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OCCURRENCE OF PORCINE DERMATITIS AND NEPHROPATHY SYNDROME IN HUNGARY

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In the past few years a characteristic, often fatal disease associated with cutaneous lesions and nephropathy has been observed in several large pig herds and household pig stocks of Hungary. In addition to general symptoms and slight fever in several cases, the disease was characterised by cutaneous lesions occurring mostly on the ventral part of the thorax and abdomen, on the extremities and ear pinnae, and in the nasal and perianal region. In the acute phase, circumscribed hyperaemic, confluent, crust-covered areas were seen. Histological examination revealed necrosis of the epithelial layer and lympho-histiocytic vasculitis in the corium, here and there accompanied by thrombosis and fibrinoid degeneration. The kidneys were pale brown and harder to tear, with cortical petechiae in most cases. By histopathological examination, intra- and extracapillary glomerulonephritis accompanied by fibrinoid exudation was seen. Some of the renal tubules were dilated, others were atrophied, and in advanced cases proliferation of the intertubular connective tissue and inflammatory cell infiltration also occurred. Necrotic vasculitis was also observed in some cases. By immunohistochemical examination IgA, IgG and IgM, and in a single case C_3 belonging to the complement system were observed in the pathologically changed skin areas and kidneys. By polymerase chain reaction (PCR), porcine circovirus type 2 (PCV-2) was detected. Bacteriological and serological examinations did not reveal infections of aetiological importance.

Key words: Porcine dermatitis and nephropathy syndrome, porcine circovirus, histopathology, immunohistochemistry, PCR, Hungary

In recent years, a pig disease primarily characterised by dermatitis and nephropathy was first described in the UK (Smith et al., 1993; White and Higgins, 1993) and subsequently in Canada (Hélie et al., 1995; Thibault et al., 1998), the Republic of South Africa (Van Halderen et al., 1995), Spain (Segalés et al., 1996), France (Solignac, 1997), the United States (Duran et al., 1997; Yaeger, 1997), the Netherlands (Sierra et al., 1997) and Austria (Meehan et al., 2001). On the basis of the typical clinical signs and pathological lesions, the disease was termed 'porcine immune complex glomerulonephritis dermatitis (PIGD) syn-

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drome' and 'porcine dermatitis and nephropathy syndrome (PDNS)' (Choi and Chae, 2001). As damage of the blood vessels can be observed already at an early stage in the above organs and it may also develop in other parts of the body, the syndrome has also been designated 'cutaneous and systemic necrotising vasculitis' (Thibault et al., 1998).

Primarily immunopathological processes are thought to play a role in the pathogenesis of vascular changes (Hélie et al., 1995; Sierra et al., 1997; Thibault et al., 1998). The aetiology of the syndrome is yet unclear.

This paper reports cases of PDNS observed in Hungary in the period between 1997 and 2000. The syndrome was observed in 27 pigs originating from 7 small stocks. The age of the affected animals varied between 35 and 120 days. The pigs were febrile (40–41 °C) and showed weakness, depression, lack of appetite, and typical cutaneous lesions. The disease led to death in 2–4 days. Morbidity remained below 1%. The applied antibiotic and symptomatic treatments were unsuccessful.

Materials and methods

Gross and histopathological examinations

After the gross pathological examination of dead pigs or organs submitted to our institute for diagnostic examination, samples were taken from the affected skin areas, kidneys and occasionally also from the brain, spleen, liver, lungs, heart and lymph nodes for histological examination. The samples were fixed in 10% formaldehyde solution and embedded in paraffin. Sections were made and stained with haematoxylin and eosin. For the detection of fibrin Weigert's stain, for the identification of fibrotic connective tissue elements van Gieson's stain, while for the visualisation of basement membranes Gömöri's silver impregnation procedure and the periodic acid–Schiff (PAS) stain were used. Lipids were stained with Fat Red in frozen sections.

