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### Summary

### Zusammenfassung

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## Case report/Fallbericht

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### Multicentric T-cell lymphoma accompanied by infiltration of the peripheral and central nervous system in a fattening pig

*Multizentrisches T-Zell-Lymphom mit Infiltration des peripheren und zentralen Nervensystems bei einem Mastschwein*

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Multicentric lymphomas, usually of B-cell origin, are rather common neoplasms in pigs, which usually affect lymph nodes and different organ systems. An uncommon manifestation of malignant lymphoma represents neoplastic peripheral nerve involvement, which has been reported in human medicine. So far, only single cases of lymphoma with manifestation in peripheral nerves (known as neurolymphomatosis) without leukemic conversion have been mentioned in different animal species others than swine.

The present case report describes the occurrence of a multicentric T-cell lymphoma in a fattening pig with marked leukocytosis. The pig was presented with symptoms of lethargy, weight loss, and fever. Bone marrow aspirate contained all stages of granulocytic and erythrocytic precursors, and a remarkable large number of eosinophiles and undifferentiated blasts. At necropsy, the carcass showed generalized lymphadenopathy and severe hepatosplenomegaly. Histological findings included neoplastic round cell infiltrations in lymph nodes, bone marrow, tonsils, lung, spleen, liver, kidneys, urinary bladder, small and large intestine, and meninges. Additionally, neoplastic cells were present in the sciatic and medial plantar nerve of the left hind leg. The diagnosis T-cell lymphoma was confirmed immunohistochemically.

To the author's knowledge, this work represents the first report of peripheral nerve involvement in a pig with multicentric T-cell lymphoma accompanied by CNS involvement and leukemia.

**Keywords:** T-cell lymphoma, leukemia, peripheral nerves, central nervous system, pig

Multizentrische Lymphome insbesondere vom B-Zell-Typ sind beim Schwein nicht ungewöhnlich und befallen Lymphknoten und weitere Organsysteme. Dagegen stellt die beim Menschen beschriebene Infiltration der peripheren Nerven eine Seltenheit dar. Bislang wurden lediglich Einzelfälle von Lymphomen mit Infiltration peripherer Nerven ohne leukämische Veränderungen des Blutbildes bei verschiedenen Tierarten, jedoch nicht beim Schwein, erwähnt. Dabei wird die Infiltration der peripheren Nerven durch Lymphome häufig als Neurolymphomatose bezeichnet.

Der vorliegende Fallbericht beschreibt das Auftreten eines multizentrischen T-Zell-Lymphoms mit deutlicher Leukozytose bei einem Mastschwein. Die klinischen Symptome waren Lethargie, Gewichtsverlust und Fieber. Ein Knochenmarkspunktat enthielt verschiedene Reifungsstufen der Erythropoese und Granulopoese, sowie eine auffällig hohe Anzahl an Eosinophilen und undifferenzierten Blasten.

Bei der Sektion wies der Tierkörper eine generalisierte Lymphadenopathie und eine hochgradige Hepatosplenomegalie auf. Histologisch zeigten sich neoplastische Rundzellinfiltrationen in Lymphknoten, Knochenmark, Tonsillen, Lunge, Milz, Leber, Nieren, Harnblase, Dünn- und Dickdarm und Meningen. Außerdem

befanden sich neoplastische Zellen im Nervus ischiadicus und Nervus plantaris medialis des linken Hinterbeins. Die Diagnose T-Zell-Lymphom wurde immunhistologisch abgesichert.

Nach den Kenntnissen der Autoren ist dies die erste Beschreibung eines Schweins mit multizentrischem T-Zell-Tumor mit Infiltration peripherer Nerven unter Beteiligung des ZNS und Ausbildung einer Leukämie.

