Porcine Research

Lymphomas in swine – a review

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Abstract. Lymphoma is the most commonly diagnosed neoplasm in pigs, and young individuals (under 1-year-old) are usually affected. Multicentric and thymic lymphomas are more often diagnosed, but other primary locations, such as the digestive tract, have been described. Immunohistochemically, most lymphomas in swine originate in B lymphocytes, except the primary thymic location. The etiology is controversial and it was hypothesized the possible involvement of an autosomal recessive gene, hence the character of familial disease. The other possibility is a viral-induced neoplasm, such as swine lymphoma type C virus (PLCP). However, the etiology of lymphoma in this species is not fully known and further studies are needed to provide additional information regarding this subject.
Key Words: neoplasm in pigs, *Sus scrofa*, tumor, autosomal recessive gene, etiology.

Introduction. Neoplastic diseases have not been widely studied in swine, although their presence in slaughtered animals has been recorded in several countries in recent decades. Overall, tumors are uncommon in swine, and most cases have been recorded in young animals (Nielsen & Moulton 1990; Drolet 2012).

Because most pigs are slaughtered at the age of 6 months or even earlier, the most commonly diagnosed tumors are those that usually occur in young animals, such as lymphoma, nephroblastoma, and melanoma (Edwards & Mulley 1999; Alsop 2005). Malignant tumors of the lymphatic system in swine were first reported in 1865 (Bostock & Owen 1973; Duran-Struuck et al 2015). Lymphoma is a general term that refers to a malignant neoplasm of lymphoid tissue (Blood & Studder 1988; Alsop 2005).

Epidemiology. Lymphoma in swine has a relatively high incidence, being considered one of the most frequently encountered neoplasms, accounting 23-41% of the tumors diagnosed in this species (Baba 2002; Jacobs et al 2002; Baba & Cătoi 2007; Ogihara et al 2012), followed by nephroblastoma and melanoma (Charles 1996; Alsop 2005). Lymphoma usually affects pigs under 1-year-old, but it was also diagnosed in individuals under 6-month-old (Baba 2002; Baba & Cătoi 2007).

There are no records regarding breed or sex predisposition. Clinical diagnosis of lymphoma is usually difficult because symptoms such as anorexia, dyspnea, and ataxia are unspecific and they can suggest other diseases (Bostock & Owen 1973; Alsop 2005).

Classification of swine lymphoma. Lymphomas in domestic animals are characterized according to their anatomic localization, as follows: multicentric lymphoma, thymic lymphoma, digestive lymphoma and cutaneous lymphoma (Moulton & Harvey 1990; Tanimoto et al 1994). Although, lymphoma is the most frequently neoplastic disease diagnosed in swine, to date there are few studies regarding this pathology. However, it is considered that multicentric and thymic lymphoma is the most common, and the other anatomic locations are rarely involved (Moulton & Harvey 1990; Tanimoto et al 1994). Digestive or alimentary tract lymphoma, that affects the ileum and mesenteric lymph nodes, was recently described (Marcato 1987; Hayashi et al 1988; Nakajima et al 1989; Kashima et al 1990; Tanimoto et al 1994).

In advanced clinical stages of multicentric or thymic lymphoma, that affect lymph nodes and thymus respectively, other organs may be involved such as spleen, liver or kidneys. In renal lymphoma, the gross and histological features have a diffuse distribution of lesions, but more frequently a nodular aspect can be observed. Grossly, the kidneys are swollen, pale or with the presence of multiple white nodules that give an irregular aspect of the surface. In some cases, the renal lesions may have a hemorrhagic aspect (Stevenson & DeWitt 1973; Marcato 1987; Drolet 2012), and they can be confused with some systemic infectious diseases (Drolet 2012). The precise mechanism of pathogenesis for the hemorrhagic lesions is not known, but they seem to be due to an underlying coagulation defect, or due to acute renal infarcts, secondary to neoplastic emboli (Drolet 2012).

In multicentric lymphoma, invariably the mesenteric lymph nodes are also involved. Usually, they are severely affected by edema, due to obstruction of lymphatic vessels with neoplastic cells (Thomson & Friendship 2012). Rarely, lungs, mammary gland, skin, serous membranes or other organs may be affected. In some individuals, the last stage of the disease, leukemia, is occasionally diagnosed (Baba 2002; Baba & Cătoi 2007; Drolet 2012).

Lymph nodes are severely hypertrophied and the normal histological structure is diffusely effaced and replaced by a neoplastic process. The spleen is severely enlarged, friable and on cross-section, numerous white nodules can be observed (Bostock & Owen 1973; Alsop 2005).

In liver and kidneys, neoplastic cells may form well-delimited nodular structures or they can have a diffuse and infiltrative aspect with secondary hypertrophy of the affected organs (Confer & Panciera 2001; Alsop 2005).