Immunohistochemistry

For the detection of immune complexes, the kidney or skin, or both, of 10 pigs were tested against porcine IgA, IgM and IgG specific serum (ICN Inc.) and human complement C_3 and C_{1q} specific serum (Sigma Aldrich Co.). These antibodies can detect the presence of immunoglobulins and members of the complement system in formalin-fixed and paraffin-embedded organs of pigs (Segalés and Domingo, 2000). The reaction was performed in microcapillary system (Shandon Inc.). Deparaffinised sections were incubated in 0.1% protease XIV solution (Sigma Aldrich Co.) at 37 °C and then in 3% H_2O_2 solution at room temperature for 10 min each. Blocking with 20% horse serum was done at room

temperature for 20 min. The sections were incubated with the primary antibody at room temperature overnight in the following dilutions: IgA: 1:2000, IgM: 1:600, IgG: 1:1500, C_3: 1:600, C_{1q}: 1:600. Antibody binding was detected by the peroxidase-antiperoxidase method (Dako) and using 3-amino-9-ethylcarbazole (Sigma Aldrich Co.). The sections were counterstained with Mayer's haematoxylin and covered with glycerol-gelatin.

Bacteriological, mycological and virological examination

The bacteriological, mycological and virological examinations were performed by the use of methods and culture media regularly used in our institute.

Detection and sequencing of the viral DNAs by polymerase chain reaction (PCR)

Viral DNA was extracted from kidney and tonsils, originating from one animal and stored at –20 °C until processed, by the method previously described in detail (Benkő, 1990). All porcine circovirus DNAs hitherto submitted to the Genbank database were compared with the help of the MultAlin programme (Corpet, 1988). Taking this comparison as a basis, a primer pair (PCcomF 5'-CGACCTGTCTACTGTGAG-3' PCcomR 5'-AGCAGTTGAGGAGTACCA-3') was selected using the PrimerSelect programme of the Lasergene programme package (DNASTAR Inc.) so as to be located on the most conserved DNA segments within the virus family. To distinguish the two PCV subgroups a primer pair specific for the PCV subgroup II was also designed (PCIIF 5'-CTCGATCTCAAGGACAACG-3', PCIIR 5'-ACAGCAGTTGAGGAGTACC-3'). The primers were produced in the Central Veterinary Institute, using a Gene Assembler Special oligonucleotide synthesiser (Pharmacia LKB).

One µl of the pretreated samples (50–100 ng) was measured into the PCR reaction mixture of 49 µl total volume, which contained the following components: 5 µl 10 × PCR buffer free of $MgCl_2$ (100 mM Tris-HCl, pH 8.3, 500 mM KCl, Sigma), 5 µl $MgCl_2$ (25 mM, Sigma), 1.5 µl of all dNTPs (10 mM, Pharmacia Biotech), 1 µl of both primers (50 pmol/µl), 0.5 µl Taq DNA polymerase (2.5 units, Sigma) and 35 µl distilled water. DNA amplification was performed with a Hungarian-made apparatus (PDR.91, BLS) according to the following programme: 94 °C for 30 sec, 51 °C for 30 sec, 72 °C for 30 sec (35 cycles), 72 °C for 5 min (1 cycle). The PCR conditions were the same in the case of both primer pairs. Porcine circovirus obtained from the Veterinary Institute of Debrecen (Hungary) was used as positive control.

The amplification product was analysed by agarose gel electrophoresis. Ten µl of the reaction mixture was run on 1.5% agarose gel (Sigma Aldrich) containing 0.5 µl/ml ethidium bromide at 120 V voltage for 40 min.

For the sequencing and further DNA-level analysis of the PCR product, the amplified DNA fragment was excised from the agarose gel, purified by the fibreglass

technique (Brosius III et al., 1996) and rendered suitable for nucleotide sequencing with an ABI 373A automatic DNA sequencer (Applied Biosystems) using the PCcomF and PCcomR PCR primers. The obtained sequences were analysed with the Lasergene programme package (DNASTAR Inc.).

Results

Gross pathological findings

By gross pathological examination, lesions were consistently found in the skin and kidneys. Cutaneous lesions consisted of circumscribed hyperaemic areas and protrusions 1–2 cm in diameter on different parts of the body, most often on the ear pinnae, on the distal parts of the extremities and in the perianal region and less frequently on the rump and back (Fig. 1). At an advanced stage the central part of these lesions assumed greyish-black colour and became necrotic. In the subcutaneous connective tissue haemorrhages and oedema developed.

