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Congenital Tumours and Tumour-Like Lesions in Calves: a Review

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1 **NEOPLASTIC DISEASE**

2 **Review**

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4 **Short title: Congenital Tumours and TumourLike Lesions in Calves**

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8 **Congenital Tumours and Tumour-Like Lesions in Calves: a Review**

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Summary

Congenital tumours and tumour-like lesions represent a group of rare disorders in both veterinary and human medicine that arise from tissue remnants and are detected during pregnancy or within the first 2 to 3 months of age. Different forms of congenital tumours and congenital tumour-like lesions have been reported in calves and their development is poorly understood. They often pose a diagnostic challenge and the referring nomenclature occasionally may be equivocal. Previous reports regarding tumour-like lesions, soft tissue, vascular, round cells tumours, and neoplasms of nervous, peritoneum and urogenital systems are summarized in this review and the role of genetic factors in the development of these conditions is discussed.

Keywords: bovine; congenital tumours; malformations; tumour like-lesions

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Introduction

Congenital tumours and tumour-like lesions arise from tissue remnants and are detected during pregnancy or within the first 2 to 3 months of life (Dorland, 1988; Smith and Philips, 2001; Alamo *et al*, 2011). As the term tumour (from the Latin word *tumor* meaning swelling) is commonly used as a synonym for neoplasm, this review encompasses tumours and tumour-like lesions which are often malformations and can mimic neoplasms. Limited numbers of congenital tumours have been recognized in human beings and animals, including calves. The purpose of this paper is to review the pathological features of congenital tumours and tumour-like lesions in calves as described in previous reports. The development of the lesions is discussed.

Congenital Tumour-Like Lesions

Hamartomas

Hamartomas are congenital tumour like-lesions characterized by an overgrowth of disorganized mature cells and tissues indigenous to the organ involved (Robinson and Robinson, 2016). They are relatively common in calves and vascular, fibrous, nasal and pulmonary forms have been reported. Vascular hamartomas are the most common and have been recognized in the gingiva (Sheahan and Donnelly, 1981; Stanton *et al*, 1984; Wilson, 1990;; Yeruham *et al*, 2004; Tsuka *et al*, 2016), heart (Sugiyama *et al*, 2007; Brisville *et al*, 2012), lung (Roth and Bradley, 1991), and cutaneous tissue (Madewell and Theilen, 1987; Yeruham *et al*, 1999; Veiga *et al*, 2017).

Gingiva vascular hamartomas appeared as reddish flat masses (2–7 × 1.5 cm diameter) and were usually located in the rostral mandibular gingival. Cardiac vascular hamartomas were located in the right atrial myocardium and were round and poorly delimited. Pulmonary vascular hamartomas appeared as spongy, non-cystic, uniformly soft, pale pink masses with a distinct lobulated patterns,

75 while cutaneous vascular hamartomas were oval, non-encapsulated or well-circumscribed, lobulated,
76 exophytic and alopecic.

77 Vascular hamartomas were of similar histological appearance with thin-walled vascular
78 channels lined by plump endothelial cells in a loose collagenous stroma. The vascular channels were
79 collapsed or empty, some contained blood, and others, particularly near the surface, were thrombosed.

80 A fibrous hamartoma in the vagina of a calf was described by Lafond *et al* (2008). The tumour
81 was composed of multiple pendulous vaginal masses, 5 to 15 cm long, that protruded through the vulva
82 and often ended as cystic structures that were filled with translucent liquid and shared a common origin
83 on a pedunculated base dotted with smaller papillary lumps. Histologically, the pendulous masses were
84 composed of well-vascularized fibrous tissue lined by stratified squamous epithelium. The tissue was
85 similar in appearance to the vaginal wall.

86 A single nasal tissue-derived hamartoma appeared as a horn-like, 1.5×3.5 cm mass in the
87 maxillary gingiva (Tsuka *et al*, 2016). The mass was composed of cartilage-like and tubular structures
88 lined by ciliated columnar epithelial cells. The mass and gingival mucosa were of similar colouration
89 and the appearance of the cartilage and epithelial cells resembled those of the nasal chambers. A
90 pulmonary hamartoma appeared as a $36 \times 22 \times 22$ cm, spongy, pale pink mass with a distinct lobulated
91 pattern (Roth and Bradley, 1991). Histologically, the mass was composed of bronchiolar and alveolar
92 structures arranged in haphazard patterns. Ascites, localized subcutaneous oedema and chronic passive
93 congestion of the liver were additional findings.

94

95 *Choristomas and Dermoids*

96 Choristomas are tumour-like lesions composed of histologically normal mature tissue in abnormal
97 anatomical locations (Kusewitt and Rush, 2007). Pulmonary choristomas represent the most
98 commonly reported form in calves (Chauvet *et al*, 1994; Medeiros de Oliveira *et al*, 2009; Bassi *et al*,
99 2010; Caswell and Williams, 2016). They appear as solitary, non-functioning, pale pink masses of

100 pulmonary tissue that lack communication with the tracheobronchial tree and receive an arterial blood
101 supply from the systemic circulation. The histological appearance is of foetal pulmonary architecture,
102 characterized by alveoli filled with a purulent inflammatory exudate. A previously unreported
103 pulmonary choristoma from the archives of the Department of Veterinary Medical Sciences,
104 University of Bologna is illustrated (Fig. 1 A, B and C).

105 Other choristomas in calves have been located in the abdominal cavity (Chauvet *et al*, 1994;
106 Medeiros de Oliveira *et al*, 2009; Bassi *et al*, 2010; Binanti *et al*, 2013). A choristoma located in the
107 perineal region of a calf was composed of mature adipose and fibrous tissue with nephrogenic rests,
108 fragments of trabecular bone, cartilage, bone marrow, mixed with mature adipose and fibrous tissue,
109 striated muscle, nerves and vessels (Binanti *et al*, 2013). Mature teratoma was not discussed as a
110 differential diagnosis (Binanti *et al*, 2013). A nasal choristoma appeared as a broad-based, haired mass
111 composed of normal nasal tissue on the nasolabial planum (Brudenall *et al*, 2008).

