



SHORT CONTRIBUTION

Hydrops fetalis associated with pulmonary hypoplasia in Dexter calves

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The occurrence of severe fetal dystocia due to hydrops fetalis associated with pulmonary aplasia in two male and pulmonary hypoplasia in one female Australian Dexter fetuses from two herds is described. Obstetrical intervention by caesarean section was required for delivery of the fetuses, with mortalities in one dam and the 3 calves. Clinical, pathological and genetic features are tabulated to assist in distinguishing pulmonary hypoplasia-associated hydrops fetalis from the more prevalent disorder of chondrodysplasia in Dexter cattle. Anasarca and complete absence or presence of only rudimentary lung tissue in a large thoracic cavity clearly distinguishes this entity from the lesions of Dexter chondrodysplasia that include severe micromelia and abundant lung tissue in a small thoracic cavity with shortened spine and rib cage. Pedigree information suggested that Dexter hydrops may be transmitted in an autosomal recessive manner.

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Hydrops fetalis describes the presence of gross oedema, or anasarca, of the subcutaneous tissue of the fetus and is usually accompanied by ascites, with serous transudate in one or more body cavities. It may be also accompanied by oedema of the placenta, particularly in association with specific abnormalities such as the hereditary 'bulldog' calf in the Dexter breed of cattle.¹ The 'bulldog' calf is the homozygous affected form of Dexter chondrodysplasia, characterised by extreme disproportionate dwarfism resulting in a rounded head, shortened maxilla, retruded muzzle, shortened spine and rib cage and pronounced micromelia. This disorder is considered to be inherited in an autosomal incomplete dominant manner and been reported widely in Dexter cattle with a minimum heterozygote frequency in the Australian Dexter population of 19% in 1998.² Studies at this institute have identified two mutations in the Australian Dexter population, and heterozygote testing is now available worldwide.³ Currently, fewer 'bulldog' calves are reported, due primarily to avoidance of matings of known or putative heterozygote animals by informed Australia and New Zealand Dexter breeders. However occasional reports have been received of calves resembling the 'bulldog' that are progeny of Dexter cattle not suspected of being heterozygous for the known mutations for chondrodysplasia.

This report describes the occurrence of three cases of severe fetal hydrops in Dexter calves with a superficial resemblance, to inexperienced observers, to the 'bulldog' calf. However the micromelia that characterises Dexter chondrodysplasia was absent.

Necropsies determined that the disorder was associated with pulmonary aplasia or hypoplasia, a malformation characterised by absence of or incomplete development of lung tissue. Dexter breeders and their veterinarians need to be alert to the probability that another defect causing fetal abnormalities and gestational difficulties may be present in their breed.

Case reports

On the same day in September 2003 two Australian Dexter cows, one near Grafton, New South Wales and another near Strathalbyn, South Australia, developed dystocia and were presented to veterinarians for obstetrical intervention. Marked abdominal distension had been observed in the Grafton heifer (W) over the previous month, such that the owners suspected the cows were having twins or possibly a 'bulldog' calf, despite the pedigree history of the animals involved not being consistent with them as being heterozygous for Dexter chondrodysplasia. Marked abdominal distension was not noted in the Strathalbyn cow (D).

At parturition, heifer W had a brownish foul-smelling vaginal discharge and a successful caesarean section was performed that delivered Calf 1, a grossly enlarged fully haired near-term oedematous male fetus weighing approximately 40 to 45 kg that appeared to have died shortly before delivery. Calf 1 had diffuse severe anasarca, with marked subcutaneous oedema primarily affecting the head and body but largely sparing the limbs. The tongue was protruding however the palate was intact. At necropsy, lung tissue could not be found in the thoracic cavity and the thoracic contents were collected for histopathology. The placenta was considered to have been oedematous.

Cow D near Strathalbyn was observed to be in parturition but the owner was concerned that her labour was not progressing and examined her per vagina and felt the calf to be a large immovable mass. Veterinary examination confirmed an oversized fetus and a caesarean section was commenced, however the procedure resulted in the cow collapsing and euthanasia was elected. Diffuse severe placental oedema was present and Calf 2, a dead grossly enlarged partially haired oedematous male fetus was removed. It was estimated to weigh approximately 60 kg and to be between 4–6 weeks premature (Figure 1). The tongue was protruding however again, the palate was found to be intact. There was an extensive area of spongy oedema in the subcutis of the lateral lower abdomen that was up to 15 cm thickness (Figure 2). At necropsy, lung tissue could not be found in the thoracic cavity. Apart from an abundance of fluid in the body cavities, other organs appeared unremarkable.

