic losses for the pig industry worldwide. In this study, we described the clinical, pathological, and molecular aspects of an outbreak of *S. suis* infection with atypically high mortality. The outbreak occurred in nursery farms integrated into a cooperative in the state of Paraná, Brazil. Of the 30 nurseries, 10 were severely affected by the pathogen and had high economic losses. Clinical signs usually started approximately 10 days after weaning and were mainly characterized by acute nervous and locomotor disorders. The mortality of the affected batches usually ranged between 8% and 10%, but in some cases, it reached 18%. Nine piglets were submitted to *post mortem* examination. Macroscopically, the synovial joints were enlarged and contained fibrinous exudates. In the central nervous system, there was hyperemia of the leptomeningeal vessels associated with deposition of fibrin and purulent exudate in the leptomeninges. In three piglets, there was thickening of the choroid plexus associated with dilation of the lateral ventricles. Microscopic lesions were characterized mainly by fibrinosuppurative inflammation, which involved the synovial membranes, leptomeninges of the brain, and spinal cord. Furthermore, it also affects the choroid plexus, ependyma, nerve roots, and central canal of the spinal cord. *S. suis* was isolated from the cerebrospinal fluid, meningeal swabs, and/or synovial fluid of 8/9 piglets, and typified as serotype 9 by multiplex PCR.

INDEX TERMS: Swine diseases, nervous system, meningitis, choroiditis, encephalomyelitis, spinal cord, *Streptococcus suis*, pigs.

RESUMO.- [**Aspectos clínicos e patológicos de um surto de infecção por *Streptococcus suis* sorotipo 9 em suínos.**] *Streptococcus suis* é um patógeno Gram positivo que habita o trato respiratório superior e pode causar doença inflamatória sistêmica grave em suínos, principalmente durante a fase de creche. *Streptococcus suis* é um patógeno reemergente e surtos representam perdas econômicas significativas a suinocultura mundial. Neste estudo descrevemos os aspectos clínicos, patológicos e moleculares de um surto de infecção por *S. suis* com mortalidade atipicamente alta. O surto ocorreu em creches integradas a uma cooperativa do estado do Paraná, Brasil. Das 30 creches, 10 foram severamente afetadas pelo patógeno e apresentavam elevadas perdas econômicas. Os sinais clínicos iniciavam em torno de 10 dias após o desmame e eram caracterizados principalmente por sinais clínicos nervosos e locomotores agudos. A mortalidade dos lotes afetados variava entre 8% e 10%, mas em alguns casos ultrapassava 18%. Nove leitões foram submetidos ao exame *post mortem*. Macroscopicamente, as articulações sinoviais

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estavam aumentadas e continham exsudato fibrinoso. No sistema nervoso central havia hiperemia dos vasos leptomeníngeos associada a deposição de fibrina e exsudato purulento nas leptomeninges. Em três leitões havia espessamento do plexo coroide associado a dilatação dos ventrículos laterais. As lesões microscópicas eram caracterizadas principalmente por inflamação fibrinossupurativa que envolvia as membranas sinoviais, as leptomeninges do cérebro e medula espinhal. Além disso, também afetava o plexo coroide, epêndima, raízes nervosas e canal central da medula espinhal. *S. suis* foi isolado do líquido cefalorraquidiano, suabe de meninge e/ou líquido sinovial de 8/9 leitões e tipificado como sorotipo 9 por PCR multiplex.

TERMOS DE INDEXAÇÃO: Doenças de suínos, sistema nervoso, meningite, coroidite, encefalomielite, medula espinhal, *Streptococcus suis*, suínos.

INTRODUCTION

Streptococcus suis is a Gram-positive coccus, previously classified into 35 serotypes, and currently classified into 29 serotypes (Staats et al. 1997, Gottschalk et al. 2007, Kerdsin et al. 2014). In Brazil, meningitis caused by *S. suis* was first diagnosed in 1980 and is enzootic in most industrial pig farms. Several serotypes have been isolated from sick pigs in Brazil: 1, 2, ½, 3, 5, 6, 7, 8, 9, 11, 14, 18, 27, and 28 and *S. suis* serotype 2 is the most prevalent serotype in Brazil (Pagnani et al. 2002, Costa et al. 2005, Matajira et al. 2020).