112 Choristomatous malformations in the ocular region are referred to as dermoids. Most occur
113 unilaterally on the eyelids, conjunctiva, membrana nictitans and cornea and appear as fleshy masses
114 with abortive hair follicle development (Brudenall *et al*, 2008).

115

116 **Congenital Soft Tissue Tumours**

117

118 *Desmoid Fibromatosis*

119 Fibromatoses represent a group of benign but locally aggressive pseudotumours arising from fasciae,
120 aponeuroses or supporting connective tissue of skeletal muscle. Histopathologically, fibromatoses are
121 characterized by infiltrative, aggressive proliferation of well-differentiated fibroblasts. Various
122 subgroups have been identified based on anatomical, biological and epidemiological features
123 (Fletcher, 2000; Cooper and Valentine, 2017; Alamo *et al*, 2011). Desmoid fibromatosis represents

124 one of these subgroups and is characterized by proliferation of uniform spindle-shaped cells
125 resembling myofibroblasts, with an abundant collagenous stroma and vascular network.

126 A single case of congenital desmoid fibromatosis has been reported in a calf (Drolet *et al*,
127 2008). A whitish pink, moderately soft, fibrous-like mass extended from the base of the ear to the
128 lateral canthus of the eye. The mass was poorly circumscribed and there was local infiltration of
129 adjacent tissues. Sheets and bundles of mature, well-vascularized fibrous connective tissue had low to
130 moderate cellularity. The tumour-like cells were strongly immunopositive for vimentin and negative
131 for desmin, smooth muscle actin and S-100 antigens.

132

133 *Lipocytic Tumours*

134 Lipocytic tumours are grouped into pure and mixed cell forms. Simple lipomas and fibrolipomas have
135 been described in calves.

136 A congenital simple lipoma in a calf appeared as retroperitoneal and perirenal deposits
137 resembling normal fat tissue (Agerholm *et al*, 2016). Adjacent tissues were compressed with no
138 evidence of local infiltration. Uniform populations of mature lipocytes with single large cytoplasmic
139 vacuoles were located in sparse connective tissue stroma.

140 Five cases of congenital infiltrative lipoma, a benign, locally invasive tumour, have been
141 reported in calves (Di Giancamillo *et al*, 2002; Sickinger *et al*, 2009; Militerno *et al*, 2011; Hobbenaghi
142 *et al*, 2015; Agerholm *et al*, 2016). The tumours were localized subcutaneously in the face, neck, tail
143 and thoracic wall and were white to yellowish, non-encapsulated and firm. Sheets of well-
144 differentiated adipocytes, that infiltrated surrounding structures including muscle tissue, were
145 associated with fibrosis and muscle atrophy (Agerholm *et al*, 2016). No evidence of metastasis was
146 detected.

147 A congenital fibrolipoma located in the retroperitoneal area of a calf was soft, whitish and
148 encapsulated (Marino *et al*, 2006). Well-differentiated adipocytes, with large fat vacuoles and flat

149 nuclei pushed to the periphery of the cells, were located in a rich network of connective tissue stroma.
150 The stroma was lobulated and extended to the capsular surface.

151

152 *Embryonal Rhabdomyosarcoma*

153 Congenital embryonal rhabdomyosarcomas originate in embryonic mesenchyme with potential
154 differentiation into skeletal muscle. A single case reported in a female Holstein calf appeared as a
155 spherical, expansile, encapsulated, subcutaneous mass on the lateral side of the head (Ulrich *et al*,
156 2014). The highly cellular mass was composed of a reticular meshwork of moderately pleomorphic,
157 small, spindle-shaped to round cells in a fibrovascular to myxoid stroma. Large, blunt, multinucleated
158 myotube-like cells (strap cells) were immunopositive for desmin. The small spindle-shaped cells were
159 positive for vimentin. Cytoplasmic bundles of myofilaments and Z bands were demonstrated within
160 the strap cells by electron microscopy.

161

162 *Myxoma*

163 Myxomas are benign tumours composed of fibroblastic or multipotential mesenchymal cells with
164 abundant myxoid stroma rich in glycosaminoglycans (Mauldin and Kennedy, 2016). A congenital
165 myxoma in a calf was identified as an infiltrative intramuscular lingual myxoma (Hobbenaghi *et al*,
166 2014). The tumour was located on the dorsum of the lingual body and appeared as an 8 × 6 × 2.5 cm
167 diameter, flabby mass. The cut surface of the mass was lobulated, pink and gelatinous. Histologically,
168 stellate, spindle-shaped and elliptical cells were loosely scattered in abundant basophilic, periodic acid
169 Schiff (PAS)-positive mucinous stroma. The tumour cells had small hyperchromatic nuclei and were
170 locally invasive. Nuclear polymorphism and mitotic figures were not observed.

171

172

173

Congenital Vascular Tumours

174

175 *Haemangioma*

176 Congenital capillary haemangioma is frequently reported in calves and have been located in the skin
177 (Kirkbride *et al*, 1973; Priestnall *et al*, 2010), gingiva (Tontis, 1994; Misdorp, 2002a), mandible
178 (Tontis, 1994), lymph node medulla (Herzog and Geishauer, 1991) and spinal cord (Cho *et al*, 1979).
179 The tumours occurred as single or multiple, ovoid, red–black masses that ranged from 0.5 to 7 cm in
180 diameter (Kirkbride *et al*, 1973; Cho *et al*, 1979; Tontis, 1994; Misdorp, 2002a; Priestnall *et al*, 2010).
181 Some oozed blood when cut and some regressed to leave a small ulcerated scar. Histologically, the
182 masses were composed of blood-filled vascular spaces lined by a single layer of well-differentiated
183 endothelium and separated by variable amounts of connective tissue stroma. Some of the blood vessels
184 were thrombosed. The endothelial cells were positive for von Willebrand factor and were surrounded
185 by small spindlyoid cells positive for alpha smooth muscle actin (Priestnall *et al*, 2010).

186 Disseminated cavernous haemangioma has been reported in calves but details are sparse
187 (Robinson and Robinson, 2016).