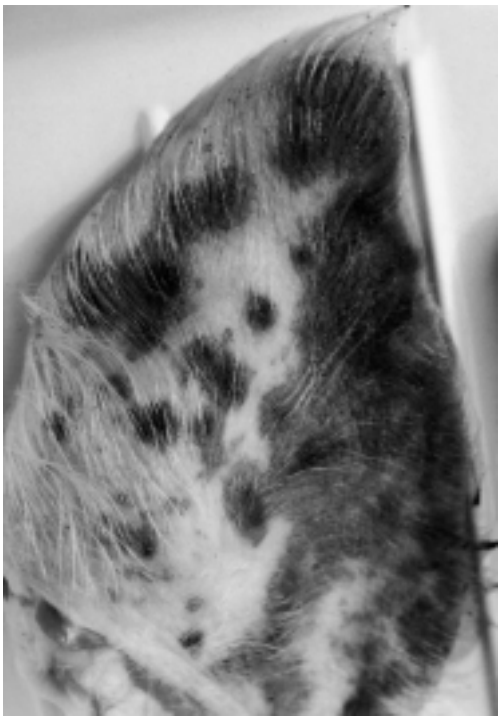

Fig. 1. Circumscribed or confluent, hyperaemic areas, here and there partially covered with crust and 1–2 cm in diameter, on the skin of the ear pinna

The kidneys were enlarged, pale and their surface was slightly lumpy. The cortical substance was tougher than normal and contained petechiae.

In addition to the renal and cutaneous changes, oesophagogastric ulcer with consequent fatal bleeding into the gastrointestinal tract occurred in one animal, catarrhal bronchopneumonia was found in three pigs, and chronic pleuritis and pericarditis with fibrous adhesions occurred in two animals.

Histopathological findings

Histopathological examination of the skin revealed lympho-histiocytic infiltration and hyperaemia in the wall of, and around, the blood vessels of the corium, in mild cases under the intact epithelial layer (Fig. 2). In more severe cases the epithelium was necrotic and some of the blood vessels running in the underlying corium contained microthrombi, while in the intervascular connective tissue infiltration with a small number of neutrophilic granulocytes was seen.

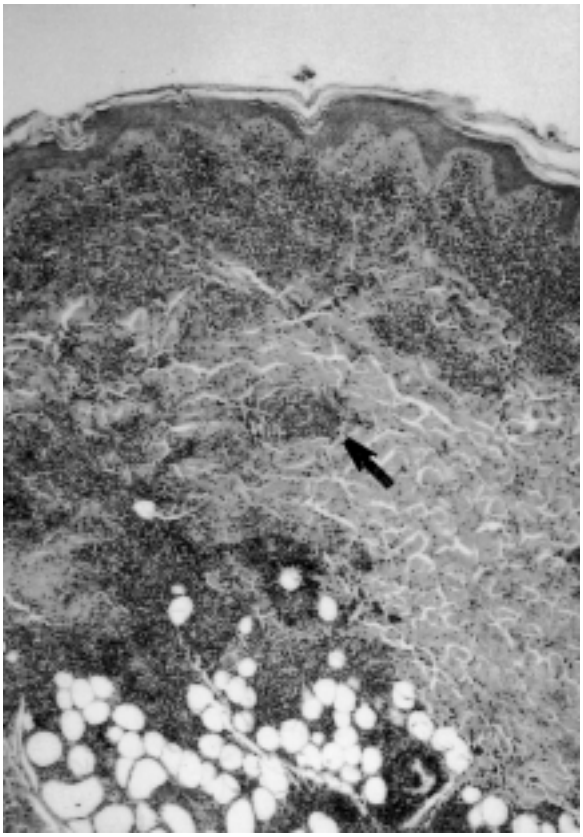

Fig. 2. Lympho-histiocytic infiltration (arrow) in the corium of the skin and in the subcutaneous connective tissue. The infiltration is mostly perivascular. Haematoxylin and eosin (H.-E.), × 40

In the kidneys exudative intra- and extracapillary glomerulonephritis was found. The Bowman's capsule contained a large amount of proteinaceous exudate with consequent compression of the capillaries (Fig. 3). In the wall of some renal blood vessels fibrinoid degeneration and inflammatory cell infiltration developed (Fig. 4). Often there was fibrosis among the tubules, with dilatation of some of the tubules and fatty infiltration in some places. Interstitial infiltration with inflammatory cells occurred only in smaller circumscribed areas.

