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Rhabdomyosarcomas in Young Pigs in a Swine Breeding Farm: A Morphologic and Immunohistochemical Study


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Abstract. Within a 6-month-period, solitary or multiple tumors were observed in 25 young pigs in their first weeks of life in a swine breeding farm. The herd comprised approximately 100 animals, and affected pigs were observed in several litters. The number of affected litters varied from one to three. Five animals, all from different litters and with a total of 11 tumors, were studied. Histologically the tumors were classified as undifferentiated sarcomas. Electron microscopic examination of the tumors (n = 3) revealed myogenic differentiation, characterized by the presence of numerous cytoplasmic filaments with longitudinal densities and cytoplasmic dense bodies. Immunohistochemically, all 11 tumors were labeled by vimentin and desmin antibodies. Two tumors from which frozen material was available were additionally labeled by a titin antibody but did not show immunoreactivity with antibodies directed against myosin and α-sarcomeric actin. The tumors were finally diagnosed as undifferentiated rhabdomyosarcomas. The high incidence of these tumors within a short period of time in multiple young animals in different litters indicates a common causative event. The clinical history suggests a genetic cause.

Key words: Desmin; intermediate filaments; myosin; neoplasm; swine; titin; vimentin.

Rhabdomyosarcomas are uncommon neoplasms both in human beings and animals. Although these tumors occur sporadically, they have been reported in a broad range of animal species, such as dogs,3,36 cats,47 cattle,9,38 horses,20,55 sheep,16 rats,51,60 mice,19,57 monkeys,7 deer,22,31 and birds.17,49 Because these tumors arise from striated muscles, they can be encountered at many sites. Most often they are found in the heart, the urinary bladder, and the appendicular musculature; however, undifferentiated mesenchymal cells with skeletal muscle differentiation potential has been suggested as a possible origin,15,52 e.g., in the brain.22

Histologically, rhabdomyosarcomas in both human beings and animals show various morphologic patterns.23,52,55 Consequently, the diagnosis of rhabdomyosarcoma can be difficult.12,28,32,46,57 These tumors can mimic other soft tissue tumors, particularly in the absence of cross-striations, which are typical for rhabdomyoblastic differentiation.55 Thus, the apparent low frequency of rhabdomyosarcoma in animals may be a result of the low degree of differentiation of many tumors that results in a nonmyogenic tumor classification.19 Conclusive morphologic features characteristic of rhabdomyosarcomas, i.e., sarcomeric components, can be detected by electron microscopy, although in poorly differentiated tumors the identification of these components may appear inconclusive.6,28,29,39,54 Immunohistochemical demonstration of muscle-specific antigens has evolved as a valuable method for establishing myogenic differentiation in soft tissue tumors12,27,28,32,46,55 and has been superior to electron microscopic tumor examination in a number of cases.6,27,54

Several antigens are more or less muscle specific, e.g., desmin, specific actins, myosins, and titin. Desmin is a cytoskeletal intermediate filament specific for muscle cells.31,46 Actin is the backbone protein of microfilaments and is present in nearly all eukaryotic cells. At least six actin isoforms are expressed in cells of higher verterbrates.35 Nonmuscle cells, smooth muscle cells, and striated muscle cells contain different isoforms of actin to which specific monoclonal antibodies have been prepared.26 Myosins are energy transducing
enzymes, present both in muscle and nonmuscle cells. Their primary structure varies highly among different cells, so nonmuscular, smooth muscle, and striated muscle or sarcomeric myosins can be differentiated. Titin is a protein exclusively present in striated muscles and is expressed very soon during differentiation of myogenic precursor cells towards striated muscle.

This paper reports the multiple occurrence of undifferentiated soft tissue tumors in young pigs in a swine breeding farm and the immunohistochemical characterization of these tumors as rhabdomyosarcomas.