**Schlüsselwörter:** T-Zell-Lymphom, Leukämie, periphere Nerven, Zentralnervensystem, Schwein

## Introduction

Malignant lymphomas are rather common neoplasms in pigs, which occur predominantly as multicentric and thymic forms. The onset of the disease is often at the age of one year or less (Drolet, 2012). In the multicentric form, lymph nodes are primarily involved and commonly symmetrically affected. In addition, neoplastic infiltrations of liver, spleen, kidneys, lungs, heart, gastrointestinal tract and bone marrow may occur (Moulton and Dungworth, 1978). Usually tissue alterations are not accompanied by leukemia (Jarrett and Mackey, 1974), but it might be seen in animals with extensive metastatic lesions (Tanimoto et al., 1994).

Lymphomas in domestic animals usually arise from either B-cells or T-cells, which can be determined by immunohistochemistry. An uncommon manifestation primarily of B-cell lymphoma is in cranial nerves and peripheral nerve roots, plexus, or nerves (Baehring and Batchelor, 2012). This kind of lymphoma is also referred to as neurolymphomatosis.

Peripheral nerve involvement of malignant lymphomas in domestic mammals is rare and only single cases have been described in dogs (Pfaff et al., 2000; Schaffer et al., 2011; Rupp et al., 2014; Ueno et al., 2014), cats (Allen and Amis, 1975; Higgins et al., 2008; Mandrioli et al., 2012), and horses (Lehmbecker et al., 2014; Westerman et al., 2014) (Tab. 1).

The following report describes an unusual manifestation of multicentric T-cell lymphoma in a pig with malignant infiltration of peripheral nerves and meninges accompanied by leukemia.

## Case Presentation

An approximately four months old crossbred castrated male pig, with about 45 kg body weight was admitted to the Clinic for Swine of the Veterinary University of Hannover for teaching purposes due to malformations of the forelegs. The pig belonged to a multiplying herd with about 400 sows. During suckling period, it was vaccinated against *Mycoplasma hyopneumoniae*, porcine reproductive and respiratory syndrome virus and edema disease with Shiga-like toxin. During weaning time it was additionally vaccinated against *Actinobacillus pleuropneumoniae*.

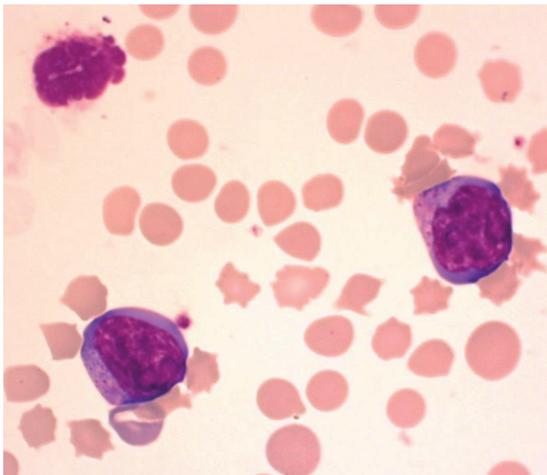
X-rays of the forelegs were taken and distal ulna osteochondrosis was diagnosed. The pig was kept in a unit with straw, and in terms of the general examination, no abnormal findings apart from a slight stiff walking on the tiptoes of both forelegs were detected.

About four weeks after admission to the clinic the pig got fever (41.2 °C) and mild diarrhoea. Antibiotic (Amoxicillin: Duphamox LA 150 mg/ml<sup>®</sup>, Zoetis Deutschland GmbH, Germany) and antiphlogistic (Meloxicam: Metacam 20 mg/ml<sup>®</sup>, Boehringer Ingelheim Vetmedica GmbH, Germany) treatments were started for a period of six days. Two days after the first treatment the pig recovered well and body temperature dropped to the normal range. Hematologic analysis revealed normocytic anemia (4.94 × 10<sup>12</sup> erythrocytes/liter (RI: 5.8–8.2 × 10<sup>12</sup> cells/liter), hemoglobin: 94 gram/liter (RI: 108–148 gram/liter), hematocrit: 28% (RI: 33–45%)) and marked leukocytosis (142.4 × 10<sup>9</sup> cells/liter (RI: 10–22 × 10<sup>9</sup>)) with 84% blast cells, showing a scant, agranular cytoplasm and promi-

