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Case Report

Chondrodysplasia Bulldog type in cattle in the state of Bahia, Brazil

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Abstract

Chondrodysplasia is a congenital or hereditary disorder of the endochondral ossification that results in several degrees of disproportionate dwarfism. Reports of this disease are scarce in the national literature and do not emphasize radiographic characteristics. The goal of this study was to describe the clinicopathological and radiographic aspects of a case of Bulldog type chondrodysplasia in a crossbred bovine fetus in the state of Bahia, Brazil. The fetus exhibited a rounded and disproportionate skull, bilateral exophthalmos, inferior brachygnathism, partial tongue protrusion, extremely short limbs, short vertebral column and ventral abdominal hernia. Radiographic evaluation revealed that the diaphysis were the only calcified bone portions of the limbs, that the vertebral column was shortened without vertebral spinal processes and that there was craniofacial disproportion. Microscopic of the femur showed an irregular epiphyseal plaque, formed by dense clusters of chondrocytes with absence of growth plate zones. The metaphysis was markedly short and consisted of thick bony trabeculae, surrounded by cartilaginous islands. It was concluded that fetuses with Bulldog type chondrodysplasia exhibit slight morphological and radiographic variation according to the affected breed and that the gene carrier of chondrodysplasia is present in the miniature Jersey and Punganur population in the state of Bahia.

Key words: skeletal dysplasia, ruminants, disproportionate dwarfism.

Introduction

Congenital defects are structural and functional abnormalities of tissues, organs or systems that can occur during embryonic or fetal development in all animal species (9). These malformations have a worldwide distribution and can result in abortions or neonatal death (20) and are responsible for important reproductive losses in cattle (17).

Among the congenital malformations in cattle, chondrodysplasia stands out. This disorder is due to changes in endochondral ossification that leads to inadequate chondrocyte maturation and, consequently, disorders in the development of the appendicular skeleton, ribs, vertebrae and base of the skull, which results in disproportionate skeletal development (22).

In cattle, this disease is associated with hereditary transmission (5, 21) and/or mineral deficiencies, such as manganese (17) and zinc (11), during the gestational period. There are five morphological classifications: Bulldog (Dexter), Telemark, Snorter (Brachiocephalic),

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Doliocephalic (long head) and Ellis van Creveld syndrome (9).

The Bulldog type is the most severe and widespread form of this condition, the fetus are usually aborted around the seventh month of gestation. It is a disease of genetic incomplete dominance, lethal in homozygosity in the Dexter breed (14). In miniature Zebu cattle, this disease has been attributed to a recessive lethal inheritance (24). In both, this condition was associated with different mutations in the *aggrecan* (*ACAN*) gene (5, 24), an aggregating proteoglycan of cartilage structure, essential for chondroskeletal morphogenesis during fetal development (5, 15). However, in Holstein cattle, this malformation has a different genetic basis, which has not been fully elucidated yet. This disease has already been attributed to autosomal recessive inheritance (1) and is currently related to mutation in *COL2A1* gene, corresponding to a dominant inheritance with incomplete penetrance or a mosaic mutation, leading to a quantitative deficit of structurally normal collagen II (2). Unlike the Dexter breed and the miniature Zebu family, the carriers of this gene have a normal phenotype (1, 2, 24).

This type of chondrodysplasia is commonly reported (1-6, 8, 12-14, 16, 18, 24, 27), but only one case was described in Bahia (10). Thus, the objective of this report, is to describe the clinical, anatomopathological and radiographic aspects of a case of Bulldog type chondrodysplasia in a bovine, male, crossbred fetus (miniature Jersey with Punganur) in the state of Bahia.

Case Report

A three-year-old miniature Jersey female cow was evaluated in the Large Animal Medical Clinic (CMGA) at the Veterinary Medicine Hospital of the Federal University of Bahia (UFBA), with nine months of gestation and dystocic delivery at the expulsion stage for 12 hours. After fetal death was confirmed, obstetric maneuvers (repositioning and forced traction) were performed to remove the fetus through the birth canal.

The fetus was a male, crossbred of Punganur with miniature Jersey and exhibited congenital malformations compatible with disproportionate dwarfism. Another similar case had already occurred on the property, and the same congenital abnormality was observed in a fetus aborted by the same cow, after natural breeding with the same breeder.