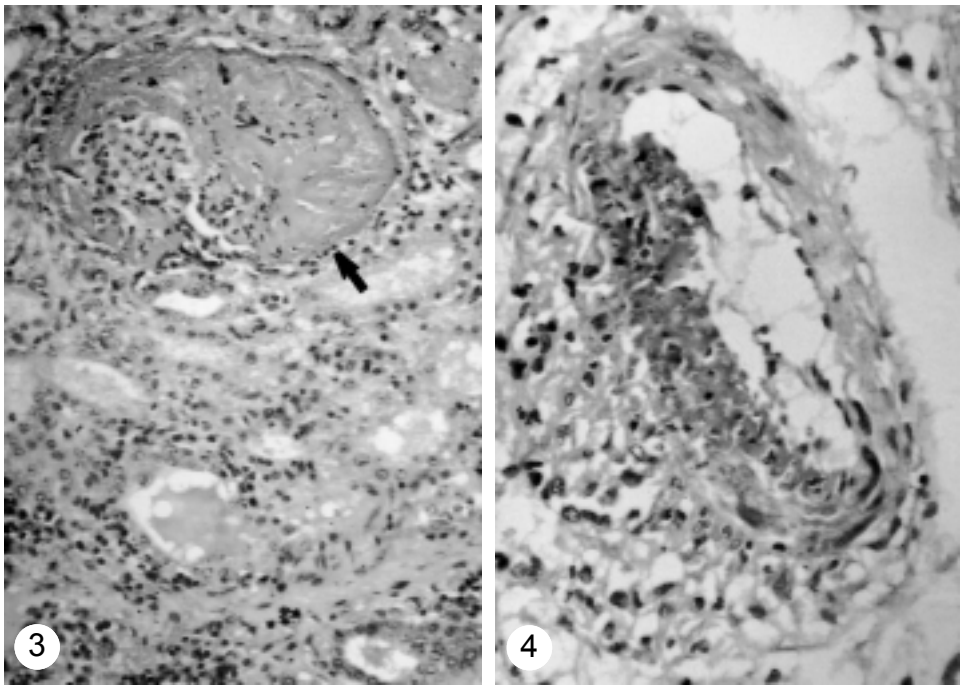

Fig. 3. Exudate of acidophilic staining (arrow) in the Bowman's capsule of the kidney, with consequent compression of the glomerulus, H.-E., × 100
Fig. 4. Fibrinoid degeneration and reactive inflammation in the wall of a renal artery. H.-E., × 200

Of the other organs examined, in two cases lympho-histiocytic infiltration was found in circumscribed areas of the brain, in each case in the wall of a blood vessel and in the perivascular areas.

Immunohistochemistry

The results of the immunohistochemical examinations are summarised in Table 1.

Table 1

Results of the immunohistochemical examinations

Animal no., examined organ	Porcine IgA specific serum	Porcine IgM specific serum	Porcine IgG specific serum	Human C_3 specific serum	Human C_{1q} specific serum
1. Skin	–	+	+	+	–
2. Skin	+	+	–	–	–
3. Skin	–	–	–	–	–
4. Kidney	–	+	–	–	–
5. Kidney	+	+	–	–	–
6. Kidney	+	–	–	–	–
7. Skin	+	+	–	–	–
Kidney	+	+	+	+	–
8. Skin	–	–	–	–	–
Kidney	+	–	–	–	–
9. Skin	+	–	+	–	–
Kidney	+	+	–	–	–
10. Skin	+	+	–	–	–
Kidney	+	+	–	–	–

Immunoglobulins were observed in the following arrangement, besides the slight background staining that was sometimes present. Immunoglobulins were seen in the epithelial layer of the skin, especially above areas infiltrated with inflammatory cells, but in some cases they were present also in the crust covering the epithelium, on and near the basement membrane of the skin (Fig. 5), in the pathologically altered renal glomeruli, in the detached epithelial cells and hyaline cylinders present in the lumen of tubules, and in the cytoplasm of the intact tubular epithelial cells (Fig. 6). In addition to this, positive reaction was seen in the cytoplasm of plasma cells in the kidney and in the serum present in the blood vessels in the skin and kidneys.

Bacteriological and mycological findings

By bacteriological and mycological examination no pathogens were detected in the affected skin areas, in the kidney or in other parenchymal organs. In three cases *Pasteurella multocida* was cultured from the lung lesions.