A month later, a second cow (T) on the same farm near Strathalbyn commenced parturition and the owner was again concerned that the cow had dystocia. Vaginal examination identified fetal oversize and veterinary assistance was sought. A caesarean section removed Calf 3, a dead 32 kg fully haired full-term female calf. The uterus and placenta appeared normal. At necropsy, moderate anasarca and subcutaneous fluid accumulation was observed in Calf 3 and although less severe than that observed in Calf 2, 7 kg of fluid was drained from the fetus. Rudimentary lungs were observed in the thoracic cavity, the left lung being 3 cm in length and consisting of two lobes, with the right lung being 4.5 cm in length and containing four ventral lobes (Figure 3). A range of organs including thoracic contents but excluding long bones were collected in 10% formalin for histopathology.



Figure 1. Calf 2: a grossly oedematous Dexter calf affected by hydrops fetalis and delivered from a cow requiring euthanasia.



Figure 3. Calf 3: hypoplastic pulmonary tissue with rudimentary malformed lung lobes from the thorax of a calf with moderate hydrops fetalis.



Figure 2. Calf 2: a grossly oedematous Dexter calf affected by hydrops fetalis with severe locally extensive subcutaneous oedema of the lower lateral left abdominal wall.

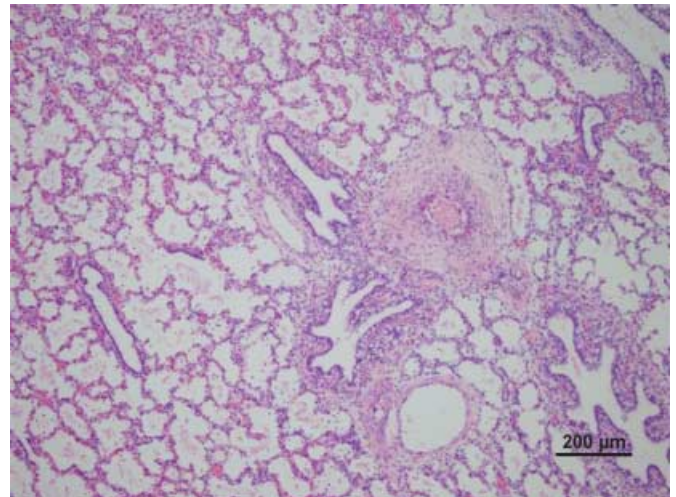


Figure 4. Calf 3: lung tissue displaying fibrous thickening of the peribronchium, increased cellularity of the alveolar septae and alveolar spaces containing an abundance of proteinaceous material plus numerous alveolar pneumocytes. Haematoxylin and Eosin.

Tissues were prepared for routine histology via paraffin embedding, sectioning at 4 to 6 μm and staining with haematoxylin and eosin. Histological examination of thoracic contents of Calf 1 identified heart, thymus and connective and adipose tissue, however failed to identify any elements of pulmonary tissue or distinguishable bronchial or tracheal tissue. In sections from Calf 3, the pleural surface of the lungs, interalveolar spaces, peribronchial areas and bronchiolar submucosa were markedly thickened with oedematous connective tissue. There was fibrous thickening of the peribronchium, increased cellularity of the alveolar septae and the alveolar spaces contained an abundance of proteinaceous material resembling surfactant, plus numerous alveolar pneumocytes (Figure 4). In the liver, the acinar structure was intact although there was moderate dissociation of the hepatic cords suggesting diffuse oedema throughout the extracellular space. Enhanced extramedullary haemopoiesis was not observed. There was diffuse hydropic change in the renal tubular epithelium and occasional tubules were dilated by birefringent crystal formation. No lesions were noted in other organs.

Examination of the pedigrees of the three hydrops cases revealed that all were member of the same family, being 3rd, 4th or 5th generation descendents respectively of Dexter dam X (Figure 5). Calf 1 was the result of a sire-daughter mating of the bull U with heifer W. Calf 2 was the result of the mating of sire B with dam D. Calf 3 was the result of a sire-daughter mating of sire R with dam T and the hydrops fetus was her third calf. Sire R had been successfully mated to 8 of his daughters, including two matings with two of his daughters, producing nine normal progeny and affected Calf 3. Dam X was the daughter of a registered Canadian Dexter cow and was conceived by artificial insemination from semen imported from a registered Canadian bull. Parentage verification was not done on any of the affected calves. However in all cases, the cow was either locked in with only one bull during mating, or hand mated, and both owners were convinced their parentage records of the affected calves were accurate. Samples from all affected calves were DNA-tested and found negative for both the known mutations for Dexter chondrodysplasia.³

