Published in final edited form as:

Xenotransplantation. 2019 March ; 26(2): e12469. doi:10.1111/xen.12469.

WILL DONOR-DERIVED NEOPLASIA BE PROBLEMATIC AFTER CLINICAL PIG ORGAN OR CELL XENOTRANSPLANTATION?

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Abstract

There is an increased incidence of certain tumors and other neoplastic disease in organ allotransplant recipients receiving immunosuppressive therapy. Following clinical pig organ xenotransplantation, will there be a risk of the development of neoplasia in the pig graft or in other tissues transplanted with it, e.g., lymph nodes?

The incidence of neoplasia in young slaughterhouse pigs is very low (<0.005%), but in older pigs is largely unknown (as most pigs are killed within the first six months of life). However, lymphosarcoma, nephroblastoma, and melanoma have been reported in pigs. These tumors should be readily identified by ultrasound or direct inspection and palpation before an organ is excised for clinical xenotransplantation, and so transfer to the human recipient should be unlikely.

Post-transplant lymphoproliferative disorder (PTLD) has been reported in pigs receiving intensive immunomodulatory therapy, particularly if this includes whole body irradiation, in an effort to induce mixed hematopoietic chimerism and immunological tolerance.

However, the pigs used as sources of organs in xenotransplantation should be free of the porcine lymphotropic herpesvirus that is a key causative factor for PTLD in pigs, and so donor-derived PTLD should not occur.

We conclude that the risk of a malignant tumor developing in a transplanted organ from a young pig is small.

Keywords

Neoplasia; Pigs; Post-transplant lymphoproliferative disorder; Tumors; Xenotransplantation

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Conflict of interest

No author declares a conflict of interest.

Introduction

In regard to xenotransplantation, the topic of donor-derived neoplasia was first reviewed in 1991¹ and first specifically investigated in 1994.² In the 1991 review, the incidence of neoplasms in pigs in the USA was reported to be approximately 0.004%.³ This estimate was made following ante-mortem and post-mortem inspection of over 83 million pigs by the US Department of Agriculture in 1972.

A search for confirmatory and more recent data revealed that, although the average lifespan of most domestic pigs is 15–27 years,^{4–6} approximately 90% of pigs are slaughtered between 4.5 and 6 months of age as sources of food.^{7,8} Hence, relatively little is known about malignancies occurring in older pigs. However, by the age of 6 months or before, the source pigs (if not miniature swine) will be of a sufficient size e.g., 90 kg, for their kidneys to be transplanted into adult human recipients. As pigs will therefore likely be used as sources of organs for clinical transplantation during the first year of life, it is important to review the data on malignancies that develop in young pigs.

Incidence of neoplasia in young pigs

Cancer in pigs is rare, with an occurrence of <40 per million slaughtered pigs (Table 1), although the incidence could be higher due to under-reporting.⁹ The actual incidence would almost certainly be higher if pigs were allowed to survive into middle life or old age.

Although all neoplasms are rare in young pigs, the most common tumors are malignant lymphoma (lymphosarcoma),^{7,9–15} nephroblastoma^{10,16–19} and melanoma.^{20,21} Slaughter data from abattoirs in Ontario for the years 1996–2003 indicated that 0.02 to 0.10 carcasses per 10,000 pigs had lymphosarcoma.¹⁵ In the years 1991–2003, 28 cases of lymphosarcoma, 4 cases of nephroblastoma, and six cases of melanoma were reported in pigs <1-year-old by the Animal Health Laboratory, University of Guelph, in Ontario, Canada. These represented only 0.1%, 0.014%, and 0.021%, respectively, of the total pigs examined in that period. Lymphosarcomas and nephroblastomas do not affect any specific breed.^{9,18,19}

Lymphosarcoma (malignant lymphoma)

Lymphosarcoma has been estimated to have an incidence of between 0.001 and 0.3%,²² and in one survey contributed 46% of all tumors in pigs,²³ and Lymphosarcoma is usually a sporadic disease⁹ although there have been reports of a high incidence in a small number of specific herds, in which the disease appeared as early as 6–12 weeks of age.^{7,24,25} The relative roles of environmental chemical exposure, including animal feed, bedding, and water, remain unknown. There is otherwise no known breed or sex predisposition.

The diagnosis can be suspected in any animal showing anorexia, dyspnea, and ataxia, but there may be no clinical signs.^{11,26} By the time loss of weight and strength has occurred, the disease is usually well-advanced. The most common specific manifestation and presenting sign is the pronounced enlargement of a number of lymph nodes. The spleen is commonly enlarged, sometimes to great dimensions. Several internal organs may also be involved, including the kidneys.²⁷ In the kidneys, tumor cells may appear as single homogenous gray-

white nodules, or as diffuse infiltrates that cause nephric enlargement.²⁸ If the diagnosis has not been made earlier, it should be possible to make it, or at least strongly suspect it, by careful examination of the major organs and lymph nodes at the time of organ excision for the purposes of transplantation.