Materials and Methods

Animals and tissues

At a swine breeding farm, skin nodules were seen in 25 young pigs within a restricted time period. Five of these animals (Nos. 1–5), all from different litters and 6, 8, 4, 4, and 20 weeks of age, respectively, were available for post-mortem examination. The other animals were destroyed by the farmer. The number of nodules examined per animal is given in Table 2. Nodule samples (n = 6) from the animal Nos. 1–3 were fixed in 10% neutral formalin, and samples (n = 5) from animal Nos. 4 and 5 were fixed in Carnoy’s solution. Samples from both nodules of animal No. 5 were also frozen in liquid nitrogen. Skeletal and cardiac muscle tissue, tendon, and uterus of a clinically healthy 7-week-old pig were used as control tissues; these tissue samples were fixed in 10% neutral formalin or Carnoy’s solution or frozen in liquid nitrogen.

Histologic methods

Tissue samples fixed in 10% buffered formalin or Carnoy’s solution were processed by conventional methods, embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin, Weigert-van Gieson, and phosphotungstic acid hematoxylin.

Electron microscopic methods

Frozen tissue samples from animal No. 5 (n = 2) and formalin-fixed material from animal No. 3 (n = 1) were used for electron microscopy. Tissue samples were fixed in 2.5% glutaraldehyde solution in 0.1 M sodium cacodylate (pH 7.2) for 5 hours and stored in storage buffer solution (400 mM saccharose in 0.1 M sodium cacodylate, pH 7.2). The samples were post-fixed in 2% OsO4, buffered with 0.1 M sodium cacodylate (pH 7.2), twice for 1 hour each time. After rinsing twice for 30 minutes each time with 0.1 M sodium cacodylate, tissue specimens were stained with 2% uranyl acetate twice for 2 hours each time at room temperature, dehydrated in a graded series of acetone, and embedded in Durcupan ACM (Fluka Ag., 9470 Buchs, Switzerland). One-micrometer sections were stained with lead citrate and examined with an EM 202 Philips electron microscope.

Immunohistochemical methods

A broad range of polyclonal and monoclonal antibodies was used; code name, original antigen, dilution, and source or reference are presented in Table 1. The antibodies directed against desmin, vimentin, glial fibrillary acidic protein, and neurofilament proteins were used on all formalin- and Carnoy-fixed tissues. Because the other antibodies cannot be used on fixed, paraffin-embedded tissues, these were used only on the frozen sections of both tumors of animal No. 5 and on frozen control tissue samples.

Antigens in formalin and Carnoy-fixed tissue specimens were visualized by an immunoperoxidase staining method as reported previously. Frozen sections were air dried, fixed in 100% acetone at –20°C for 10 minutes, briefly air dried, and incubated with 0.3% H2O2 in methanol for 30 minutes to block endogenous peroxidase activity. Sections were rinsed in 0.05 M phosphate-buffered saline (PBS, pH 7.4) three times for 10 minutes each time, briefly air dried, and preincubated with 1% normal swine serum in PBS for 20 minutes at room temperature. Then the primary antisera were applied, diluted as indicated in Table 1 in 1% normal swine serum in PBS, and incubated for 1 hour at room temperature in a humid atmosphere. After incubation, the sections were rinsed in PBS three times for 10 minutes each time, and thereafter incubated with peroxidase-conjugated anti-mouse IgG (Dakopatts, Inc., Glostrup, Denmark) diluted 1:20 in PBS for 1 hour at room temperature. After three washing steps in PBS of 10 minutes each, the antigens were visualized with 0.3% H2O2 and 0.5% 3,3′-diaminobenzidine tetrahydrochloride (DAB, Sigma Chemical Co., St. Louis, MO), diluted in 0.05 M Tris/HCl buffer (pH 7.6) during a 2–3 minute incubation step. The sections were counterstained with Mayer’s hematoxylin for 1 minute, dehydrated, and mounted.