The malformed calf was radiographed using Siemens® equipment model Multix B and computerized image acquisition system AGFA® CR30-X. Multiple views were taken to contemplate images of the entire body. The fetus showed craniofacial disproportion with midfacial retraction, the vertebral corpora were short without evidence of vertebral spinal processes with only the primary ossification center. There was no evidence of the primary ossification nuclei of the vertebral arch and the secondary ossification nuclei of the vertebral epiphyses. The bones of the pelvic limbs were seen only as small segments of mineralized bones, separated from each other, giving an appearance of "loose" bones, only identifiable by their location. These segments corresponded to the diaphyseal portion of the femur, tibia, metatarsals, distal, middle and proximal phalanx. A small bone segment was also visible in the topography of the tarsus. Similarly, in the thoracic limb, only small calcified bone segments, corresponding to the diaphyseal region of the scapulae, humerus, radius and ulna, metacarpal and proximal, middle and distal phalanges, were visible (Fig. 1).

After the radiographic examination, the cadaver was submitted for necropsy in the Veterinary Pathology Laboratory (LPV) of HOSPMEV-UFBA. The length between the nape and sacrum of the fetus was 45 cm. The calf had a rounded and disproportionate skull, moderate bilateral exophthalmos, inferior brachygnathism, partial tongue protrusion, extremely short limbs, Varus deformity and intense joint mobility in the hindlimbs, short vertebral column, high tail insertion and ventral abdominal hernia with eventration, measuring 4.5 x 5.0 cm (Fig. 2).

Samples for histopathology were taken, fixed in 10 % neutral buffered formalin for histology. Before processing, bones were decalcified in a 20% formic acid solution. The material was processed by routine methods, embedded in paraffin, sectioned at 5 μm and stained with hematoxylin-eosin (HE). Selected bone sections were also stained by Masson's Trichrome to highlight chondrocytes.

Microscopic evaluation of the epiphysis and metaphysis of many long bones (femur, humerus, tibia and ulna) showed extensive areas of immature cartilage with an irregular epiphyseal plaque, forming dense clusters of chondrocytes with disorganized columns embedded within amounts of eosinophilic chondroid matrix and absence of growth plate zones (abnormalities). The metaphysis was markedly short and consisted of thick bone trabeculae with occasional disorganized cartilaginous islands (Fig. 3). The bone trabeculae were short, with poor mineralization.

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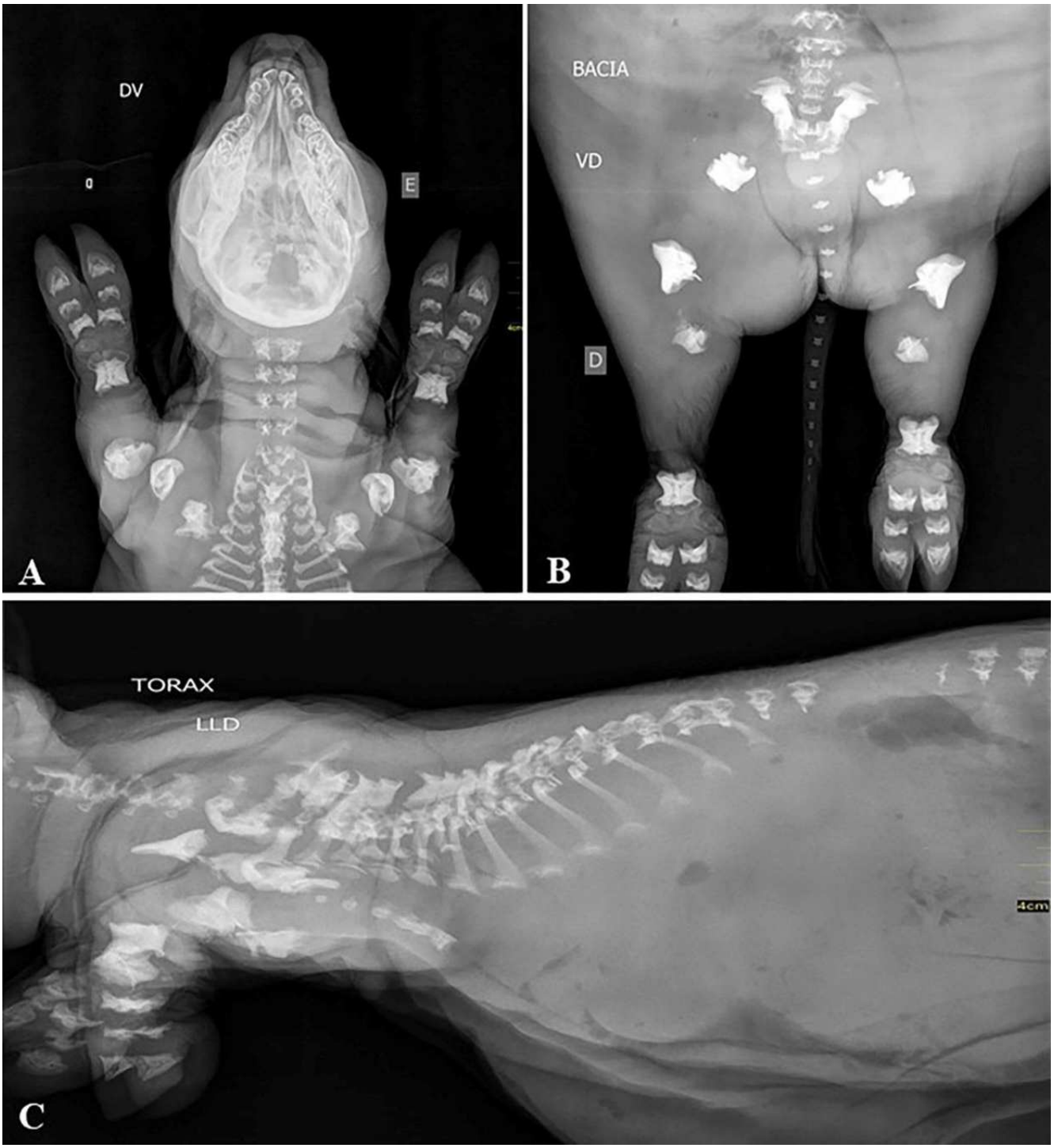