Piglets are infected with *S. suis* at birth, as they pass through the vaginal canal, probably through the respiratory route. Horizontal transmission is highly important, especially during outbreaks, when sick pigs release a high number of bacteria, thereby increasing transmission through direct contact or aerosol. The presence of predisposing factors that decrease immunity contribute to disease occurrence (Cloutier et al. 2003, Gottschalk & Segura 2019), which normally affects piglets from one week after weaning until the end of the nursery, when maternal immunity declines, but clinical cases are also seen in pigs of other ages, and each herd may have its own occurrence profile (Clifton-Hadley 1983, Lapointe et al. 2002, Cloutier et al. 2003, Gottschalk & Segura 2019).

Meningitis, polyserositis, valvular endocarditis, pneumonia, and polyarthritis are among the main lesions described in *S. suis* infections in pigs and humans (Gottschalk & Segura 2019). The most known change caused by *S. suis* in the central nervous system (CNS) of pigs is fibrinopurulent meningitis (Madsen et al. 2002, Miller & Zachary 2017) and can extend to the choroid plexus, ependyma, nerve roots, and spinal cord (Miller & Zachary 2017).

This report describes the clinical, pathological, and molecular aspects of an outbreak of *S. suis* serotype 9 infection in pigs, which affected several farms integrated with the same cooperative, with high atypical morbidity and mortality.

MATERIALS AND METHODS

A technical visit was carried out in a cooperative located in the state of Paraná, Brazil, to investigate a problem that had occurred for at least 15 months. The cooperative worked on an integration system, which includes 76 breeding units, 30 nursery units, and 250 growing-finishing farms. Clinical and epidemiological data were obtained from company veterinarians and from the farm employees during visits.

Piglets with severe nervous signs were euthanized, and tissue samples, including organs of the thoracic and abdominal cavities, brain, spinal cord, and joint capsule, were collected and fixed in 10% buffered formalin. After 48 hours of fixation, serial cuts of the central nervous system of all pigs were performed. Fragments of the frontal, temporal, and occipital cortex, cerebellum, and brainstem (at the level of the midbrain and medulla oblongata) were obtained. The spinal cord was divided into cervical, thoracic, lumbar, and sacral regions. At least two fragments from each spinal region were evaluated. The tissues were routinely processed for histology and stained with hematoxylin and eosin (HE). The lesions observed using optical microscopy and were graded according to severity as mild (+), moderate (++), and severe (+++). Refrigerated samples of meningeal swabs, and synovial and cerebrospinal fluids (CSF) were collected for bacterial isolation and characterization.

Collected samples were cultured in Blood Agar (sheep blood 7%, Mueller Hinton, Kasvi®, Brazil) and MacConkey Agar (Kasvi®, Brazil). Plates were incubated at 37°C aerobically and examined after 24, 48, and 72 hours. *Streptococcus suis* isolates were identified by their cultural, morphological, tinctorial, and biochemical characteristics using a simplified scheme based on Markey et al. (2013). Capsular typing of *S. suis* was performed using multiplex PCR, as described by Kerdsin et al. (2014).

RESULTS

The disease occurred in nursery farms integrated into a cooperative in the state of Paraná, Brazil. Of the 30 nursery farms, 10 showed severe *Streptococcus suis* associated diseases, resulting in significant economic losses. These nurseries housed piglets that were 28±7 days-old, and the batches were mixed with pigs of different origins (sometimes up to 15 origins). Piglets were vaccinated with a commercial vaccines for porcine circovirus type 2, *Mycoplasma hyopneumoniae*, *Glaesserella* (*Haemophilus*) *parasuis*, and *S. suis* serotype 2, at 21 days of age, and were boosted at 42 days of age. The sows were not vaccinated against *S. suis.*

According to the cooperative veterinarians and farm employees, the clinical signs usually started about 10 days after weaning and housing of piglets in the nurseries (35 to 45 days of old). Antibiotic therapy was carried out with several antimicrobials, both parenteral and throughout drinking water, but the clinical efficacy was unsatisfactory; a few sick animals recovered. Most piglets died or were euthanized because of poor prognosis. Mortality usually ranged between 8% and 10%, but in some cases, it reached 18%. The clinical cases occurred in piglets from different origins and different nurseries, regardless of the management, facilities, and body condition of the piglets. In some batches of growing pigs, the disease also occurred, but the morbidity rates and mortality were lower.

The early signs were characterized by apathy, fever (41°C), stiff and enlarged joints, mainly the carpal and tarsal, in addition to reluctance to move, with preference to remain in sternal decubitus. When encouraged to walk, the piglets showed muscle tremors and fell to the ground. Within 24 hours, these clinical signs evolved to lateral decubitus, opisthotonos, nystagmus, and paddling (Fig.1).