A chronic granulomatous disease in pigs with histological features similar to those of Hodgkin's disease in humans has been described,²⁹ and a thymic form of the disease has been reported in pigs.¹⁵ A few cases (approximately 5%) have been reported where lesions are found in the viscera without any detectable lymph node involvement. The heart is rarely affected but, if so, it is almost always the base of the heart and the walls of the atria that are involved, occasionally with later extension to the ventricles.⁷ Primary pulmonary malignancies are rare, but secondaries from lymphosarcoma can be seen in the lung.³⁰

Some animals afflicted with the condition demonstrate exceedingly high white blood cell counts with a predominance of lymphocytes – the leukemic form of the disease.

Renal tumors

The most common primary renal tumors in pigs are nephroblastomas, whereas adenocarcinomas are rare, though renal adenomas and hemangiomas can occur. Clear cell renal carcinomas have not been reported in pigs. Secondary tumors are more common than primary tumors, the most common secondary tumor being lymphosarcoma.^{10,16,17}

A 1968 review of tumors of the kidney in pigs indicated they were rare, with an incidence of 4.3 per million.¹⁷ Nephroblastoma has an incidence of approximately 0.02% and is seen most often in pigs under the age of one year. Metastatic lesions are rare, but can occur, usually in the renal and sub-lumbar lymph nodes and occasionally elsewhere. There is no evidence of sex predisposition and no association with any other renal disease.

Skin tumors

Melanoma is rare in pigs, but some breeds are more prone to its development, e.g., Sinclair miniature swine, Duroc.^{31,32} Miniature swine have a higher prevalence of cutaneous melanoma,^{32–35} and in some breeds, e.g., Sinclair, Hormell, the predisposition can be inherited.^{36–39} However, it can also be seen in conventional pigs.^{40–43} Melanomas are found most often in the jowl (cheek) and flank regions, and thus can be differentiated from melanosis. (which is a very common pigmentary entity, but discreet nodular masses are not present). Lesions, believed to be metastatic from skin melanoma primaries, have been found in many internal organs. Unlike humans, melanoma is extremely uncommon in the unpigmented skin of white pigs, e.g., Landrace, Large White, and is not associated with exposure to ultraviolet radiation. Most melanomas in Sinclair miniature swine are malignant, though some regress spontaneously³⁷. In contrast, very few melanomas in Duroc pigs are malignant.^{44,45}

Cutaneous mast cell tumors have been described, but are also rare, with one study citing only 5 cases in 664 million pigs examined.^{46,47} They tend to arise several years after birth.

Hepatic tumors

Primary liver malignancy is rare in young pigs.^{8,48,49} However, *hepatocellular carcinomas* have been reported in Vietnamese pot-bellied pigs, but generally do not develop until the pig is old, with an average age of presentation being 16 years.⁵⁰ The most common clinical signs are decreased appetite and weight loss. Half of the cases have possible intrahepatic metastases, with occasional extrahepatic metastases.

Other tumors

Cardiac rhabdomyoma has been seen in stillborn red wattle pigs, and in those of the same breed that died from other causes, usually following sudden death, most probably from conduction dysfunction.^{51,52} Their size may vary from less than a millimeter to several centimeters.⁵¹ *Rhabdomyosarcomas* can originate from heart muscle, urinary bladder, or the appendicular skeleton, and are occasionally seen in pigs <6 months of age.⁵³

Vietnamese pot-bellied pigs have an increased propensity for *genital tract tumors*, especially tumors of the uterus. These tumors more commonly infiltrate locally, rather than metastasize. Leiomyoma and leiomyosarcoma have also been reported in Vietnamese pot-bellied pigs aged 11–14 years.⁵⁴

Endocrine tumors are rarely observed in pigs,⁵⁵ but a malignant pheochromocytoma has been reported.⁵⁶

To our knowledge, there is no evidence that any of the current genetic manipulations made to pigs that will be used as sources of organs for xenotransplantation will increase the risk of malignant change taking place in their tissues⁵⁷. However, it is theoretically possible that, if a tumor develops in a pig kidney that expresses certain humanized proteins, e.g., CD55 (human decay-accelerating factor), endothelial protein C receptor (EPCR), its malignant potential might be potentiated.^{58,59}

Post-transplantation lymphoproliferative disorder (PTLD)

PTLD is a potentially fatal complication of immunosuppressive therapy in clinical allotransplantation,^{60–62} and represents an abnormal proliferation of B cells with varied presentations that can range from polymorphic expansion to malignant monoclonal lymphoma.^{63–65} Host-type and donor-type PTLD can occur after organ and, particularly, bone marrow allotransplantation.

There have been a number of reports of PTLD in pigs exposed to intensive immunomodulatory or immunosuppressive regimens, particularly if subjected to irradiation and/or profound T cell depletion.^{66–69} It was also reported after allogeneic spleen transplantation in immunosuppressed miniature swine.⁷⁰ There has been a very low incidence after pig kidney allotransplantation,⁷⁰ but it has been reported in pigs undergoing liver allotransplantation, in which a porcine virus responsible for the respiratory and reproductive syndrome (PRRS) was identified in the lymphoid tissue of the recipients.⁷¹ Its development is usually associated with dramatic increases in the white blood cell count,

particularly of B lymphocytes, and of serum IgM,⁷⁰ which are therefore of diagnostic significance.

