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

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(Article begins on next page)

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,  $1.5 \times 3.5$  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  $\alpha$ -oestrogen  
307 receptor,  $\alpha$ -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  $\mu$ 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  $\mu$ 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  $\mu$ 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  $\mu$ m. (Courtesy of Dr Gianfranco Militerno,  
410 University of Bologna, Italy).

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