**TABLE 1:** Cases of lymphoma with peripheral nerve involvement in domestic animals described in the literature

Author	Species	Immunophenotype	Extension of neoplastic cells into peripheral organs	White blood cell count	Involvement of the CNS
Pfaff et al. (2000)	Dog	Not evaluated	Yes	n. m.*	meninges
Schaffer et al. (2012)	Dog	B-cell lymphoma	Yes	n. m.*	none
Ueno et al. (2014)	Dog	T-cell lymphoma	Yes	no abnorm.**	pituitary gland
Rupp et al. (2014)	Dog	T-cell lymphoma	Yes	no abnorm.**	leptomeninges
Lehmbecker et al. (2014)	Horse 1	T-cell rich B-cell lymphoma	Yes	n. m.*	none
	Horse 2	T-cell rich B-cell lymphoma	Yes	n. m.*	pituitary gland, brain, cervical spinal cord
	Horse 3	T-cell rich B-cell lymphoma	Yes	n. m.*	brain
Westermann et al. (2014)	Horse	Neutropic T-cell rich B-cell lymphoma	No	no abnorm.**	spinal cord meninges
Higgins et al. (2008)	Cat	B-cell, Burkitt-type lymphoma	No	n. m.*	none
Mandrioli et al. (2012)	Cat	T-cell lymphoma	No	n. m.*	brain stem, leptomeninges, cervical spinal cord

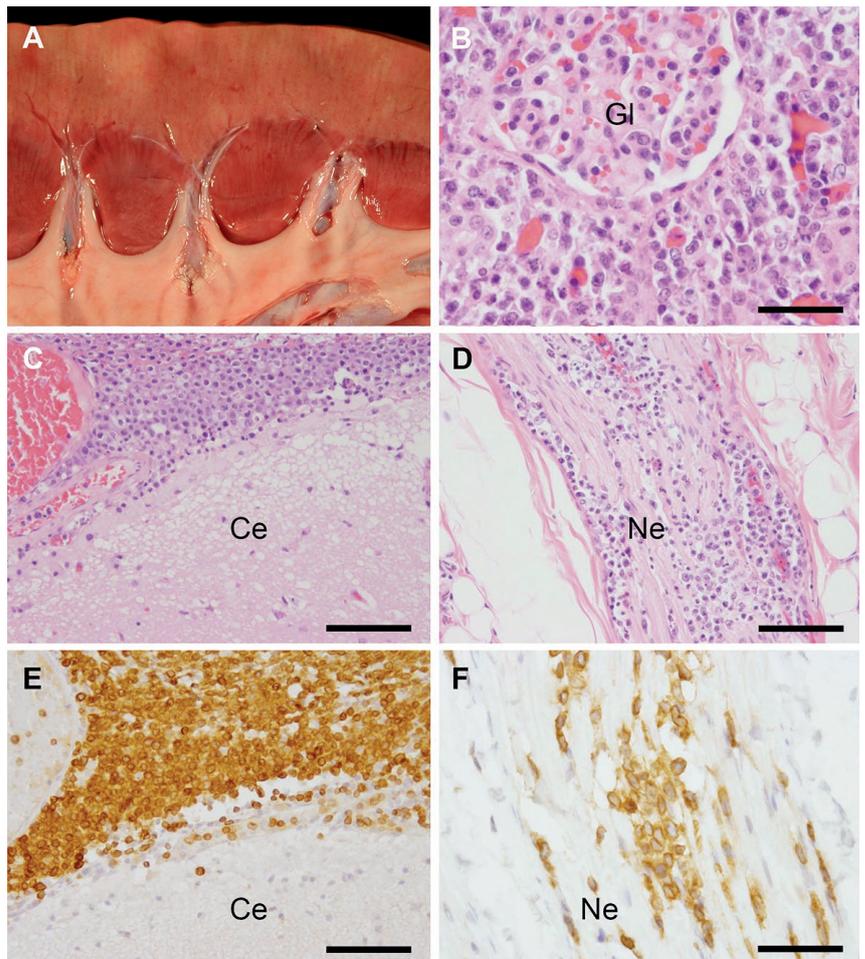
\*n. m. not mentioned, \*\*no abnormalities