PCR findings

By PCR, porcine circovirus (PCV) was detected from both the kidney and the tonsil with either primer pair used. As a positive PCR was obtained also with a primer specific for the PCV II subgroup, the detected virus is likely to be a member of the pathogenic PCV II subgroup. On the basis of electrophoresis in agarose gel, the size of the amplification product was approx. 450 base pairs, which corresponds to the value expected when designing the primer. The base

sequence of the obtained fragment was determined, and thus it could be compared with all other porcine circoviruses already characterised on DNA level. The circovirus detected in this work was found to have 99.5–99.8% homology with members of the PCV II subgroup and only 82.6% homology with those of the other subgroup. The possible etiological role of PRRS virus and Aujeszky's virus was excluded.

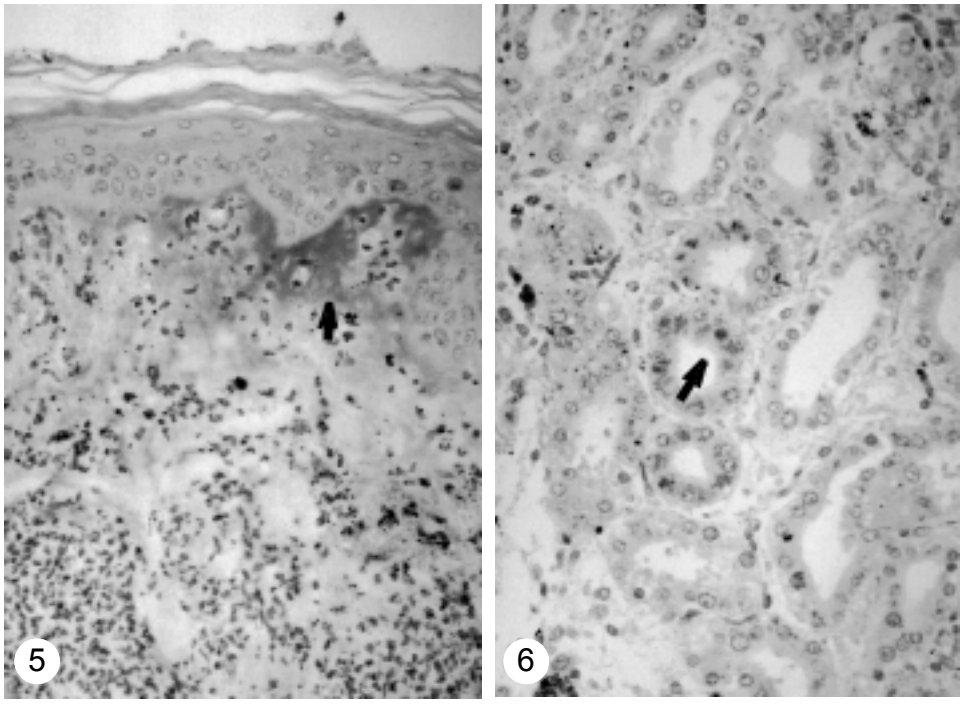

Fig. 5. Deposition of IgM in the skin as well as in and around the basement membrane of the epithelium overlying the inflamed area (arrow). Immunohistochemical preparation, counterstained with Mayer's haematoxylin, × 200

Fig. 6. Deposition of IgM within the cytoplasm of epithelial cells of the renal tubule (arrow). Immunohistochemical preparation, counterstained with Mayer's haematoxylin, × 200

Discussion

On the basis of the clinical signs, pathological and immunohistochemical findings, the disease cases observed in this study seem to be identical with the syndrome described in the foreign literature as porcine dermatitis and nephropathy syndrome (PDNS), porcine immune complex glomerulonephritis dermatitis (PIGD) syndrome or cutaneous and systemic necrotising vasculitis (Smith et al., 1993; White and Higgins, 1993; Hélie et al., 1995; Van Halderen et al., 1995;

Segalés et al., 1996; Duran et al., 1997; Sierra et al., 1997; Solignac, 1997; Yaeger, 1997; Thibault et al., 1998).

Of the pathogenic bacteria occurring in pigs, previous studies have suggested the aetiological involvement of *Streptococcus* species, *Salmonella typhimurium* and *Pasteurella multocida* (Sierra et al., 1997; Thibault et al., 1998; Thomson et al., 2001). Porcine reproductive and respiratory syndrome (PRRS) virus (Thibault et al., 1998) and circoviruses (Segalés et al., 1996; Segalés and Domingo, 2000; Rosell et al., 1999; Rosell et al., 2000) have been detected in the deposited immune complexes separately and also in the same cases simultaneously (Choi and Chae, 2001).