188

189 *Lymphangioma*

190 Congenital lymphangiomas are benign tumours characterized by abnormal proliferation of lymphatic
191 vessels (Mauldin and Kennedy, 2016; Hendrick, 2017). They tend to occur in the subcutis along the
192 ventral midline and limbs and appear as poorly demarcated, dermal masses that are soft and spongy to
193 the touch. Clear, serous to milky, fluid exudation has been reported. A single case has been reported
194 on the lower forelimb of a 6-month-old foetal calf (Misdorp, 2002a). Vascular spaces lined by
195 endothelial cells were separated by loose oedematous stroma containing aggregates of lymphoid cells.
196 The endothelial cells were immunopositive for von Willebrand factor, which is expressed by both
197 vascular and lymphatic endothelium.

198

199 *Haemangiosarcoma*

200 A single case of congenital haemangiosarcoma has been reported in a stillborn calf (Badylak, 1983).
201 Reddish-brown, 1.5 to 3.5 cm in diameter, smooth, firm nodular masses were located in the skin,
202 skeletal muscles, bones, kidneys, spleen, mesentery, liver, lungs and heart. The cut surfaces were dark
203 brown with blood-filled cystic spaces that caused compression of the normal adjacent tissue.
204 Histologically, the vascular spaces were lined by pleomorphic spindle-shaped cells with local tissue
205 invasion. The mitotic index of the tumour cells was low (<1 per high-power field).

206

207 **Congenital Round Cell Tumours**

208

209 *Multicentric Lymphoma*

210 Bovine malignant lymphoid tumours are well-characterized and include enzootic leukosis, caused by
211 bovine leukemia virus (BLV), and sporadic forms, namely congenital multicentric lymphoma (CML),
212 juvenile multicentric lymphoma, cutaneous lymphoma and thymic lymphoma. CML is one of the most
213 commonly recorded tumours in calves (Cotchin, 1960; Overgoor, 1963; Misdorp and Dodd, 1968;
214 Herzog and Geishauer, 1991; Yeruham *et al*, 1999; Misdorp 2002a; Yamamoto *et al*, 2007; Beytut and
215 Özba, 2012). Although BLV is known to infect bovine foetuses and new-born calves, most cases of
216 CML are sporadic and occur independently of BLV infection. Multiple lymph nodes usually are
217 affected with thoracic and abdominal cavity involvement. Skin and brain lesions have been described
218 and skeletal muscle involvement is rare.

219 The immunohistochemical assessment of bovine lymphomas is well documented and the
220 predominant type is diffuse large B-cell lymphoma (Vernau *et al*, 1997; Beytut and Özba, 2012).
221 Primitive B-lymphocytes and plasma cells may lack surface immunoglobulins and demonstration of
222 cytoplasmic immunoglobulins may be helpful in the identification of the tumour cell lineage in
223 newborn calves.

224

225 *Cutaneous Mast Cell Tumour*

226 Congenital cutaneous mast cell tumours have been described as randomly distributed nodular masses
227 that were sometimes ulcerated (Yeruham *et al*, 1999; Smith and Phillips, 2001; Palyada *et al*, 2008).
228 The skin of one affected calf was thickened and wrinkled because of diffuse tumour cell infiltration
229 and resembled that of a Chinese Sharpei dog. Hair loss was absent and peripheral lymph nodes were
230 not enlarged (Palyada *et al*, 2008). Poorly-defined aggregates of neoplastic mast cells in the lung,
231 spleen and skeletal muscles of one calf with cutaneous mast cell tumours represent the only report of
232 metastasis (Smith and Phillips, 2001). A previously unreported mast cell tumour from the archives of
233 the Department of Veterinary Medical Sciences, University of Bologna is illustrated (Fig. 1 D, E and
234 F).

235

236 **Congenital Tumours of the Nervous System**

237

238 *Schwannosis*

239 Schwannosis is a benign peripheral nerve sheath tumour characterized by spontaneous invasion and
240 proliferation of aberrant Schwann cells into the central nervous system with peripheral myelination of
241 central axons. Typical cases in humans lack obvious gross tumour formation (Adelman and Aronson,
242 1972; Perry, 2010). A single case, in which no noticeable mass was detected, has been reported in a
243 calf with hydrocephalus (Miranda *et al*, 2019). Lesions were bilaterally located in the dorsal and
244 ventral roots at all levels of the spinal cord and the dorsal spinocerebellar tract in the medulla
245 oblongata. Plaques of proliferated spindle cells, admixed with myelinated axons, extended into the
246 dorsal, ventral, and lateral funiculi and grey matter. Proliferated spindle cells expressed myelin protein
247 zero and periaxin, proteins that are absent in the central myelin (Miranda *et al*, 2019).

248

249 *Medulloblastoma*

250 The term medulloblastoma is conventionally limited to embryonal tumours that originate in the
251 cerebellum. Tumours of similar histological appearance in other sites in the brain are referred to as
252 primitive neuroectodermal tumours (Cantile and Youssef, 2016). Medulloblastomas are of uncertain
253 origin and thought to arise from neuronal progenitor cells beneath the pia mater of the cerebellum
254 (Jolly and Alley, 1969; Fankhauser *et al*, 1982; Cantile and Youssef, 2016). The molecular
255 mechanisms governing neuronal progenitor cell neurogenesis are poorly elucidated. The tumours are
256 usually located in the cerebellar vermis, grow rapidly and are highly malignant with a symptomatic
257 duration of only a few months.

258 Medulloblastomas in calves appear as round, well-circumscribed, soft, grey to red infiltrating
259 masses with necrosis and haemorrhage in the cerebellum and hindbrain (Fankhauser *et al*, 1982;
260 Ciorba and Avalos-Umanzor, 1987; Guarda and Biolatti, 1987; Bianchi *et al*, 2015). The tumour cells
261 are rounded, pyriform or elongated and arranged in clumps or palisades with complete or incomplete
262 Homer Wright rosette formation. Mitotic figures are frequent. Positive immunolabelling occurred for
263 several neuronal markers including neuron specific enolase and synaptophysin (Cantile and Youssef,
264 2016). The occurrence of the tumour in twin calves, reported by Fankhauser *et al* (1982), is suggestive
265 of genetic involvement. A previously unreported medulloblastoma from the archives of the
266 Department of Veterinary Medical Sciences, University of Bologna is illustrated (Fig. 2 A and B).