**FIGURE 1:** Wright-Giemsa stained blood smear showing blast cells with scant cytoplasm and prominent nucleoli (objective x100)

nent nucleoli (Fig. 1). Segmented neutrophils ( $4.27 \times 10^9$  cells/liter, RI:  $1.0\text{--}8.2 \times 10^9$  cells/liter) were within the physiological range, whereas banded neutrophils ( $2.14 \times 10^9$  cells/liter, RI:  $0\text{--}1.5 \times 10^9$  cells/liter), and eosinophils were increased ( $1.42 \times 10^9$  cells/liter, RI:  $0\text{--}1.3 \times 10^9$  cells/liter). Hematologic findings were indicative of lymphoid leukemia.

Two days after the last treatment, the body temperature increased again ( $41.6^\circ\text{C}$ ). The pig showed progressive listlessness and anorexia, hemorrhagic diarrhea and recumbency. Because of the poor general condition and prognosis, the animal was euthanised, and a bone marrow aspiration was taken from the sternum. Afterwards, the carcass was submitted for necropsy to the Department of Pathology, University of Veterinary Medicine of Hannover.



**FIGURE 2:** A) Multiple white foci and striation of the renal cortex and medulla. B) Monomorphic infiltration of neoplastic round cells in the renal interstitium. Gl = glomerulum; HE-stain; scale bar =  $50 \mu\text{m}$ . C) Diffuse meningeal infiltrates of neoplastic round cells in the brain. Ce = cerebrum; HE-stain; scale bar =  $100 \mu\text{m}$ . D) Endoneurial infiltrates of neoplastic round cells in the sciatic nerve. Ne = nerve; HE-stain; scale bar =  $100 \mu\text{m}$ . E) CD3 expression of neoplastic round (T-cell lymphoma) in the meninges. Ce = cerebrum; Avidin biotin peroxidase method; scale bar =  $100 \mu\text{m}$ . F) CD3-expression of neoplastic round cells (T-cell lymphoma) in the sciatic nerve. Ne = nerve; avidin biotin peroxidase method; scale bar =  $50 \mu\text{m}$ .

**TABLE 2:** Differential cell counts of sternal bone marrow aspirate

Cell type	Number of cells/1000 counted cells
<b>Myelopoietic cells</b>	
Segmented neutrophils	37
Banded neutrophils	42
Metamyelocytes	47
Myelocytes	26
Promyelocytes	6
Myeloblasts	2
Eosinophilic cells	31
Basophilic cells	2
<b>Erythropoietic cells</b>	
Normoblasts	311
Proerythroblasts	158
Erythroblasts	28
<b>Other cell types</b>	
Lymphocytes	11
Plasma cells	2
Monocytes	2
Morphologically undifferentiated blasts	295

Smears prepared from the bone marrow aspirate contained numerous marrow particles and revealed scattered granulocytic and erythrocytic precursors. A remarkable large number of eosinophils and undifferentiated blasts with light blue cytoplasm were observed in Wright-Giemsa stained smears (Tab. 2).

At postmortem examination a severe generalized lymphadenopathy with enlarged visceral and parietal lymph nodes up to 6 cm in diameter with mottled, partly nodular cut surface could be seen. Additionally, a massive hepatomegaly and splenomegalie were observed. The kidneys showed multifocal to coalescing white areas in the cortex and medulla (Fig. 2A). In the abdominal cavity 600 ml of a turbid serous fluid with fibrin was found. No gross abnormalities of peripheral nerves and CNS were found.