Whereas human PTLN is an Epstein-Barr (EBV)-associated complication following clinical organ transplantation, porcine PTLN is related to the porcine lymphotropic herpesvirus, a gammaherpesvirus.^{72,73} Indeed, PTLN has been reported in monkeys after pig kidney xenotransplantation and after monkey kidney allotransplantation.⁶¹ In both allogeneic and xenogeneic models, it was demonstrated to be associated with gammaherpesvirus-induced B cell proliferation.

However, the pigs used as sources of organs in xenotransplantation should be free of the porcine lymphotropic herpesvirus that is a key causative factor for PTLN in pigs, and so donor-derived PTLN should not occur. Therefore, if PTLN occurs in an immunosuppressed recipient of a pig organ xenograft, it will almost certainly be of recipient B cell origin.

Comment

The incidence of malignant tumors in pigs <6 months old is very low. With careful examination, laboratory evaluation, and the use of appropriate imaging techniques, it should be possible to exclude most tumors before the organ is excised and transplanted. Direct examination of the organs at the time of excision of the organ should also indicate whether a tumor or a metastasis is present.

The most common mode of spread of *lymphosarcomas* is lymphomatous, and the exact origin is often unknown, but is probably from lymph nodes or Peyer's patches. If visual inspection is insufficient to confirm that the lymph nodes surrounding the potential xenograft organ are free of tumor, noninvasive modalities, e.g., ultrasonography, computed tomography, or magnetic resonance imaging, may clarify the situation. The liver is a common site for metastases of lymphosarcoma and melanoma, and so imaging investigations may be diagnostically useful. However, screening and imaging pigs is difficult, and whenever there is doubt as to the presence of a tumor, a different pig should be selected.

Monitoring of the pigs will include regular examination of sentinel animals. Most viruses that can infect pigs (except PERV) can be eliminated by rearing under designated pathogen-free conditions. (The founder pigs will have been bred by Cesarean section to avoid any microbiological contamination from the sow, but subsequent generations will be born naturally.) If essential, though this is not generally believed to be necessary, PERV can be eliminated by genetic engineering techniques.^{74,75} We suggest that this high-health status should reduce the possibility of neoplasia developing, particularly tumors that might possibly be related to reactivation of viruses.

Conclusions

We suggest that the risk of a malignant tumor developing in a pig under the age of 6 months that is to be used as the source of an organ for clinical xenotransplantation is small. Careful visual examination of the pig and its organs during the 'donor' operation should be sufficient

to exclude any malignant condition. There are several noninvasive tests that can confirm the absence of a tumor, but, when in any doubt, it would probably be sensible to select another pig. If PTLTD develops, it would be of recipient origin.

Whether tumors will develop in the immunosuppressed recipient remains uncertain, but the incidence is likely to be similar to that in patients with allografts (unless the intensity of immunosuppressive therapy has to be greater). Long-term monitoring for de novo neoplasia will be required.

We conclude that most neoplasms occurring in human recipients of a pig kidney graft are likely to arise from host (not pig) tissues. However, it can be speculated that components of the donor-derived lymphoid system (transplanted with the pig organ) may undergo uncontrolled proliferation after transplantation in an immunosuppressed host harboring xenozoonotic lymphotropic viruses. At present, there is no model to assess this possibility, but it should be borne in mind when monitoring patients in future clinical trials.

Acknowledgements

Work on xenotransplantation at the University of Alabama at Birmingham is supported in part by NIH NIAID U19 grant AI090959.

Abbreviations

PERV	Porcine endogenous retrovirus
PTLD	Post-transplant lymphoproliferative disorder

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Table 1:

Neoplasms reported in pigs *

Organ system	Type of neoplasm
Skin and appendages	<i>Melanoma</i> , papilloma, squamous cell carcinoma
Musculoskeletal	Osteo(sarco)ma, chondro(sarco)ma, fibrosarcoma
Lymphatic	<i>lymphosarcoma</i> including <i>lymphoblastoma</i> , Large cell lymphoma, chronic granulomatous disease, myeloid leukemia, $\gamma\delta$ T cell lymphoma, plasma cell tumors, mastocytoma.
Respiratory	Nasal mucosa tumor
Cardiovascular	Rhabdomyoma (heart)
Digestive	Hepatocellular carcinoma, gastric carcinoma, mesothelioma
Urinary	<i>Nephroblastoma</i>
Genital adenocarcinoma,	Leiomyoma, Testicular, ovarian (granulosa cell, cystadenoma), teratoma, mammary gland tumor
Endocrine	Adrenocortical (adenoma, carcinoma), pheochromocytoma, thyroid neoplasms
Nervous	Primary neoplasms

* Although still rare, the more common tumors are indicated in italics and underlined.