One farrow-to-nursery and two nurseries were visited, and nine piglets were submitted to *postmortem* examination.

The synovial joints were enlarged, mainly in the hind limbs (4/9) (Fig.2). Upon opening, the synovial fluid was increased, slightly yellowish with fibrin filaments. The synovial membrane was red, and the joint capsule was distended by a gelatinous material (edema) (inset Fig.2). Gross changes in the central nervous system were not evident in all piglets. There was a slight engorgement of the vessels of the leptomeninges (hyperemia) (Fig.3), in the cerebral hemispheres of four piglets. On the leptomeninges of three piglets, there were yellow, opaque, and sometimes fibrillar areas (interpreted as fibrin and purulent exudate). In three piglets, thickening of the choroid plexus (Fig.4) associated with slight dilation of the lateral ventricles was observed on the cut surface of the brain.

Histologically, the articular capsule presented deposition of fibrin, edema, infiltration of neutrophils, lymphocytes, plasma cells, and macrophages (5/9), in addition to synoviocyte hyperplasia and necrosis of the synovial membrane (2/9) (Fig.5). Histological changes in the central nervous system were discriminated according to the anatomical distribution and severity (Table 1). The leptomeninges of the brain (including the cerebral cortex, cerebellum, and brain stem) were variably thickened by fibrin deposition and inflammatory infiltrate (Fig.6) of intact and degenerate neutrophils, in addition to fewer lymphocytes, plasma cells, and macrophages. These inflammatory cells were also eventually observed around blood vessels in the neuropil (perivascular cuffs). Intact and degenerate neutrophils and clear vacuoles were eventually observed in the gray matter of the telencephalon (2/9) (Fig.7). Free bacteria in the leptomeninges were clearly visible through HE staining in only one case. The subependymal region was thickened by similar inflammatory cells and perivascular cuffs (6/9). Erosions of the ependymal lining (4/9) were also observed, and the lateral ventricles were filled with inflammatory cells, fibrin, and few sloughed ependymal cells (3/9). In one case, there were also bacterial aggregates inside the ventricles (1/9) (Fig.8). The papillae of the choroid plexus of all piglets were thickened by similar inflammatory infiltrates and edema (Fig.9), with multifocal areas of rupture of the choroid epithelium (6/9) (Fig.10).