For histopathological examination, tissue samples (sternal bone marrow, lymph nodes [gastric, sternal, popliteal, lumbar], tonsils, lung, spleen, liver, kidneys, urinary bladder, small intestine, large intestine, brain [cerebrum, cerebellum, brain stem], and peripheral nerves [sciatic, plantar]) were collected, fixed in 10 % non-buffered formalin, and embedded in paraffin wax. Sections ( $5 \mu\text{m}$ ) were stained with hematoxylin and eosin (HE). For phenotypical characterization of neoplastic

round cells immunohistochemistry was performed by using the avidin biotin peroxidase method (Alldinger et al., 1996). All antibodies were diluted in phosphate buffered saline with bovine serum albumine (PBS/BSA, pH 7.1). Antibodies specific for CD3 (rabbit polyclonal, DakoCytomation, Hamburg, Germany, dilution 1:1000) for detecting T cells, CD 79a (mouse monoclonal, DakoCytomation, Hamburg, Germany, dilution 1:60) for detecting B cells and lysozyme (rabbit polyclonal, DAKO, Glostrup, Denmark, dilution 1:200) were used. Porcine lymph nodes were used as positive control tissue. For negative controls primary antibodies were replaced by ascites fluid from non-immunized BALB/c mice (Cedarlane, Ontario, Canada) or normal rabbit serum (Sigma Aldrich Chemie GmbH, Munich, Germany).

Histology revealed the presence of monomorphic neoplastic round cell infiltrates in the lymph nodes, bone marrow, tonsils, lung, spleen, liver, kidney (Fig. 2B), urinary bladder, and intestine as well as in cerebral and cerebellar meninges (Fig. 2C). In addition, peri- and endoneural round cell invasions were found within the sciatic (Fig. 2D) and medial plantar nerve of the left hind leg. Using immunohistochemistry it could be shown that the majority of neoplastic round cells expressed CD3 (Fig. 2E and 2F) while no expression of CD79a and lysozyme was observed within the tumor, a pattern characteristic of T-cell origin (multicentric T-cell lymphoma).

## Discussion

Although lymphoma is the most common neoplasm in swine the etiology is still unknown. C-type virus particles with supposed oncogenic properties have been described to be associated with cases of porcine lymphosarcoma (Skavlen et al., 1986; Hayashi et al., 1988). Furthermore, few reports mention the occurrence of hereditary lymphomas in pig (McTaggart et al., 1971; Head et al., 1974; Ogihara et al., 2012), although no breed predisposition can be observed (Jacobs et al., 2002). Peripheral nerve involvement of malignant lymphomas in domestic animals is rarely described, only in fowls suffering from Marek's disease, which is induced by an oncogenic herpesvirus causing T-cell lymphoma, it can be observed frequently.

In man neoplastic infiltrates in peripheral nerves, usually of B-cell origin, is rarely accompanied by leukemia (Grisariu et al., 2010), but it is frequently associated with secondary brain lesions (Jellinger and Radaszkiewicz, 1976). The involvement of the CNS differs case-by-case in the reports from domestic animals and changes in blood cell counts have not been described (Tab. 1). All mentioned cases were accompanied by neurological deficits, like ataxia, lameness and paralysis, which could not be observed in the presented case. In man, asymptomatic cases of peripheral nerve infiltration were also described (Padma et al., 2014). Generally, peripheral nerve lymphoma (neurolymphomatosis) is classified in four clinical presentations: painful involvement of nerves or roots, painful or painless cranial neuropathy, painless involvement of peripheral nerves, and involvement of a single peripheral nerve with or without pain (Baehring et al., 2003).

This work represents the first report of a multicentric T-cell lymphoma in a pig accompanied by leukemia and malignant infiltration of peripheral nerves and menin-

ges. In contrast to reports of lymphomas with peripheral nerve involvement in other animal species, the pig did not show any signs of neurological deficits, which is in accordance to clinical observations in man, and leads to the assumption that the involvement of nerves in multicentric lymphomas remains frequently undiscovered.

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## Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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