Figure 1. Radiographic images of the bovine fetus with Bulldog type chondrodysplasia. **A.** Head and thoracic limbs, in which only bone segments are visible, probably corresponding to the diaphyseal regions of the scapulae, humerus, radius and ulna, metacarpals and proximal, middle and distal phalanges. **B.** Pelvic limbs, in which the pelvis and small mineralized bone segments are identified, possibly related to the diaphysis of the femurs, tibias, metatarsals, proximal, medium and distal phalanges, in addition to a small bone segment in tarsal bone topography. **C.** Thorax, part of the abdomen and spine, in which short vertebrae corpora are identified, with no evidence of vertebral spinal processes with only the primary ossification center, without evidence of the primary ossification nuclei of the vertebral arch and secondary ossification nuclei of the vertebral epiphyses.

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Figure 2. Bulldog type chondrodysplasia in a bovine fetus. **A.** Dorsal view. Shortening of spine. **B.** Ventral view. Intense micromelia, bulging abdomen and ventral abdominal hernia. **C.** Side view. disproportionate skull, moderate exophthalmos, inferior brachygnathism and intense micromelia. **D.** Ventral abdominal hernia with eventration, measuring 4.5 x 5.0 cm with exposure of intestinal loops.

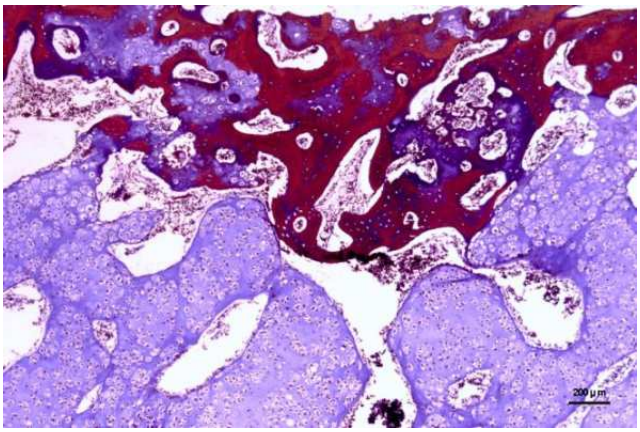


Figure 3. Epiphysis/Metaphysis of crossbred bovine femur with Bulldog type chondrodysplasia. Disorganized epiphyseal plaque forming dense chondrocyte clusters without differentiation between growth zones. Metaphysis was short and consisted of thick bone trabeculae, with poor calcification. Masson's Trichrome, scale bar: 200 µm.