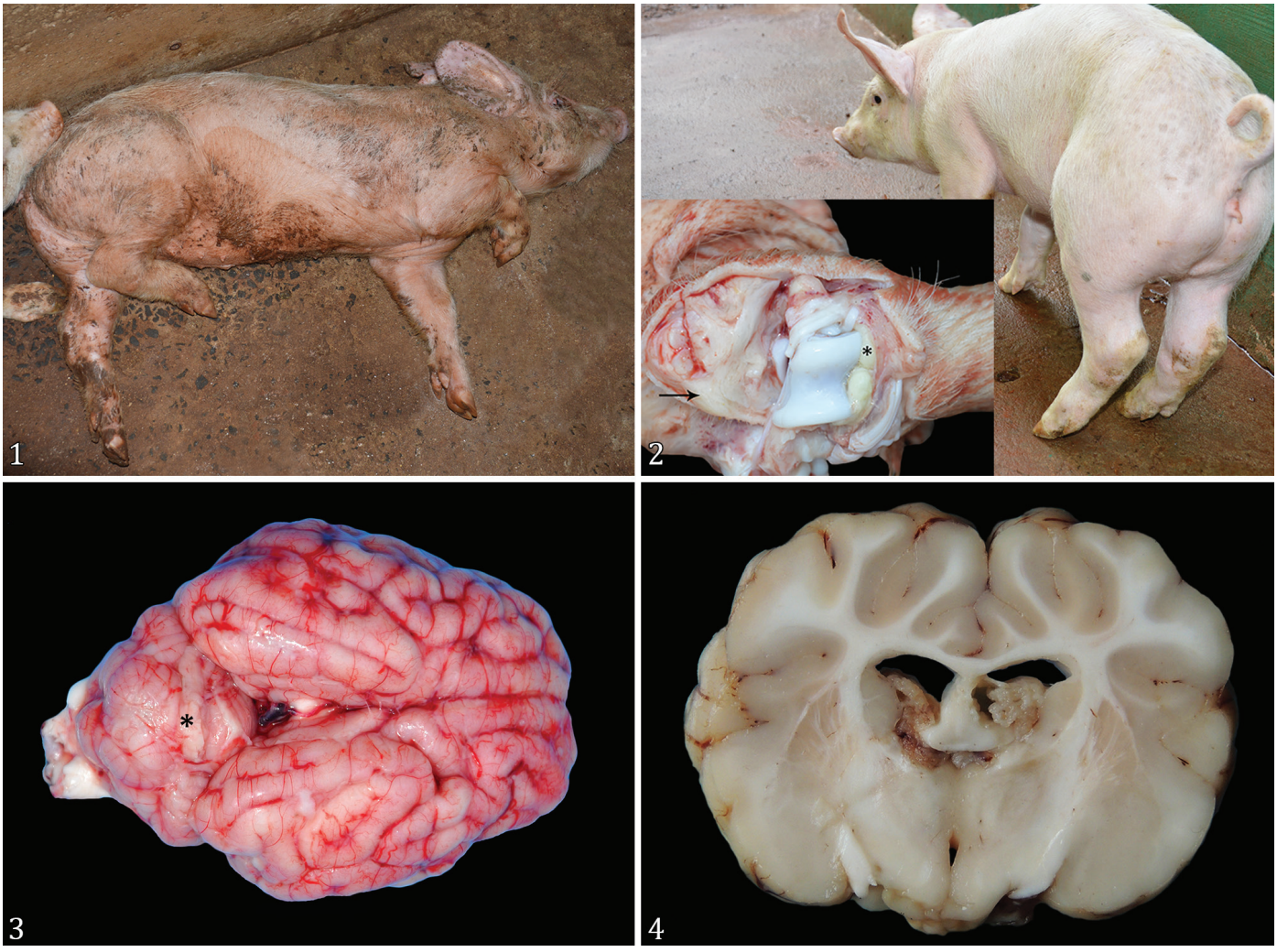

Fig.1-4. (**1**) Clinical features and gross lesions in pigs with *Streptococcus suis* infection. Piglet in lateral decubitus with paddling movements. (**2**) Pig with enlarged tarsal joints. Inset: at the opening of the joint there were fibrin filaments (asterisk) and the articular capsule was distended by a gelatinous material (edema) (arrow). (**3**) Brain: there is hyperemia of leptomeninges with fibrin deposition on the cerebellum (asterisk). (**4**) Cut surface of the brain: thickening of the choroid plexus associated with slight dilation of the lateral ventricles.