267

268 **Congenital Tumours of the Peritoneum and Urogenital Systems**

269

270 *Mesothelioma*

271 Congenital mesotheliomas are relatively frequent in calves and have been reported in the abdominal
272 cavity (Baskerville, 1967; Misdorp, 2002a and b), pleural cavity (Schamber *et al*, 1982; Baskerville,
273 1967), pericardial cavity (Takasu *et al*, 2006) and tunica vaginalis of the testis (Peli *et al*, 2018). The

274 tumours appear as multiple, firm, variably-sized, sessile or pedunculated nodules and are usually
275 accompanied by copious, yellowish–red effusion. Serosal surfaces were thickened in these cases with
276 villous projections of cuboidal, squamous or columnar epithelial cells and sclerosis. Giant cells and
277 necrosis were present, the tumour cells seemed less differentiated than those seen in mesothelioma in
278 adult animals (Misdorp, 2002a) and were immunopositive for cytokeratin and vimentin. A previously
279 unreported mesothelioma from the archives of the Department of Medical Veterinary Sciences,
280 University of Bologna, is illustrated (Fig. 2 C and D).

281

282 *Nephroblastoma*

283 Nephroblastomas, also known as Wilms tumours, originate in the primitive metanephric blastema in
284 the retroperitoneum. Reports of cases in the bovine foetus are lacking in detail (Misdorp 2002b;
285 Cianciolo and Mohr, 2016). Nephroblastomas are usually unilateral and appear as multiple expansile
286 masses in the affected kidney. Cut surfaces are lobulated, greyish–white, soft and myxomatous and
287 larger tumours have extensive haemorrhagic necrosis. Reflecting the biological potential of the
288 metanephric blastema, the tumours contain a variety of epithelial and mesenchymal components,
289 including some not typically associated with the kidney. A typical pattern is one of islands of epithelial
290 cells undergoing differentiation into tubules or glomerulus-like structures, surrounded by peripheral
291 zones of stroma. Neoplastic mesenchymal elements including fibrous, myxoid, lipid, myoid,
292 chondroid and osteoid forms dominate in some tumours and may occur singly or in varying
293 combinations and proportions (Nielsen *et al*, 1976). The immunoreactivity of bovine nephroblastoma
294 is not reported. Consistent expression of cytokeratin 19 has been reported in tubular structures in
295 porcine nephroblastomas (Grieco *et al*, 2006).

296

297 *Sertoli Cell Tumour of the Testis*

298 Sertoli cell tumours, also known as sustentacular cell tumours, arise from the supporting cells of the
299 seminiferous tubules (Agnew and MacLachlan, 2017). Three cases have been described in calves, one
300 in a neonatal German Holstein calf (Vissiennon *et al*, 2016) and two in newborn calves, both sired by
301 the same Shorhorn bull (Palmer *et al*, 1980). Each of the latter two calves had only one testis. Affected
302 testes were enlarged, soft and reddish purple with small greyish areas divided into lobules by light
303 fibrous bands. Densely cellular tumours showed well-formed tubules lined by polygonal cells with
304 round to elongated nuclei and scant eosinophilic cytoplasm. Less densely cellular tumours were
305 composed of groups of vacuolated cells divided into small lobules by vascular connective tissue stroma
306 (Palmer *et al*, 1980, Vissiennon *et al*, 2016). The tumour cells were immunopositive for α -oestrogen
307 receptor, α -inhibin, vimentin and S-100 antigens.

308

309 *Interstitial (Leydig) Cell Tumour of the Testis*

310 Interstitial cell tumours of the testis arise from the interstitial (Leydig) cells. A congenital interstitial
311 cell tumour has been described in a 1-month-old calf (Lopez *et al*, 1994) in which both testicles were
312 undescended. The left testicle was notably enlarged, dark red and soft with scattered areas of necrosis.
313 Histologically, monomorphic populations of polyhedral cells, with distinct cytoplasmic borders and
314 abundant eosinophilic cytoplasm, were supported by well-vascularized bands of connective tissue
315 stroma. Antibodies against luteinizing hormone and 3-beta-hydroxysteroid dehydrogenase represent
316 useful markers for accurate identification of interstitial cell tumours as shown in the dog (Peters *et al*,
317 2002).

318

319 *Teratomas*

320 Teratomas arise from pluripotential cells that undergo neoplastic transformation into two or more germ
321 cell types. They occur most often in the gonads and contain tissue that is foreign to the site (Mahour,
322 1988; Ibrahim and Ali, 2018). A single case has been reported in a calf and appeared as a large 5.5 kg

323 mass in the abdominal cavity (Hjärre, 1924). The mass was composed of multiple different fully
324 differentiated tissues including adipose tissue, nervous tissue and epithelium. However, Binanti *et al*
325 (2013) have reported a case of choristoma that resembled a mature teratoma.

326

327 *Yolk Sac Tumours*

328 Yolk sac tumours are primitive germ cell tumours derived from the embryonic yolk sac, allantois, or
329 extra-embryonic mesenchyme. Most cases in humans develop in the testes or ovaries.

330 Four cases of yolk sac tumours have been reported in calves (Kagawa *et al*, 1998; Sasaki *et al*,
331 2012; Sakaguchi *et al*, 2013; Schindewolffs *et al*, 2015). Three of these cases involved the testes and
332 one the abdominal cavity. Nodular masses were reddish–white, cystic and gelatinous. The tumour cells
333 were arranged in different histological patterns including myxomatous, reticular, polyvesicular
334 vitelline and endodermal sinus, and were immunopositive for alpha-fetoprotein. Variable findings
335 were obtained using other immunohistochemical markers and were related to the histological patterns.

336

337 *Embryonal Carcinoma*

338 Embryonal carcinomas are derived from poorly differentiated embryonal epithelium. The histological
339 appearance is of poorly differentiated epithelial cells forming solid, papillary, cyst-like and tubular
340 patterns of growth embedded in abundant fibrous stroma (Agnew and MacLachlan, 2017).

341 A single case of embryonal carcinoma has been reported in a calf (Aihara *et al*, 2011). Multiple
342 variable-sized, yellowish–white nodules were closely spaced on the lining of the abdominal cavity and
343 the serosal surfaces of abdominal organs. The tumour cells were characterized by indistinct cell
344 borders, eosinophilic granular PAS-positive cytoplasm and nuclear anisokaryosis. Mitotic figures,
345 including atypical forms, were frequent and multinucleated cells and vascular invasion were
346 prominent. The tumour cells were positive for alpha-fetoprotein, carcinoembryonic antigen and
347 cytokeratin.