Previously reported, there are only a few studies that evaluated the cytological features of swine lymphoma (Migaki 1969; Hayashi et al 1988). Approximately 60% of the total number of 136 lymphoma cases in swine was large cell type (Valli 2007; Valli et al 2017).

In a study performed on 200 cases, cytological classification of lymphomas was performed according to the criteria used in domestic animals, as follows: lymphocytic lymphoma (42%), lymphoblastic lymphoma (34%), histiocytic lymphoma (15%) and mixed type (9%) (Migaki 1969). In another study performed on 36 cases, the majority of the diagnosed lymphomas were Burkitt or mixed type, but the classification criteria used was from human medicine (Hayashi et al 1988). Burkitt type lymphoma is more frequently diagnosed in dogs and cats, but it can be also diagnosed in swine, bovine, horse and mouse (Valli et al 2017).

Lymphoma in swine resembles non-Hodgkin lymphomas in humans (Kadota & Nakajima 1988; Nakajima et al 1988; Baba 2002; Baba & Cătoi 2007).

Tanimoto et al (1994), evaluated 11 cases of digestive lymphoma and they were histologically classified according to National Cancer Institute Working Formulation in diffuse large B-cell lymphoma (10 cases), a single case of mixed lymphoma, large and small cell lymphoma, respectively.

In a previous study, six cases of swine lymphoma were grouped in four histological types according to World Health Organization (WHO) criteria used in humans (Hoshino et al 2006; Ogihara et al 2012). Histological subtypes as: signet ring cell lymphoma (Kadota & Niibori 1985; Ogihara et al 2012), lymphoepithelioid lymphoma (Kadota 1987; Ogihara et al 2012) and T cell-rich B cell lymphoma (Tanimoto & Ohtsuki 1998; Ogihara et al 2012) were diagnosed, although they are rarely diagnosed even in humans (Ogihara et al 2012).

Immunohistochemical studies showed that most lymphomas in swine are originated from B lymphocytes, except for the thymus location (Kadota et al 1986; Tanimoto et al 1994).

B-cell lymphomas are frequently diagnosed in a digestive location in both swine and ovine because they originate in Peyer's patches or in other intestinal lymphoid structures such as mucosa-associated lymphoid tissue (MALT) (Valli et al 2017).

Etiology. Lymphomas in swine are most likely caused by the interaction of environmental factors, hereditary factors, and infectious agents. In several species, viruses, such as bovine leukemia virus, avian leukosis virus and feline leukemia virus, are recognized as responsible for neoplastic diseases (Alsop 2005).

Currently, two major etiologies are mentioned as causative factors of lymphoma in swine: presence of an autosomal recessive gene, therefore the familial character of the disease, but also the possibility of involvement of a C-type virus, which was identified in neoplastic cells, but attempts of experimental inoculation failed (Moulton & Dungworth 1987; Valli 1993; Baba 2002; Baba & Cătoi 2007).

Busse et al (1978) studied the possibility that lymphoma in swine is induced by porcine lymphoma C-type particle (PLCP), an oncornavirus related to feline leukemia virus. However, serological analyses of healthy animals, affected individuals and experimentally infected showed no differences. The research group concluded that PLCP is an endogenous retrovirus and most likely it is not the etiological agent in swine lymphoma (Alsop 2005).

There are few data regarding the hereditary or familial lymphoma in swine (Ogihara et al 2012). In a herd, 53 lymphomas in young piglets were associated to inbreeding (Head et al 1974; Ogihara et al 2012), and in another study, two sows (dam and offspring) were diagnosed with lymphoid neoplasm, one of them presenting also splenomegaly (Saito et al 1982; Ogihara et al 2012).

Also, McTaggart et al (1979) associated lymphoma in a herd of Large White breed in Scotland with the involvement of an autosomal recessive gene (Alsop 2005).

It is well known that chemical substances are responsible of the high rate of occurrence of lymphoma cases in humans, but in animals it is not known if exposure to chemical substances plays a significant role in spontaneous tumorigenesis (Cullen et al 2002; Alsop 2005).

Conclusions. Currently, the precise etiology of lymphoma in swine is not fully understood. Factors as chemical substances, viral agents or even an inherited-pattern of diseases have been proposed, but without the possibility to establish a link to the disease. Due to multiple similarities with lymphoma in humans, further studies are required because swine could serve as an animal model.

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Received: 01 November 2019. Accepted: 09 December 2019. Published online: 17 December 2019.
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How to cite this article:
Popa R., Toma C., Marica R., Biriș A., Tăbăran F., 2019 Lymphomas in swine – a review. Porc Res 9(1):34-38.