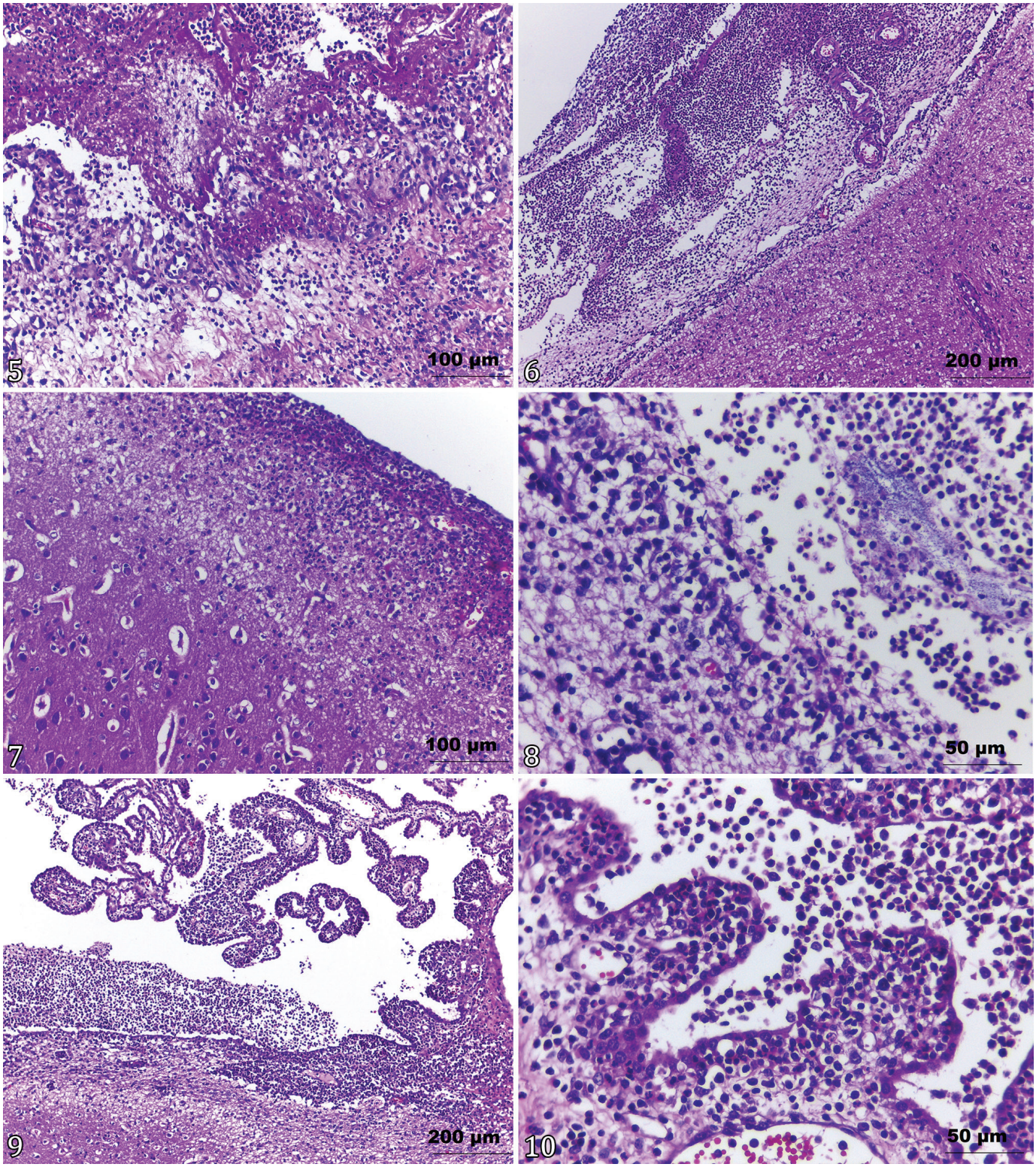

Fig.5-10. (5) Histological lesions in pigs with *Streptococcus suis* infection. Articular capsule: multifocal necrosis of the synovial membrane associated with fibrin deposition, edema, infiltration of neutrophils, lymphocytes, plasma cells, and macrophages (fibrinosuppurative arthritis). HE, obj.20x. (6) Brain stem: the leptomeninges are thickened by fibrin deposition and a severe inflammatory infiltrate composed mainly of neutrophils (fibrinosuppurative meningitis). HE, obj.10x. (7) Occipital cortex: in the gray matter there is infiltration of intact and degenerate neutrophils and clear vacuoles in the neuropil. HE, obj.20x. (8) Lateral ventricle: there is a diffuse thickening of the choroid plexus (choroid plexitis) and ependymal region (ependymitis) by an inflammatory infiltrate similar to the described in the leptomeninges. Similar inflammatory cells are seen inside the ventricle along with fibrin filaments. HE, obj.10x. (9) Lateral ventricle with ependymitis, besides sloughed ependymal cells and bacterial aggregates inside the ventricle. HE, obj.40x. (10) Choroid plexus: inflammatory infiltrate of neutrophils, lymphocytes, and plasma cells with an area of rupture of the choroid epithelium. HE, obj.40x.

The spinal cords of all the pigs presented fibrinosuppurative meningitis, in at least one segment, similar to that described in the brain, which extended to the epineurium of the spinal nerve roots (Fig.11). The central canal was often filled with inflammatory cells, and some ependymal epithelial cells presented an elongated cytoplasm (Fig.12). In 5/9 cases, there was multifocal or focally extensive necrosis of the ependymal cells, with extension of the inflammation to the adjacent gray and white matter (Fig.13), associated with necrosis, occasional Gitter cells, perivascular cuffs, and vasculitis. In the adjacent white matter, there were multifocal areas of vacuolization with axonal spheroids (Wallerian degeneration) (4/9) (Fig.14). Lesions in the spinal central canal and parenchyma were more severe in pigs with the longest clinical course (five days). In the *rete mirabile*, a mild to moderate inflammatory infiltrate of neutrophils, lymphocytes, and plasma cells was observed around the arterioles (2/9). The same inflammation was also noted in the capsule of the trigeminal ganglia and epineurium of the trigeminal nerves (1/9).

Bacteriological examination revealed Gram-positive cocci that occurred singly or in chains of varying lengths. Alpha-hemolytic and small colonies (1mm after 48 h of incubation), catalase-negative, oxidase-negative, non-motile were classified as *Streptococcus* spp., and complementary fermentation tests of inulin, lactose, mannitol, raffinose, salicin, sorbitol, and trehalose confirmed the isolates as *S. suis.* Bacterial growth was observed in meningeal swabs (7/9), synovial fluid (3/5), and cerebrospinal fluid (2/4). In 8/9 cases, *S. suis* could be cultured from at least one sample. Finally, in multiplex PCR, all colonies were typed as *S. suis* serotype 9.