348

349

Congenital Tumours and Genetics

350

351 Damage to the cellular genome or altered expression of genes is common in virtually all
352 neoplasms. Knowledge of these genetic aberrations is well advanced in humans and has been made
353 possible by technological advances in DNA sequencing and other methods that permit genome-wide
354 analysis of tumour cells. Similar studies in veterinary medicine, and especially in cattle, are limited. A
355 syndromic disorder in Belgian Blue cattle, characterized by osteoporosis and gingival hamartomas,
356 has been associated with a missense mutation in the *CLCN7* gene localized on the bovine chromosome
357 25 (Sartelet *et al*, 2014). Affected animals are stillborn or slightly premature, have small body size and
358 ascites, an abnormal skull shape, inferior brachygnathism, blindness, protruding tongue and gingival
359 hamartomas of variable sizes (up to 15 cm diameter) located on the lower jaw. The liver and kidneys
360 are hypertrophied. A congenital Sertoli cell tumour in cattle associated with the autosomal sex
361 determining gene *SOX9* has been reported (Schindewolf *et al*, 2015). Genetic, transcriptomic and
362 direct reprogramming experiments suggest that differentiation of supporting cell progenitors into
363 male-specific Sertoli cells or female-specific granulosa cells is controlled by the presence or absence
364 of *SOX9* and aberrant *SOX9* may be at the basis of tumour development (Ramoun *et al*, 2017). Another
365 hypothesis has been advanced by Palmer *et al* (1980), who observed that two Shorthorn calves with
366 Sertoli cell tumours were roan in colour with ample white areas. Interference with oestrogen receptivity
367 in Shorthorns carrying the *W* gene for white coat in single or double copy was suggested.

368

369 A hereditary predisposition for bovine peripheral nerve sheath tumours (PNSTs) has been
370 described in Danish Holstein cattle (Grossi *et al*, 2014). A preliminary genome-wide association study
371 was completed on DNA isolated from 28 affected and 28 non-affected Holsteins to identify loci in the

372 bovine genome involved in the development of PNSTs. A single nucleotide polymorphism on
373 chromosome 27 reached genome-wide significance.

374

375 Mast cell tumours in cattle comprise less than 1% of all bovine neoplasms and statistical evidence of
376 breed predisposition is not recorded (Tamlin *et al*, 2020). Despite well-documented differences in the
377 clinical presentation and biological behaviour of mast cell tumours in different species, mutations in
378 the *Kit* proto-oncogene are regularly identified in neoplastic mast cells of dogs, cats and humans and
379 contribute to mast cell carcinogenesis. That the *KIT* gene is also likely to be implicated in the
380 development of mast cell tumours in other species is indicated by aberrant cytoplasmic KIT protein
381 immunolabelling in ferrets, horses and cattle (Tamlin *et al*, 2020).

382

383

384

Conclusions

385 A multiplicity of different congenital tumours and tumour-like lesions have been described in calves.
386 Much has yet to be learned about the development of these conditions and information on possible
387 genetic associations is limited. Calves represent a valuable resource for further studies in this area.

388

389

Legends of the figures

391

392 Fig. 1. 15-day-old female Holstein-Friesian calf, congenital pulmonary choristoma (A) Well-
393 circumscribed mass in ventral cervical region not covered by skin and had doubled in size in the
394 previous 14 days. Bar, 10 cm. (B) Cross-section of the mass showing lobulated lung-like tissue with
395 purulent foci. Bar, 10 cm. (C) The tissue in the mass is fibrosed and bronchiolar-like structures are
396 inflamed (arrows). HE. Bar, 200 μ m. Male Holstein Friesian calf, congenital cutaneous mast cell

397 tumour (D–F). (D) Thickened areas of skin on the face and muzzle at 5 months of age. Bar, 10 cm.
398 (E) Periocular and muzzle lesions are less prominent at 1 year of age and skin lesions elsewhere on
399 the body vary in size and some are ulcerated. Bar, 40 cm. (F) Neoplastic mast cells intermingled with
400 eosinophils. HE. Bar, 100 μ m. Inset: metachromatic granules in cytoplasm of neoplastic mast cells.
401 Toluidine blue.

402

403 Fig. 2. 10-day-old female Holstein Friesian calf, congenital medulloblastoma (A and B). (A) Tumour
404 has a soft gelatinous appearance. Bar, 10 cm. (B) Densely cellular neoplasm composed of elongated
405 and ovoid cells, with scant cytoplasm and hyperchromatic nuclei. HE. Bar, 200 μ m. (Courtesy of Dr
406 Gianfranco Militerno, University of Bologna, Italy). (C) Widely disseminated nodular lesions on
407 peritoneal serosa of a 1-month-old male Belgian Blue–Holstein Friesian crossbred calf, congenital
408 mesothelioma. Bar, 20 cm. (D) Lobular proliferation of epithelioid cells with occasional rosette-like
409 structures in lesions shown in Fig. 2D. HE. Bar, 200 μ m. (Courtesy of Dr Gianfranco Militerno,
410 University of Bologna, Italy).

411

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References

- 413 Adelman LS, Aronson SM (1972) Intramedullary nerve fiber and Schwann cell proliferation within
414 the spinal cord (schwannosis). *Neurology*, **22**, 726–731.
- 415 Agerholm JS, McEvoy FJ and Goldschmidt MH (2016) Congenital infiltrative lipomas and
416 retroperitoneal perirenal lipomas in a calf. *Acta Veterinaria Scandinavica*, **58**, 19.
- 417 Agnew DW, MacLachlan NJ (2017) Tumors of the genital systems. In: *Tumors in Domestic*
418 *Animals*, 5th Edit, Meuten DJ, Ed, Wiley Blackwell, Raleigh, pp 689–722.
- 419 Aihara N, Yamamoto N, Takagi T, Une Y (2011) Embryonal carcinoma in the abdominal cavity of a
420 male calf. *Journal of Veterinary Diagnostic Investigation*, **23**, 598–602.