Results

Clinical history

At a swine breeding farm consisting of approximately 100 animals, skin nodules of various sizes were observed in 25 young pigs. The lesions had been noticed by the farmer in several animals during the first weeks of life, whereas in others they became apparent at about 4 weeks of age. The number of lesions per animal varied from one to five. The main clinical signs were locomotion disturbances and ulceration of the lesions due to traumatic injury by littermates. All affected pigs were born between August 1989 and January 1990 and were from different litters from different sows. Only a small number of littermates (one to three) was affected. The occurrence on the farm of pigs showing these lesions ceased after January 1990. The time-limited occurrence of the lesions could not be related to changes in management, vaccination program, disease status, or food. The breeding program was performed with three boars. Two of these boars were discharged from the breeding program and slaughtered in September 1989 and November 1989, respectively. One of these had produced a litter containing affected pigs after mating with one of its own daughters. Unfortunately, no further data could be obtained because of poor herd management, and experimental cross-breeding was not possible.
Table 1. Code name, original antigen, dilution used, and source or reference of the antibodies used to label porcine tumors.

<table>
<thead>
<tr>
<th>Code*</th>
<th>Original Antigen</th>
<th>Dilution</th>
<th>Source or Reference No.</th>
</tr>
</thead>
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<tr>
<td>Desmin†</td>
<td>Chicken gizzard desmin</td>
<td>1:80</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>Vimentin†</td>
<td>Calf lens vimentin</td>
<td>1:80</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>GFAP‡</td>
<td>Human spinal cord GFAP</td>
<td>1:80</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>NF‡</td>
<td>Human brain NF proteins</td>
<td>1:10</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>RD 301‡</td>
<td>Chicken gizzard desmin</td>
<td>Undiluted</td>
<td>8</td>
</tr>
<tr>
<td>RV 203‡</td>
<td>Bovine lens vimentin</td>
<td>1:5</td>
<td>50</td>
</tr>
<tr>
<td>RAC1‡</td>
<td>Human α-sarcomeric actin</td>
<td>Undiluted</td>
<td>50</td>
</tr>
<tr>
<td>MF20‡</td>
<td>Chicken pectoralis myosin</td>
<td>1:5</td>
<td>Dev. Stud. Hybr. Bank§</td>
</tr>
<tr>
<td>RCK 102‡</td>
<td>Human keratin types 5, 8</td>
<td>1:10</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>RCK 103‡</td>
<td>Human keratin types 5 and others</td>
<td>1:10</td>
<td>48</td>
</tr>
<tr>
<td>RCK 105‡</td>
<td>Human keratin type 7</td>
<td>1:10</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>RCK 107‡</td>
<td>Human keratin type 14</td>
<td>Undiluted</td>
<td>63</td>
</tr>
<tr>
<td>DE-K18‡</td>
<td>Human keratin type 18</td>
<td>1:200</td>
<td>25</td>
</tr>
<tr>
<td>RGE 53‡</td>
<td>Human keratin type 18</td>
<td>1:10</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>6B10‡</td>
<td>Human keratin type 4</td>
<td>1:5</td>
<td>Euro-Diagnostics B.V.</td>
</tr>
<tr>
<td>LP2K‡</td>
<td>Human keratin type 19</td>
<td>1:10</td>
<td>Amersham Ltd.</td>
</tr>
<tr>
<td>DE-K10‡</td>
<td>Human keratin type 10</td>
<td>1:100</td>
<td>24</td>
</tr>
<tr>
<td>8.7‡</td>
<td>Human keratin types 14 (17)</td>
<td>1:200</td>
<td>25</td>
</tr>
</tbody>
</table>

* GFAP = glial fibrillary acidic protein; NF = neurofilament proteins.
† Polyclonal antibody.
‡ Monoclonal antibody.
§ Developmental Studies Hybrida bank, maintained by the Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, MD, and the Department of Biology, University of Iowa, Iowa City, IA, under contract No. 1-HD-6-2915 from NICHD.