DISCUSSION

This study describes an outbreak of *Streptococcus suis* associated disease caused by *S. suis* serotype 9, which was associated with clinical outbreaks diagnosed in several farms integrated with the same cooperative, with high mortality, resulting in high economic losses. *S. suis* is the most important porcine streptococcal pathogen and is globally distributed. The morbidity and mortality of the disease is usually less than 5%; however, under some circumstances, the mortality can reach up to 20% (Cloutier et al. 2003, Fittipaldi et al. 2012, Gottschalk & Segura 2019), similarly to the outbreak reported here.

Vertical, direct, indirect and aerosol transmission, without nose-to-nose contact, are described for infections by *S. suis* (Robertson et al. 1991, Dee & Corey 1993, Berthelot-Hérault et al. 2001). The mixture of piglets infected (by their mothers) and piglets not infected in the post-weaning period, allows transmission and the clinical outbreaks of the disease (Cloutier et al. 2003). The occurrence of meningoencephalomyelitis in piglets with different origins may be a consequence of horizontal transmission, when they are regrouped in the nursery farms. In our study, some nursery batches clinically affected were composed of up to 15 different origins, which represent an important predisposing factor.

High genotypic, phenotypic and geographic variability exits among strains within the same serotype of *S. suis.* Besides, *S. suis* uses an arsenal of virulence factors to evade the host immune system. Together, these characteristics have challenged the development of efficacious vaccines to fight this important pathogen (Segura 2015). In an experimental study with serotype 2 bacterin, high titers of opsonizing

Table 1. Intensity and distribution of lesions seen in piglets with *Streptococcus suis* serotype 9 acute meningoencephalomyelitis

Location in the CNS	Piglets								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
Leptomeninges									
FC	++	-	+	+	-	+	+++	+	++
TC	+	-	+	+	+	+	+++	+	+
OC	++	-	-	+	-	+	+++	+	++
CER	++	-	+	++	-	+	+++	++	++
BS - MB	+	-	-	++	+	++	+++	+	++
BS - MO	+	-	-	++	-	++	+++	++	++
CR	+	-	+	++	+	+	+++	++	+
TR	+	-	++	+	-	+	+++	+	++
LR	+	+	+	++	-	+	+++	+	++
SR	+	+	-	+	-	+	++	++	+
Choroid plexus	+++	+	+	++	+	+++	++	+++	+++
EP and SE	++	-	-	+	-	++	++	+++	++
CC and SC									
CR	++	+	-	++	+	++	+	+++	+++
TR	+++	-	-	++	-	+++	+	++	+++
LR	+	-	-	++	-	+++	+	+	+++
SR	++	-	-	++	-	+++	+	++	+
Clinical course (days)	2	1	2	2	2	5	2	4	5

FC = frontal cortex, TC = temporal cortex, OC = occipital cortex, CER = cerebellum, BS = brainstem, MB = midbrain, MO = medulla oblongata, CR = cervical region, TR = thoracic region, LR = lumbar region, SR = sacral region, EP = ependyma, SE = subependymal region, CC = central canal, SC = spinal cord; (+) mild lesions, (++) moderate lesions, (+++) severe lesions, (-) absent lesions.

antibodies were induced against the homologous strain, but the same did not occur for the heterologous serotype 9 strain (Baums et al. 2009). The lack of cross-immunity between the heterologous strains of *S. suis* was probably one of the reasons for the difficult control of the outbreak reported here, since *S. suis* serotype 9 was extensively isolated from the sick piglets, and the vaccine used initially is based on *S. suis* serotype 2 strain. Alternatively, an autogenous vaccine based on the strains isolated from the farms could be a rational strategy to attenuate the disease. The immunization program must consider the time of clinical presentation of the disease, once the protective immunity can be reached only after the second dose of the vaccine. Vaccination of sows can be an interesting strategy, but the studies in this area show divergent results and, in general, maternal vaccination does not exclude the necessity of active vaccination of piglets to lengthen the protection (Baums et al. 2010, Segura 2015).

The clinical signs in acute cases of the disease include fever, lameness, incoordination, lateral recumbency, nystagmus, rhythmic paddling, and opisthotonos (Clifton-Hadley 1983, MacInnes & Desrosiers 1999, Miller & Zachary 2017) similar to those seen in this outbreak. Temperature rise is often the first clinical sign seen in experimental studies (Beineke et al. 2008, Büttner et al. 2012, Rieckmann et al. 2019), and this is a response to acute inflammation (Ackermann 2017).