421 Alamo L, Beck-Popovic M, Gudinchet F, Meuli R (2011) Congenital tumors: imaging when life just
422 begins. *Insights Imaging*, **2**, 297–308.

423 Badylak SF (1983) Congenital multifocal hemangiosarcoma in a still-born calf. *Veterinary*
424 *Pathology*, **20**, 245–247.

425 Baker J C, Hultgren B D, Larson V L (1982) Disseminated cavernous hemangioma in a calf. *Journal*
426 *of the American Veterinary Medical Association*, **181**, 172–173.

427 Baskerville A (1967) Mesothelioma in the calf . *Veterinary Pathology*, **4**, 149–156.

428 Bassi P, Gentile A, Militerno G (2010) Retroperitoneal pulmonary choristoma in a newborn calf.
429 *Journal of Veterinary Diagnostic Investigation*, **22**, 1008–1010.

430 Beytut E, Özba B. (2012) Congenital lymphoma of B-cell lineage in a newborn calf. *Turkish Journal*
431 *of Veterinary and Animal Sciences*, **36**, 77–83.

432 Bianchi E, Bombardi C, Bassi P, Bolcato M, Gentile A *et al* (2015) Bilateral trochlear nerve palsy as
433 a consequence of cerebellar medulloblastoma: clinical and pathological findings in a calf. *Journal of*
434 *Veterinary Internal Medicine*, **29**, 1117–1121.

435 Binanti D, Prati I, Locatelli V, Pravettoni D, Sironi G *et al* (2013) Perineal choristoma and atresia ani
436 in 2 female Holstein Friesian calves. *Veterinary Pathology*. **50**, 156–158.

437 Brisville AC, Buczinski S, Chénier S, Francoz F (2012) A cardiac vascular hamartoma in a calf:
438 ultrasonographic and pathologic images. *Journal of Veterinary Cardiology*, **14**, 377–380.

439 Brudenall DK, Ward DA, Newman S (2008) Bilateral corneoconjunctival dermoids and nasal
440 choristomas in a calf. *Veterinary Ophthalmology*, **11**, 202–206.

441 Cantile C, Youssef S (2016) Nervous System. In: *Jubb, Kennedy, and Palmer's Pathology of*
442 *Domestic Animals*, 6th Edit, Vol 1, MG Maxie, Ed, Elsevier, St. Louis, pp 250–406.

443 Caswell JL, Williams KJ (2016) Respiratory System. In: *Jubb, Kennedy, and Palmer's Pathology of*
444 *Domestic Animals*, 6th Edit, Vol 2, MG Maxie, Ed, Elsevier, St. Louis, pp 465–1152.

445 Chauvet AE, Lipsitz D, Burek K, Bailey CS (1994) Pulmonary choristoma in a calf. *Canadian*
446 *Veterinary Journal*, **35**, 441–442.

447 Cho CY, Cook JE, Leipold HW (1979) Angiomatous vascular malformation in the spinal cord of a
448 Hereford calf. *Veterinary Pathology*, **16**, 613–616.

449 Cianciolo RE, Mohr FC (2016) Urinary System. In: *Jubb, Kennedy, and Palmer's Pathology of*
450 *Domestic Animals*, 6th Edit, Vol 2, MG Maxie, Ed, Elsevier, St. Louis, pp 376– 464.

451 Ciorba A, Avalos-Umanzor E (1987) Medulloblastoma in a calf in Costa Rica. *Archivio Veterinaria*
452 *Italiano*, **32**, 133–134.

453 Cooper BJ, Valentine BA (2017) Tumors of the Muscle. In: *Tumors in Domestic Animals*, 5th Edit,
454 Meuten DJ, Ed, Wiley Blackwell, Raleigh, pp 460–461.

455 Cotchin E (1960) Tumors in farm animals. *Veterinary Record*, **72**, 816–823.

456 Di Giancamillo M, Lombardo R, Beretta S, Pravettoni D, Cipone M *et al* (2002) Congenital facial
457 infiltrative lipoma in a calf. *Veterinary Radiology & Ultrasound*, **43**, 46–49.

458 Dorland NW (1988) *Dorland's Illustrated Medical Dictionary*, 27th Edit. WB Saunders, Philadelphia.

459 Drolet R, Sweet W, Desrochers A (2008) Congenital desmoid fibromatosis in a Holstein heifer.
460 *Canadian Veterinary Journal*, **49**, 892–894.

461 Fankhauser R, Fatzer RM (1982) Medulloblastome bei verschiedenengeschlechtlichen
462 willingskalbern. *Schweizer Archiv fur Tierheilkunde*, **124**, 363–367.

463 Fletcher CDM (2000). Soft tissue tumors. In: *Diagnostic Histopathology of Tumors*, 2nd Edit,
464 Churchill Livingstone, London, pp 1473–1540.

- 465 Gessler M, König A, Bruns GA (1992) The genomic organisation and expression of the WT1 gene.
466 *Genomics*, **12**, 807–813.
- 467 Grieco V, Riccardi E, Belotti S, Scanziani E (2006) Immunohistochemical study of porcine
468 nephroblastoma. *Journal of Comparative Pathology*, **134**, 143–151.
- 469 Grossi AB, Agerholm JS, Christensen K, Jensen HE, Leifsson PS *et al* (2014) A hereditary
470 disposition for bovine peripheral nerve sheath tumors in Danish Holstein cattle. *Acta Veterinaria*
471 *Scandinavica*, **56**, 85.
- 472 Guarda F, Biolatti B (1987) Medulloblastoma cerebellare in due vitelli. *Summa*, **4**, 33–35.
- 473 Hendrick MJ (2017) Mesenchymal tumors of the skin and soft tissue. In: *Tumors in Domestic*
474 *Animals*, 5th Edit, Meuten DJ, Ed, Wiley Blackwell, Raleigh, p 163.
- 475 Herzog H, Geishauer T (1991) Kongenitale Neubildungen beim Kalb. *Tierärztliche Umschau*, **46**,
476 277–282.
- 477 Hjärre A (1924) Teratoblastom i bukfilan hos nyfödd kalv. *Skandinavisk Veterinärtidskrift*, **12**, 137–
478 162.
- 479 Hobbenaghi R, Dalir-Naghadeh B, Nazarizadeh A (2015) Coincidence of congenital infiltrative
480 facial lipoma and lingual myxoma in a newborn Holstein calf. *Iranian Journal of Veterinary*
481 *Research*, **16**, 306–309.
- 482 Horwich A, Shipley J, Huddart R (2006) Testicular germ-cell cancer. *Lancet*, **367**, 754–765.
- 483 Ibrahim A, Ali MM (2018) Surgical manipulation of dorsal thoracolumbar massive presumed
484 teratoma in a buffalo-Calf: clinical findings and differential considerations. *Journal of Animal*
485 *Science and Research*, **2** (2): [dx.doi.org/10.16966/2576-6457.116](https://doi.org/10.16966/2576-6457.116)
- 486 Jolly RD, Alley MR (1969) Medulloblastoma in calves. *Pathologia Veterinaria*, **6**, 463–468.