Gross and histologic findings

The lesions in all 25 animals had an identical aspect. Only lesions (n = 11) of the five pigs available for postmortem examination could be studied in more detail. The lesions ranged in size from 2-3 cm to 35-40 cm and often were ulcerated. Nonulcerated lesions (Fig. 1) were not firmly attached to the skin, which could be moved freely over the lesions. Dissection of the lesions revealed a firm mass, sometimes with central necrosis, located in the skeletal musculature (Fig. 2) of the scapula or the thoracic wall or in the psoas and gluteus muscles. Tumors located in the thoracic wall penetrated through the intercostal spaces into the thorax but still appeared to be covered by the parietal pleura. In one pig, invasion into the spinal canal occurred through the intervertebral foramen, resulting in compression of the spinal cord. One animal (No. 4) had tumor metastases in the cervical lymph node.

Upon histologic examination, all tumors showed identical histomorphologic features. The tumors appeared to be ill defined, with infiltrative growth into the surrounding tissues, were very cellular, and were composed of monotonous sheets of closely packed cells separated by thin bands of fibrous tissue (Fig. 3). Sometimes an alveoluslike pattern was observed. Necrotic and hemorrhagic areas were abundant, and scattered foci of calcification were seen. The tumor cells were small and round to spindle shaped and showed slight to moderate anisocytosis. Nuclei were hypochromatic and round to oval, with inconspicuous nucleoli, and were surrounded by eosinophilic cytoplasm; they also showed distinct anisokaryosis (Fig. 3). Mitotic figures were scarce. No specific nuclear or cytoplasmic morphologic characteristics were present; therefore, the tumors were histologically classified as undifferentiated sarcomas.

Electron microscopy

On electron microscopic examination, tumor cells were characterized by the presence of often abundant intracytoplasmic filaments regularly arranged in longitudinal bundles with numerous longitudinal densities; several dense bodies were also observed (Fig. 4). A variable number of mitochondria were found both located in the center of the cell and at the cell periphery (Fig. 4). Some cells contained dense glycogen particles. Occasionally desmosomelike junctions were observed between neoplastic cells.

Immunohistochemistry

Most relevant immunohistochemical findings in both tumor and control tissues are presented in Table 2. In
control tissues, both the polyclonal and the monoclonal antibody (MoAb) directed against vimentin specifically stained tendon tissue. The polyclonal desmin antibody stained skeletal, cardiac, and smooth muscle; the desmin MoAb RD 301 only labeled cardiac and smooth muscle. The MoAbs directed against α-sarcomeric actin (RAC1), myosin (MF20), and titin (9D10) only stained skeletal muscle. The glial fibrillary acidic protein and neurofilament proteins antibodies only reacted with intrinsic nerve fibers.

All tumor tissue samples were stained by the polyclonal antibodies directed against desmin and vimen-

Fig. 1. Pig No. 3, 4 weeks old. The tumor appears as a bulging nonulcerated skin nodule at the back.

Fig. 2. Tumor; pig No. 3, 4 weeks old. The tumor is located in skeletal musculature and its cut surface is composed of white-greyish, firm tissue with central necrosis and hemorrhage.

Fig. 3. Tumor; pig No. 3, 4 weeks old. The tumor consists of closely packed clusters of tumor cells separated by thin bands of fibrous tissue. Tumor cells have hypochromatic nuclei with distinct anisokaryosis and usually inconspicuous nucleoli. HE. Bar = 20 μm.

Fig. 4. Electron micrograph. Pig No. 5, 20 weeks old. Tumor cells contain numerous cytoplasmatic filaments with a large number of longitudinal densities and several dense bodies (arrows). Bar = 0.5 μm.

tin, with a heterogeneous staining pattern (Fig. 5). Vimentin immunoreactive tumor cells showed diffuse cytoplasmic staining; endothelial cells and fibroblasts were also stained. Tumor cells positive for desmin usually showed diffuse cytoplasmic staining, but strongly positive perinuclear globules were observed occasionally. The tumor cells were not stained by the glial fibrillary acidic protein and neurofilament proteins antibodies. The frozen tumor samples were only stained
Table 2. Immunohistochemical findings* in tumor tissue samples and control tissue samples as revealed by the most relevant antibodies.