The mechanisms by which *S. suis* manages to cross the blood-brain barrier are not well understood. *S. suis* adheres to and invades the microvascular endothelial cells of the brain (Vanier et al. 2004), affects the function and integrity of the choroid plexus (Feng et al. 2010), and reaches the cerebrospinal fluid (Miller & Zachary 2017). The choroid plexus of all piglets in this study showed some degree of lesion, possibly due to the invasion of the agent through this location. The ventricular dilation observed in some pigs in this study may be a consequence of the obstruction of the ventricular system by cellular debris and fibrin, which causes blockages in the drainage of CSF (non-communicating hydrocephalus) (Miller & Zachary 2017). Erosions of the ependymal lining of

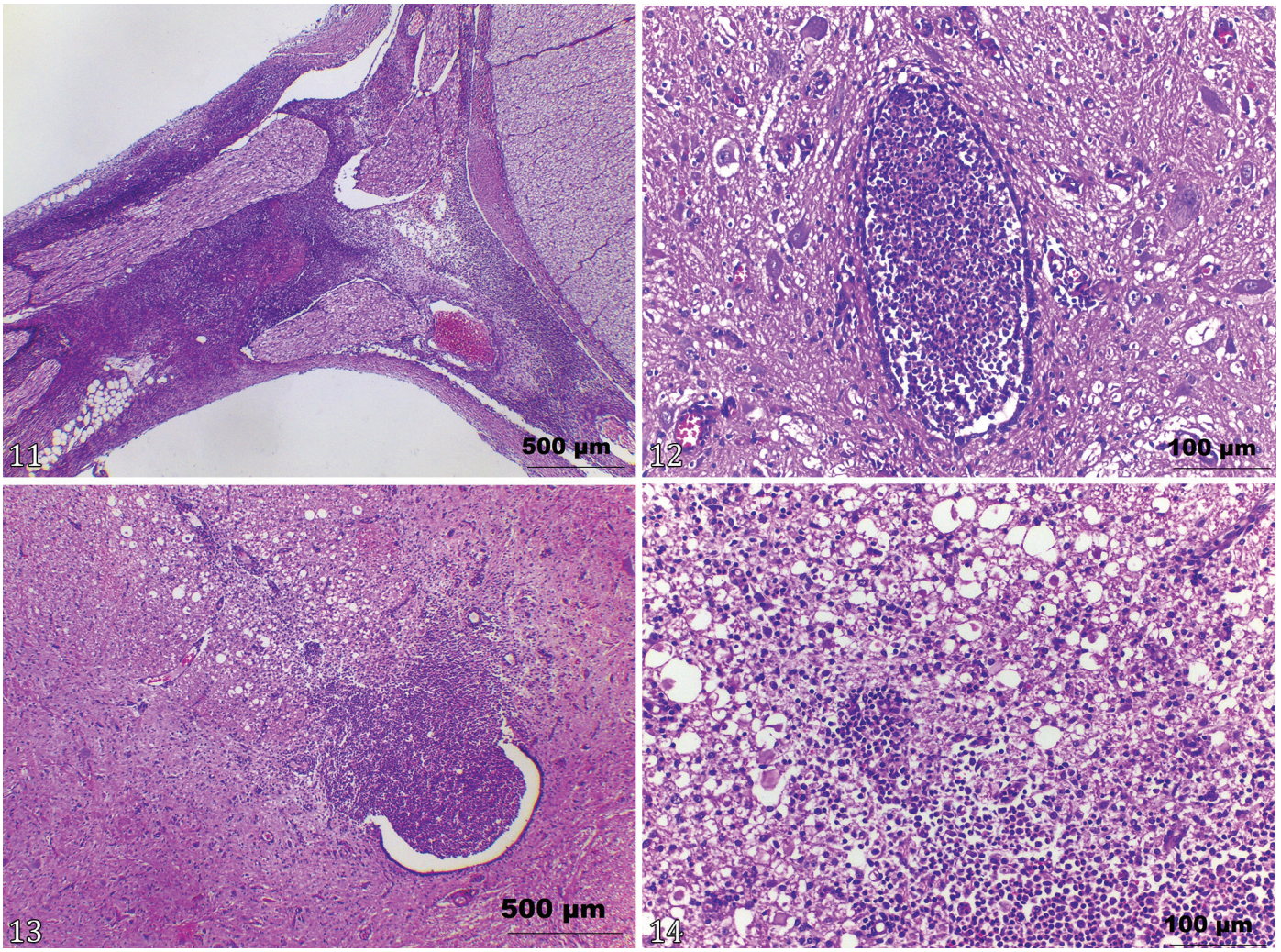

Fig.11-14. (**11**) Histological lesions in the spinal cord of pigs with *Streptococcus suis* infection. Spinal cord: the leptomeninges are thickened by suppurative inflammatory infiltrate, which extended to the epineurium of the spinal nerves roots. HE, obj.4x. (**12**). Spinal cord: central canal filled with inflammatory cells. HE, obj.20x. (**13**) Spinal cord: necrosis of ependymal cells of the central canal with extension of the inflammation to the adjacent gray and white matter. HE, obj.4x. (**14**) Spinal cord: multifocal areas with parenchymal loss (necrosis), besides clear spaces and axonal spheroids (Wallerian degeneration). HE, obj.20x.

ventricles and central canal of the spinal cord may be present (Sanford 1987, Vandevelde et al. 2012) and were common findings in our study.

Necrotic foci can be seen in the brain stem, cerebellum, and cervical spinal cord of pigs infected with *S. suis* (Miller & Zachary 2017). In our cases, necrotic foci were common in the spinal cord, usually involving the parenchyma adjacent to the central canal. These changes affected more severely the pigs with longer clinical course, and extended to all the spinal cord regions.

The main central nervous system changes described in *S. suis* infection are meningoencephalitis, plexitis, choroiditis and ependymitis (Sanford 1987, Miller & Zachary 2017). Spinal cord lesions are rarely described in the literature. The inflammatory infiltrate observed in the brain's leptomeninges may extend to the spinal cord, involving cranial nerve roots and extend to the central cervical spinal canal (Sanford 1987, Miller & Zachary 2017). In our study, this finding was frequently observed.

Lesions caused by *S. suis* are predominantly associated with fibrinosuppurative inflammation as a result of the invasion of the brain, joints and serous cavities (Williams & Blakemore 1990, Madsen et al. 2002), while subacute or chronic lesions are characterized by infiltration of mononuclear cells (Sanford 1987, Karstrup et al. 2011). The microscopic lesions observed in this study were mainly fibrinosuppurative, what is consistent with an acute clinical course (Miller & Zachary 2017).