Discussion

The diagnosis of Bulldog type chondrodysplasia was established based on macroscopic and radiographic findings and confirmed by histopathological examination. The macroscopic changes found were similar to those described in chondrodysplastic bovines of the Bulldog type of breeds Jersey (6, 27), Punganur (10), Scottish Highland (3), Belted Galloway (12), Dexter (14), Holstein (1, 2, 13), Nellore (18) and miniature Zebus (24). Except for the absence of cleft palate and superior brachygnathism, malformation commonly described in cattle with Bulldog type chondrodysplasia (2, 3, 6, 12, 14). The cleft palate occurs due to the incomplete fusion of the frontal process with the maxillary processes (26). However, in Punganur cattle with Bulldog type chondrodysplasia, cleft palate has not been reported yet (10), so it is possible that the occurrence of this malformation may be related to breed. The absence of cleft palate in the present case (Punganur crossbred fetus) reinforces this hypothesis. Descriptions of inferior brachygnathism were not found in the literature and may be related to the fact that they are a crossbred fetus, since the animals that present superior brachygnathism were of pure breeds.

The histopathological findings described in the literature in cases of Bulldog type chondrodysplasia (1-3, 5, 6, 10, 12 14, 18, 24, 27) are similar to those observed in the present case. They are mainly characterized by epiphyseal plaque with extensive areas of immature

cartilage and clusters of disorganized chondrocytes embedded within variable amounts of eosinophilic and degenerate chondroid matrix (3, 12, 27). The metaphysis were similarly composed of dysplastic cartilage with thick bony trabeculae poor mineralized (3, 14).

Some authors evaluated bone lesions in cattle with Bulldog type chondrodysplasia by radiographic exams (1, 2, 3, 5), variations were verified according to the affected breed. Aborted fetuses of Scottish Highland cattle showed dysraphism of the vertebrae, bifid thoracic spinous, absence of pelvic limbs and severe maxillary brachygnathism (3). In Dexter breed, vertebral platyspondyly, extreme shortening of the ribs, craniofacial disproportion with midfacial retraction, prognathism and micromelia have been described (5). Radiographic findings in miniature Jersey and Punganur or crossbred cattle have not been described yet. However, it was found in the present study that the main characteristics of craniofacial disproportionality, midfacial retraction, vertebral column shortening and micromelia were like those described for Scottish Highland (3), Dexter (5) and Holstein (1, 2) fetuses, except for the inferior brachygnathism.

Studies of this type of congenital malformation in cattle are infrequent in Brazil (6, 9, 16, 18, 20, 27) and rare in the Northeast (10). Recently, in Rio Grande do Sul, a retrospective study (1978-2012) conducted by the Regional Diagnostic Laboratory of the Federal University of Pelotas (UFPel), found 14 cases of chondrodysplasia in cattle, of which the Bulldog type occurred in 21,4% (3/14) of the cases, all in Jersey cows (6). Except for the state of Rio Grande do Sul, data on the epidemiology and importance of this malformation are unknown in the country. It is noteworthy that the disease was only recently described in Bahia (10), thus this is the second report of the occurrence of Bulldog chondrodysplasia in the state. Among the few reports found in the national literature (6, 10, 16, 27), it has been observed that, in most cases, Jersey cattle (6, 16, 27) are affected and, in Bahia, the Punganur breed (10), which indicates dissemination of the gene in the national ox herd, consequence of the high consanguinity, which is very common in small farms that use a single breeder (16).

Corroborating to this theory, the case described here was the offspring of a miniature Jersey cow with a Punganur ox, which had previously gestated a calf with the same morphological characteristics. It is believed that this malformation is related to a mutation in the aggrecan gene (ACAN), since the importance of this gene is recognized in Bulldog chondrodysplasia in miniature zebus (24) and the Punganur is a miniature Zebu breed.

Another important differential diagnosis for congenital malformations in cattle in the Brazilian Northeast is intoxication by *Mimosa tenuiflora*, popularly known as "black jurema". This malformation occurs in the form of an outbreak, especially in drought conditions (25). Affected calves generally exhibit arthrogryposis and atresia ani, and in some cases, blindness, corneal dermoid, microphthalmia and corneal opacity (9). In the present case, the possibility of teratogenicity induced by the ingestion of the plant by the pregnant miniature cow was excluded based on the morphological aspect of the fetal lesions and the absence of the plant on the farm where the animals were kept.

Regarding the morphological differentiation between the five types of chondrodysplasia, some considerations can be made. Unlike the Bulldog type phenotype, Telemark chondrodysplastics have shorter rotated limbs with a large, rounded head and short snout (6); the Snorter type has as main characteristic the heavy and labored breathing and broad head with bulging forehead. On the other hand, the Dolichocephalic has an elongated head with a thin snout (23) and animals affected by Ellis van Creveld's syndrome, have short, bulky and arched limbs (19). Additionally, the Bulldog chondrodysplastic is the only one that is lethal (5). The knowledge of such characteristics is important for the recognition of the type of chondrodysplasia involved in a herd.