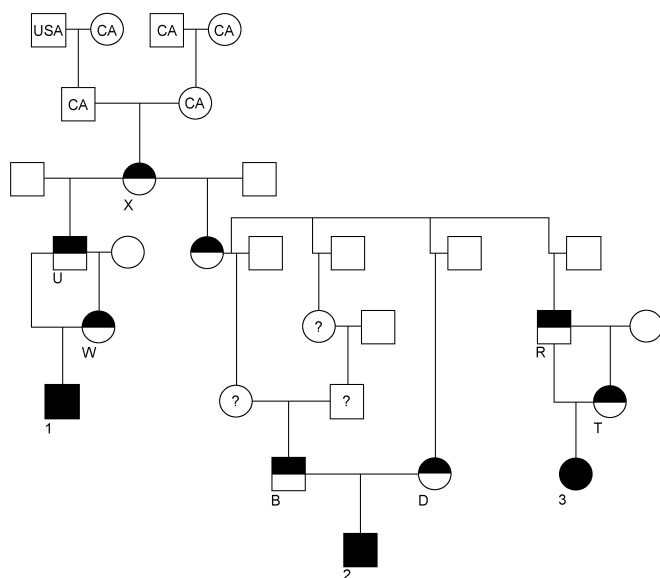


Figure 5. Pedigree relationships of the family of cow X. Males are depicted by squares and females by circles. Full shading designates homozygous affected, half shading designates putative heterozygote and '?' designates status unknown but possibly heterozygous for Dexter hydrops fetalis. 'USA' and 'CA' within a symbol indicate that an animal is registered in the USA or Canadian herdbook, respectively.

Discussion

The grossly oedematous appearance of two of the calves was considered consistent with severe hydrops fetalis and was accompanied by placental oedema. The extreme accumulation of excessive fluid in the subcutaneous tissues and body cavities resulted in a marked increase in body weight and was associated with pulmonary aplasia. The third calf was less severely affected but moderate accumulation of fluid in the subcutis and body cavities in addition to marked pulmonary hypoplasia, but not involving the placenta, was considered consistent with a diagnosis of fetal hydrops. The hydrops fetalis appears to have been a progressive development in utero in late gestation, leading to fetal dystocia and associated with development of hydropsamnion, resulting in death of the calves at the onset of parturition.

Hydrops fetalis has rarely been reported in Australian livestock, with an outbreak reported in sheep associated with suspected fetal anaemia,⁴ and an occurrence in miniature Angus dwarf calves associated with twinning.^{5,6} Absence of enhanced hepatic extramedullary haemopoiesis in Calf 3 suggests that fetal anaemia was not a component of Dexter hydrops, as occurs in ovine hydrops.⁴ Although hydrops fetalis has been noted in Dexter chondrodysplasia,¹ it was not present in the early recorded cases in Australia² and was rarely reported in the many subsequent cases reported to these authors. However the majority of Dexter 'bulldogs' examined have been fetuses spontaneously aborted in mid-gestation. As moderate hydrops was present in two 'bulldog' calves that survived until term, and there have been reports of abdominal distension in Dexter cows prior to delivery of 'bulldog' calves, it is considered that fetal hydrops is a variable feature in Australian Dexter chondrodysplasia that is more likely to be found if the fetus is aborted in late gestation or survives until onset of parturition.

The absence of detectable lung tissue in two cases and severely hypoplastic lungs in the third calf, are indicative of a severely dis-

ordered fetal circulation, inconsistent with post-natal life. The degree of oedema observed in the fetus or neonate with hydrops was considerable, causing the animal to appear grossly bloated and deformed to the owner and veterinarian. The extensive swelling of the subcutis of the head and body plus tongue protrusion in a 'bloated' appearing calf with hydrops may superficially resemble 'bulldog' calves, especially with the rounded head, shortened maxilla, retruded muzzle and tongue protrusion of the chondrodysplastic calf.² However consideration of a full spectrum of the pathology of chondrodysplasia and particularly the absence of micromelia and cleft palate, assists in differentiating the disorders (Table 1). The marked micromelia due to shortening of long bones from failure of endochondral ossification in Dexter chondrodysplasia, was not present in these cases of Dexter pulmonary hypoplasia. Despite the long bones being unavailable for histological confirmation of the presence of normal endochondral ossification, the two phenotypes are clearly distinguishable.