<table>
<thead>
<tr>
<th>Code†</th>
<th>Antibodies</th>
<th>Animal No. (number of tumors)</th>
<th>Control tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original Antigen</td>
<td>1 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Paraffin embedded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmin‡</td>
<td>Chicken gizzard desmin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vimentin‡</td>
<td>Calf lens vimentin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GFAP‡</td>
<td>Human spinal cord GFAP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NF§</td>
<td>Human brain NF proteins</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Frozen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD 301§</td>
<td>Chicken gizzard desmin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RV 203§</td>
<td>Bovine lens vimentin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RAC1§</td>
<td>Human α-sarcomeric actin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MF20§</td>
<td>Chicken pectoralis myosin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GD10§</td>
<td>Bovine heart titin</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* + = positive reaction; 0 = negative reaction; – = not done.
† GFAP = glial fibrillary acidic protein; NF = neurofilament proteins.
‡ Polyclonal antibody.
§ Monoclonal antibody.

by the MoAbs against vimentin (RV 203) and titin (9D10) (Fig. 6). In the control tissues, only uterine epithelial cells were stained by seven out of the ten keratin MoAbs used; RCK 102, RCK 103, RCK 105, DE-K18, RGE 53, and 8.7. The frozen tumor samples did not react with any of the keratin MoAbs.

Discussion

All 11 tumors examined from the five pigs showed similar histomorphologic features compatible with poorly differentiated soft tissue tumors. The ultrastructural presence of bundles of filaments, as observed in the tumor samples examined electron microscopically, indicates the possible myogenic nature of the neoplastic cells; however, poorly differentiated cells of many types may contain abundant cytoplasmic filaments. The characteristic ultrastructural features of well differentiated rhabdomyosarcomas, i.e., alternating bands of thick and thin filaments and Z-lines, were not observed in the pig tumors studied, although some characteristic but nonspecific features such as glycogen particles and peripherally located mitochondria were present in some tumor cells, as in human rhabdomyo-

Fig. 5. Tumor; pig No. 1, 4 weeks old. Staining of tumor cells by the polyclonal desmin antibody is heterogeneous. Immunoperoxidase, anti-chicken gizzard desmin, Mayer’s hematoxylin counterstain. Formalin-fixed section.

Fig. 6. Tumor; pig No. 5, 20 weeks old. There is heterogeneous staining of tumor cells by the titin monoclonal antibody. Immunoperoxidase, anti-bovine heart titin, Mayer’s hematoxylin counterstain. Cryostat section.
In human beings, dense bodies have been encountered in childhood rhabdomyosarcoma-like tumors, and desmosomal-like junctions have been observed between tumor cells in poorly differentiated rhabdomyosarcomas. The presence of filaments with longitudinal densities has been considered exclusive to human embryonal rhabdomyosarcomas. The ultrastructural features of the swine tumors in this study are concordant with the histologically undifferentiated character of the tumors and indicate a myogenic origin. The muscle cell origin of the lesions was further supported by the results of the immunohistochemical assays. Although the presence of desmin has been considered to be restricted to muscle cells, this intermediate filament protein has also been found occasionally in several nonmuscle cell types. In addition, some tumors considered to be nonmyogenic are desmin positive. Desmin labeling of tumor cells has been established as a strong indicator of the myogenic character of both human and animal rhabdomyosarcomas. It is not certain if the staining is specific to desmin. However, the absence of desmin expression in poorly differentiated rhabdomyosarcomas and, in vimentin, is often expressed in poorly differentiated rhabdomyosarcomas. Vimentin expression is gradually lost during this differentiation process and is absent in mature myofibers of skeletal muscle. Titin most probably constitutes a scaffold for the other muscle proteins, e.g., fast and slow myosin, which appear in more differentiated muscle cells. Thus, tumor cell differentiation can be determined by the expression of the different markers. Consequently, myosin and sarcomeric actin labeling is often absent in less differentiated rhabdomyosarcomas, and vimentin is often expressed in poorly differentiated rhabdomyosarcomas. However, some desmin-negative rhabdomyosarcomas have been demonstrated to be actin positive, probably due to deregulation of the genetic differentiation program resulting in altered order in which specific proteins appear in the neoplastic muscle cells. Conclusively, the presence of desmin, vimentin, and titin staining and the absence of labeling with myosin and α-sarcomeric actin in the swine tumors emphasizes the highly undifferentiated myogenic differentiation stage of these rhabdomyosarcomas.