487 Kagawa Y, Ohosaki A, Ohosaki R, Katsuta O, Tsuchitani M *et al* (1998) Testicular yolk sac
488 carcinoma in a calf. *Veterinary Pathology*, **35**, 220–222.

489 Kirkbride CA, Bicknell EJ (1972) Nephroblastoma in a bovine fetus. *Veterinary Pathology*, **9**: 96–
490 98.

491 Kirkbride CA, Bicknell EJ, Robl MG (1973) Hemangioma of a bovine fetus with a chorangioma of
492 the placenta. *Veterinary Pathology*, **10**, 238–240.

493 Kusewitt DF, Rush LJ (2007) Neoplasia and tumor biology. In: *Pathologic Basis of Veterinary*
494 *Disease*, 4th Edit, MB McGavin, JF Zachary, Eds, Mosby, St. Louis, pp 253–298.

495 Lafond JF, Mulon PY, Drolet R (2008). Fibrous vaginal hamartoma in a newborn calf. *Canadian*
496 *Veterinary Journal*, **49**, 61–62.

497 López A, Ikede B, Ogilvie T (1994) Unilateral interstitial (Leydig) cell tumor in a neonatal
498 cryptorchid calf. *Journal of Veterinary Diagnostic Investigation*, **6**, 133–135.

499 Madewell BR, Theilen GH (1987) Tumours of the skin and subcutaneous tissue part III. Skin tumors
500 of mesenchymal origin. In: *Veterinary Cancer Medicine*, 2nd Edit, BR Madewell, GH Theilen, Eds,
501 Lea and Febiger, Philadelphia, pp 282–309.

502 Marino F, Salvaggio A, Macrì D (2006). Congenital retroperitoneal fibrolipoma and osteochondroma in
503 a calf. *Veterinary Record*, **158**, 772.

504 Mahour GH (1988) Sacrococcygeal teratomas. *CA: A Cancer Journal For Clinicians* **6**, 362–367.

505 Mauldin E, Peters-Kennedy J (2016) Integumentary system. In: *Jubb, Kennedy, and Palmer's*
506 *Pathology of Domestic Animals*, 6th Edit, Vol 1, MG Maxie, Ed, Elsevier, St. Louis, pp 509–736.

507 Medeiros de Oliveira D, Araújo Medeiros JM, de Araújo AL, da Anunciação Pimente L, Pierezan F
508 *et al* (2009) Pulmonary choristoma associated with calf meningocele. *Ciência Rural*, **39**, 2652–2654.

509 Militerno G., Sconza S, Bassi P, Diana A, Fiore F *et al* (2011) Congenital cervicofacial lipoma in a
510 Holstein Friesian calf. *Summa*, **2**, 57–60.

511 Miranda IC, Taylor KR, Castleman W, de Lahunta A, Summers BA *et al* (2019) Schwannosis in
512 three foals and a calf. *Veterinary Pathology*, **56**, 783–788.

513 Misdorp W, Dodd DC (1968) Bovine leukosis and localized lymphosarcoma in the Netherlands: a
514 histopathologic study. *Netherlands Journal of Veterinary Science*, **1**, 179–187.

515 Misdorp W (2002a). Tumours in calves: comparative aspects. *Journal of Comparative Pathology*,
516 **127**, 96–105 .

517 Misdorp W (2002b) Congenital tumours and tumour-like lesions in domestic animals. 1. Cattle A
518 review. *Veterinary Quarterly*, **24**, 1–11.

519 Nielsen SW, Mackey LJ, Misdorp W (1976) Tumours of the kidney. *Bulletin of the World Health*
520 *Organization*, **53**, 237–245.

521 Overgoor GHA (1963) Congenitale leucose bij een te vroeg geboren kalf. *Tijdschrift voor*
522 *Diergeneeskunde*, **188**, 664–666.

523 Palmer NC, King AB and Basrur PK (1980) Sertoli cell tumor in two related newborn Shorthorn
524 calves. *Canadian Veterinary Journal*, **21**, 317–319.

525 Palyada KS, Scott DW, Schlafer DH, Czajkowski M (2008) Diffuse cutaneous mastocytosis in a
526 newborn calf. *Veterinary Dermatology*, **19**, 184–186.

527 Peli A, Bolcato M, Roccaro M, Gentile A, Militerno G (2018) Mesothelioma in cattle: two case
528 reports. *Large Animal Review*. **24**, 89–92.

529 Perry A (2010) Familial tumor syndromes. In: *Practical Surgical Neuropathology, A Diagnostic*
530 *Approach*. A Perry, DJ Brat, Eds, Churchill Livingstone, Philadelphia, pp 427–453.

531 Peters MA, Teerds KJ, van der Gaag I, de Rooij DG, van Sluijs FJ (2002) Use of antibodies against
532 LH receptor, 3beta-hydroxysteroid dehydrogenase and vimentin to characterize different types of
533 testicular tumour in dogs. *Reproduction*, **121**, 287–296.

534 Priestnall SL, De Bellis F, Bond R, Alony-Gilboa Y, Summers BA (2010) Spontaneous regression of
535 congenital cutaneous hemangiomas in a calf. *Veterinary Pathology*, **47**, 343–345.