The findings of fibrinosuppurative meningoencephalitis and arthritis in this study are similar to the lesions described for clinical field cases and also in experimental conditions (Beineke et al. 2008, Greeff et al. 2011, Büttner et al. 2012, Willemse et al. 2019). Endocarditis, pneumonia, pleuritis, and peritonitis are more common in pigs with longer clinical course, and were described in pigs 11 days post-infection (Büttner et al. 2012). These lesions were not observed in this study, possibly due to the acute character of the disease in the piglets selected for necropsy, which were sick for one to five days.

Enlarged joints, fever, lethargy, and reluctance to move can be seen in other bacterial infections such as *Erysipelothrix rhusiopathiae*, *Glaesserella* (*Haemophilus*) *parasuis*, *Actinobacillus suis*, *Mycoplasma hyosynoviae*, *Mycoplasma hyorhinis,* and *Trueperella pyogenes* (Madson et al. 2019). The agent involved can be confirmed by culture or PCR from samples of the lesions. Muscle tremors, lateral recumbency, and paddling can be seen in salt poisoning. Salt poisoning has an eosinophilic (acute) or lymphoplasmacytic (chronic) meningoencephalitis in the microscopic lesion in the brain (Dritz et al. 2019).

Incoordination, limb paralysis and recumbency also occur in cases of viral polioencephalomyelitis. However, this disease tends to be non-febrile, does not present with arthritis, and the microscopic lesions are characterized by nonsuppurative encephalomyelitis and ganglioneuritis with evident neuronal degeneration and necrosis (Hammerschmitt et al. 2021).

CONCLUSIONS

Streptococcus suis serotype 9 is responsible for a severe clinical disease in piglets, characterized mainly by nervous and locomotor clinical signs. The central nervous system lesions are mainly characterized by fibrinosuppurative inflammation, which involves not only the leptomeninges, but also the choroid plexus, ependyma, and spinal cord.

The occurrence of outbreaks of the disease with high mortality may be associated with: i) mixture of piglets from different origins in the post-weaning period and ii) the lack of cross-immunity between heterologous strains of *S. suis*, especially when the circulating strain is not included in the vaccine used.

Authors' contributions.- Hammerschmitt M.E., Schwertz C.I., Lopes B.C., Pereira P.R., Frandoloso R. & Driemeier D. made substantial contributions to the interpretation of data and approved the version to be published.

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