In a restricted number of human and murine rhabdomyosarcomas, the presence of tumor cells reactive for keratin proteins has been observed, particularly with respect to keratins 8, 18, and 19. This keratin expression pattern is considered to be a reminiscence of embryonal muscle development because during embryogenesis skeletal muscle cells transiently express keratins. Swine rhabdomyosarcoma cells did not stain for keratins, whereas swine endometrial epithelial cells reacted with seven out of ten keratin MoAbs. Additionally, some human rhabdomyosarcomas show neurofilament proteins reactivity, which could not be shown in the described pig tumors.

The porcine tumors showed light and electron microscopic features compatible with those of embryonal rhabdomyosarcomas in human beings, i.e., the undifferentiated character, the organization of tumor cells in sheets or bands, the cellular morphologic characteristics, and the presence of filaments with longitudinal densities. In these tumors, as in the described neoplasms, evidence of cross-striation often cannot be
established. The immunohistochemical findings in the porcine tumors are greatly in accordance with findings in childhood rhabdomyosarcomas, which are almost always stained with antibodies directed against desmin and vimentin, whereas a variable number of tumors does not react with actin and myosin antibodies. In human beings, this tumor type is almost exclusively encountered in children and is only occasionally seen in adolescents and rarely in adults. It is one of the most frequent occurring neoplasms in childhood. Rhabdomyosarcomas also have been reported in young animals, e.g., in horses, sheep, dogs and rats. The tumors described in the present study were all noticed in young pigs, possibly indicating a congenital nature of these neoplasms. Congenital skeletal muscle neoplasms have been previously reported in dogs and pigs. The multiple occurrence of the rhabdomyosarcomas in 25 young pigs in different litters on one swine breeding farm within a very limited period of time is most remarkable and obviously contradictory to the reported very low incidence of such tumors in animals. These data suggest a common causative event in the described pig rhabdomyosarcomas. The cause of spontaneous rhabdomyosarcomas is unknown, however, these tumors can be induced experimentally, in animals by carcinogens, by implantation of heavy metals or their derivatives, by inoculation with sarcoma viruses, and by irradiation. Because one of the boars produced an affected litter after mating with one of its own daughters and no new cases occurred after this boar was discharged from the breeding program, a genetic factor is suspected. In human beings, genetic factors have been associated with the occurrence of familial juvenile rhabdomyosarcomas as a possible exceptional event. A possible genetic predisposition for rhabdomyosarcomas in BALB/cJ mice has also been reported.

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Note added in proof.

The authors' attention has been directed to two swine breeding farms in different regions of The Netherlands on which young pigs were present with tumors showing histomorphologic and immunohistochemical features identical to the described cases. On one farm, only one 2-day-old piglet was affected. On the other farm, however, affected young pigs were quite regularly observed in different litters from different sows. In some animals, the tumors were noticed at birth. After one of the four boars participating in that farm’s breeding program was discharged, no additional affected pigs were observed.