536 Rahmoun M, Lavery R, Laurent-Chaballier S, Bellora N, Philip GK *et al* (2017) In mammalian
537 foetal testes, SOX9 regulates expression of its target genes by binding to genomic regions with
538 conserved signatures. *Nucleic Acids Research*, **45**, 7191–7211.

539 Robinson WF, Robinson NA (2016) Cardiovascular System. In: *Jubb, Kennedy, and Palmer's*
540 *Pathology of Domestic Animals*, 6th Edit, Vol 3, MG Maxie, Ed, Elsevier, St. Louis, pp 16–101.

541 Roth L, Bradley GA (1991) Pulmonary hamartoma in a calf. *Journal of Comparative Pathology*,
542 **105**, 471–474.

543 Sakaguchi K, Matsuda K, Suzuki H, Yamamoto N, Kondo Y *et al* (2013) Testicular yolk sac tumor
544 of myxomatous, reticular, and polyvesicular vitelline type in a newborn calf. *Journal of Veterinary*
545 *Diagnostic Investigation*, **25**, 811–815.

546 Sartelet A, Stauber T, Coppieters W, Ludwig CF, Fasquelle C *et al* (2014) A missense mutation
547 accelerating the gating of the lysosomal Cl⁻/H⁺-exchanger CIC-7/Ostm1 causes osteopetrosis with
548 gingival hamartomas in cattle. *Disease Models & Mechanisms*, **7**, 119–128.

549 Sasaki H, Goyama T, Noda Y, Matsumoto K, Yoshiyasu K *et al* (2012) Perforating abomasal ulcer
550 caused by yolk sac tumor in a Holstein calf. *Journal of Veterinary Diagnostic Investigation*, **24**, 804–
551 806.

552 Schamber GJ, Olson C, Witt LE (1982) Neoplasms in calves (*Bos taurus*). *Veterinary Pathology*, **19**,
553 629–637.

554 Scharnhorst V, van der Eb AJ, Jochemsen AG (2001) WT1 proteins: functions in growth and
555 differentiation. *Gene*, **273**, 141–161.

556 Schindewolf L, Dierks C, Heppelmann M, Gähle M, Piechotta M *et al* (2015) Testicular yolk sac
557 tumor and impaired spermatogenesis in a Holstein Friesian calf. *Systems Biology in Reproductive*
558 *Medicine*, **61**, 314–319.

559 Sheahan BJ and Donnelly WJC (1981) Vascular hamartomas in the gingiva of two calves. *Veterinary*
560 *Pathology*, **4**, 562–564.

561 Sickinger M, Wasieri J, Koehler K, Doll K, Reinacher M (2009) Congenital infiltrative lipomas in a
562 calf. *Journal of Veterinary Diagnostic Investigation*, **21**, 719–721.

563 Smith BI, Phillips LA (2001) Congenital mastocytomas in a Holstein calf. *Canadian Veterinary*
564 *Journal*, **42**, 636–637.

565 Stanton ME, Meunier PC, Smith DF (1984) Vascular hamartoma in the gingiva of two neonatal
566 calves. *Journal of the American Veterinary Medical Association*, **184**, 205–206.

567 Sugiyama A, Ozaki K, Takeuchi T, Narama I (2007) Cardiac vascular hamartoma in two slaughtered
568 cattle. *Journal of Comparative Pathology*, **136**, 202–205.

569 Tamlin VS, Bottema CDK, Peaston AE (2020) Comparative aspects of mast cell neoplasia in
570 animals and the role of *KIT* in prognosis and treatment. *Veterinary Medicine and Science*, **6**, 3–18.

571 Takasu M, Shirota K, Uchida N, Iguchi T, Nishii *et al* (2006) Pericardial mesothelioma in a neonatal
572 calf. *Journal of Veterinary Medical Science*, **68**, 519–521.

573 Tsuka T, Morita T, Tanaka H, Kono S, Murahata Y *et al* (2016) Nasal tissue-derived hamartoma in
574 the maxillary gingiva of a calf. *BMC Veterinary Research*. **12**, 19.

575 Tontis A (1994) Kongenitales kavernöses Hiimangiom beim Brown-Swiss-Kalb, ein seletenes orales
576 Blastom. *Tierarztliche Praxis*, **22**, 137–139.

577 Ulrich R, Buck B, Distl O, Wohlsein P (2014) Congenital embryonal rhabdomyosarcoma of the head
578 in a red and white German Holstein calf. *Tierarztl Prax Ausg G Grosstiere Nutztiere*, **42**, 100–105.

579 Veiga IB, Welle M, Agerholm JS (2017) Congenital cutaneous panadnexal papillomatous
580 hamartomas in a calf. *Journal of Comparative Pathology*, **157**, 183–187.

581 Vernau W, Jacobs RM, Valli VEO, Heeney JL (1997) The immunophenotypic characterization of
582 bovine lymphomas. *Veterinary Pathology*, 1997, **34**, 222–225.

583 Vissiennon T, Freick M, Kilic E, Schmidt T, Dänicke S *et al* (2016) Sertoli cell tumour in a neonate
584 calf: an unusual congenital tumour. A case report. *Tierarztl Prax Ausg G Grosstiere Nutztiere*, **44**,
585 371–378.

586 Wilson RB (1990) Gingival vascular hamartoma in three calves. *Journal of Veterinary Diagnostic*
587 *Investigation*, **2**, 338–339.

588 Yamamoto S, Wada Y, Ishikawa Y, Kadota K (2007) Precursor B-1 B cell lymphoma in a newborn
589 calf. *Journal of Veterinary Diagnostic Investigation*, **19**, 447–450.

590 Yeruham IB, Perl S, Orgad U (1999) Congenital skin neoplasia in cattle. *Veterinary Dermatology*,
591 **10**, 149–156.

592 Yeruham IB, Abramovitch I, Perl S (2004) Gingival vascular hamartoma in two calves. *Australian*
593 *Veterinary Journal*, **82**, 152–153.

594 Zhang Z-Y, Xu J, Ren Y, Yao Y, Li KK-W *et al* (2014) Medulloblastoma in China:
595 clinicopathologic analyses of SHH, WNT, and non-SHH/WNT molecular subgroups reveal different
596 therapeutic responses to adjuvant chemotherapy. *PLoS ONE*, **9**(6): e99490
597 doi:10.1371/journal.pone.0099490.