Abnormal pulmonary pathology is found in Dexter chondrodysplasia, but is considered the result of a shortened rib cage that reduces the thoracic cavity and compresses the lungs during development, resulting in the multilobulated appearance of lung tissue.² External compression of developing fetal lung may impair both anatomical and biochemical maturation of the alveoli and possibly impair maturation of pulmonary surfactant production. It is probable that moderate pulmonary hypoplasia with a reduction in the number of functional alveolar units that can occur in cases of Dexter chondrodysplasia, accounts for the presence of fetal hydrops in cases that survive to late gestation or term. Death of neonatal 'bulldog' calves that survive their gestation period is considered more likely due to collapse of the trachea due to the abnormal cartilage development.

As placental oedema invariably accompanies severe fetal oedema, clinical signs of hydroamnion are expected to be present in fetal hydrops. The owner of Calf 1 was alarmed at the abdominal swelling displayed by the dam of the affected calf; however the owner of Calves 2 and 3 commented that these two cows merely appeared to be in advanced pregnancy with very good body condition. Abdominal swelling has occasionally been reported in cows that subsequently aborted or delivered 'bulldog' calves, however this is not a consistent observation in the Australian Dexters (unpublished observation).

In humans, massive oedema of the newborn infant has been recognized for at least 3 centuries and a causal relationship with maternal-fetal blood group incompatibilities was recognised soon after red cell antigens were identified. Fetal hydrops was considered to be primarily the consequence of severe maternal isoimmunisation to fetal blood group antigens foreign to the mother. However few current cases are due to immune mechanisms. Many causes for non-immune hydrops have been recognised, including haematological disorders, infections, chromosomal abnormalities, tumours and congenital anomalies, including pulmonary hypoplasia.^{7,8} In the majority of current human cases, the diagnosis of hydrops fetalis is made prenatally.⁸

The pathophysiological events leading to fetal hydrops have been poorly understood until recent studies conducted in sheep produced fetal hydrops by occlusion of lymphatic drainage, obstruction of cardiac venous return, and induced fetal anaemia or tachycardia.^{9,10} However many physiological disturbances have been noted in human fetal hydrops, including elevations in

Table 1. Distinguishing features of fetal hydrops and chondrodysplasia in Australian Dexter cattle.

Feature	Fetal hydrops	Chondrodysplasia
Mode of inheritance	Probable autosomal recessive	Incomplete dominance with 'bulldog' homozygote affected, 'short' legs in heterozygotes
Probable pathogenesis	Severe pulmonary aplasia or hypoplasia	Failure of endochondral ossification
Clinical signs in dam	Severe abdominal distension	Occasional moderate abdominal distension
Clinical signs in calf	Moderate to severe anasarca, normal leg length and palate	Possible mild to moderate anasarca, severely shortened leg length, domed skull, cleft palate
Necropsy findings in dam	Severe hydroamnion in 2 of 3 cases	Possible hydroamnion, 'short leggedness'
Necropsy findings in calf	Absence of lung tissue or severely reduced lung size in a normal appearing thoracic cavity	Multiple lobing and compression of abundant lung tissue in a reduced thoracic cavity, marked micromelia and abdominal herniation

aldosterone, renin, norepinephrine, and angiotensin I, which are considered probable secondary consequences. Also seen are increased coenzyme Q10, placental vascular endothelial growth factor, and endothelin and decreased cytokine interleukin-3 levels, all of uncertain significance. Of interest is a 3 to 5-fold increase in atrial natriuretic peptide (ANP) that accompanies both human fetal hydrops with cardiac anomalies or isoimmunisation, and ovine hydrops induced by obstruction of venous return, sustained tachycardia, or induced anaemia. As vascular permeation of albumin is enhanced and cardiovascular and renal homeostatic adaptations are influenced by ANP, a key role for ANP in fetal hydrops has been suggested, particularly as ANP levels return to normal with resolution of the hydrops.¹⁰

In this study, the available pedigree information, with all three Dexter hydrops calves having both phenotypically normal parents that were direct descendents from cow X, suggests that Dexter hydrops is possibly the homozygous state for a defective gene transmitted in an autosomal recessive manner. However as numbers are limited, advice of further cases is requested, particularly to explore whether the variation in pathological expression of the hypoplasia is related to gender of the calf. As a newly recognised potential new inherited disorder, Dexter hydrops may be a valuable animal model for future studies of hydrops fetalis associated with pulmonary aplasia or hypoplasia.

Subsequent to the submission of this paper in February 2005, the authors became aware of a similar observation of pulmonary hypoplasia and anasarca in 3 Shorthorn fetuses submitted to north American diagnostic laboratories between February and June 2005.¹¹ The lesions described appear remarkably similar to those of Dexter pulmonary hypoplasia and as in our cases in the Dexter breed, the emergence of a new congenital, possibly inherited defect is suspected in the Shorthorn breed (D Steffen, personal communication).

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