Drugs, chemical substances, dietary allergens and antigens of endogenous origin are also suggested to play a role in the pathogenesis of PDNS (Sierra et al., 1997).

The results of numerous recent studies from all over the world indicate that the characteristic skin and kidney lesions and the formation of immune complexes are caused by porcine circovirus type 2 (Allan et al., 1998; Ellis et al., 1998; Ellis et al., 1999). Circovirus (PCV-2) antigens have been detected in the organs, monocyte-macrophage cells, renal tubular epithelial cells and vascular endothelial cells of pigs that died of PDNS in Spain (Robbins et al., 1981; Segalés and Domingo, 2000), the United Kingdom (Gresham et al., 2000), Northern Ireland, Argentina and The Netherlands (Segalés and Domingo, 2000). By PCR we have also detected PCV-2 from Hungarian cases of PDNS.

The nucleotide sequence of a PCV-2 virus strain detected from a case of postweaning multisystemic wasting syndrome (PMWS) occurring in a Southern Hungarian pig herd (Kiss et al., 2000) was compared with that of the virus strain found by us. In the 451 base pair long nucleotide sequences nucleotide difference occurred in three places, two of which involved amino acid change. Considering the highly conservative nature of the DNA sequence studied, the difference found between the two Hungarian porcine circovirus strains isolated from a case of PDNS and a case of PMWS, respectively, can be considered substantial. Comparing that nucleotide sequence with that of PCV-2 strains isolated in North America (Fenaux et al., 2000), only a single nucleotide difference associated with amino acid change is found. The difference found between the two Hungarian circoviruses also suggests that the isolates originate from two separate courses of epizootics. This, however, will have to be confirmed by further investigations.

In the cases presented here, IgA, IgG, IgM and C_3 protein fractions were detected in the skin and kidney by immunohistochemical examinations. This supports the notion that immunopathological process play a role in the pathogenesis of the disease. The deposited proteins are considered to be immune complexes and their formation is attributed to antigen-antibody binding (Hélie et al., 1995; Sierra et al., 1997; Thibault et al., 1998). Our results obtained by studying

the tissue distribution of immunoglobulins are mostly consistent with the findings of earlier investigations. In contrast, components of the complement system were detected only rarely or not at all in this study. There are two possible explanations for this finding and for the absence of immunoglobulins from the skin of two animals despite the presence of gross lesions. One possibility is that the antigen to be detected sustained such damage during tissue fixation and processing which rendered it undetectable. The other possible explanation is that the antigens sought by us were disrupted in the deposited immune complexes by the physiological degradation processes taking place in the organism.

The pathogenesis of vascular lesions is yet unclear. One hypothesis is that the deposition in the blood vessel wall of immune complexes formed in the circulating blood may play a role. Another possibility is a cellular immune reaction directed at the deposited immune complexes or perhaps at an own antigen component. The possibility of direct vascular damage caused by certain pathogens can neither be excluded (Sierra et al., 1997; Thibault et al., 1998).

The cutaneous lesions seen in pigs are similar to those observed in systemic lupus erythematosus (SLE), an immunopathological condition occurring in humans. Human cases of that disease are also characterised by vasculitis seen in the corium of pathologically altered skin areas showing red plaque formation. Vasculitis is associated with lymphocytic infiltration and fibrinoid degeneration in the blood vessel walls. In about 70% of the cases renal lesions (proliferative or membranous glomerulonephritis) also occur (Robbins et al., 1981).

Of the other nephropathies of pigs, ochratoxicosis (Balkan nephropathy) occurs also in Hungarian pig herds (Glávits et al., 1993). It is characterised by degenerative changes (tubulonephrosis) and, at an advanced stage, focal or diffuse renal fibrosis associated with atrophy of the renal parenchyma. However, in this disease no vascular changes of immunopathological nature can be observed in the kidneys or in other organs.

The presence of leptospira, Aujeszky's disease virus and PRRS virus infection in our cases were excluded. PMWS did not occur on the affected farms.

Because of its clinical symptoms (fever, cutaneous haemorrhages) and some of its pathological lesions (petechiae in the renal cortex), porcine dermatitis nephropathy syndrome has differential diagnostic importance, as it has to be distinguished from certain infectious pig diseases, first of all from swine fever.

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