When there is an abortion of a bovine close to the seventh month of gestation, whose fetus presents several morphological changes, such as disproportionate skull, shortened limb, short vertebral column, tongue protrusion, cleft palate and abdominal hernia (14), the diagnosis of Bulldog chondrodysplasia should be considered. However, diagnostic confirmation must be performed by histopathological examination (8). It is worth mentioning that there are tests to detect the mutation in ACAN gene in the parents and fetus (5, 24), which can be used in future genetic studies in the Punganur breed.

References

1. Agerholm JS, Arnbjerg J, Andersen O. Familial chondrodysplasia in Holstein calves. J Vet Diagn Invest. 2004;16(4):293-98.
2. Agerholm JS, Menzi F, McEvoy FJ, Jagannathan V, Drögemüller C. Lethal chondrodysplasia in a family of Holstein cattle is associated with a de novo splice site variant of COL2A1. BMC Vet Res. 2016;12(1):100.
3. Cabrera LC, McNabb BR, Woods ES, Cartoceti NA. Hydrops associated with chondrodysplasia of the fetus in a miniature Scottish Highland cow. J Am Vet Med Assoc. 2016;248(5):552-6.
4. Carmichael J. "Bull-Dog" in African Cattle. Nature. 1993;131(3320):878.
5. Cavanagh JAL, Tammen I, Windsor PA, Bateman JF, Savarirayan R, Nicholas FW, Raadsma HW. Bulldog dwarfism in Dexter cattle is caused by mutations in ACAN. Mamm Genome. 2007;18(11):808-14.
6. Coelho ACB, Marcolongo-Pereira C, Soares MP, Quevedo PS, Riet-Correa F, Schild AL. Condrodisplasia em bovinos no Sul do Rio Grande do Sul. Pesq Vet Bras. 2013;33(10):1195-200.
7. Craig LE, Dittmer KE, Thomopson KG. Bones and joints. In: Maxie MG, editor. Jubb, Kennedy &

Palmer's Pathology of Domestic Animals. Missouri: Elsevier; 2016. p. 16-163.
8. Crew FAE. The bull-dog calf: a contribution to the study of achondroplasia. Proc R Soc Med. 1924;17(Sect Comp Med):39-58.
9. Dantas AFM, Riet-Correa F, Medeiros RMT, Galiza GJN, Pimentel LA, Anjos BL, Mota RA. Malformações congênitas em ruminantes no semiárido do Nordeste Brasileiro. Pesq Vet Bras. 2010;30(10):807-15.
10. Silva RMM, Biscarde CEA, Souza AC, Pereira AL, Campos-Santos M, Macêdo JTSA, Pimentel LA, Pedroso PMO. Condrodisplasia tipo Dexter em bovino mestiço Punganur. Proceedings of the VII ENDVET 2014- Encontro Nacional de Diagnóstico Veterinário 7th; 2014 nov 10-13; Cuiabá, Brasil.
11. Dittmer KE, Thompson KG, Hassell C. Chondrodysplasia associated with summer drought in calves. N Z Vet J. 2015;63(3):174-6.
12. Dittmer KE, Thompson KG, Hogan T. Severe generalised chondrodysplasia in miniature cattle breeds. N Z Vet J. 2017;65(5):282-3.
13. Häfliger IM, Behn H, Freick M, Jagannathan V, Drögemüller C. A COL2A1 de novo variant in a Holstein bulldog calf. Anim Genet. 2019;50(1):113-4.
14. Harper PAW, Latter MR, Nicholas FW, Cook RW, Gill PA. Chondrodysplasia in Australian Dexter cattle. Aust Vet J. 1998;76(3):199-202.
15. Kiani C, Chen L, Wu YJ, Yee AJ, Yang BB. Structure and function of aggrecan. Cell Res. 2002;12(1):19-32.
16. Marcolongo-Pereira C, Schild AL, Soares MP, Vargas Jr SF, Riet-Correa F. Defeitos congênitos diagnosticados em ruminantes na Região Sul do Rio Grande do Sul. Pesq Vet Bras. 2010;30(10):816-26.
17. McLaren PJ, Cave JG, Parker EM, Slocombe RF. Chondrodysplastic calves in northeast Victoria. Vet Pathol. 2007;44(3):342-54.
18. Moura E, Prado AMRB, Pimpão CT, Murakami CT, Ribeiro DR. Genetic and pathoanatomical features of the bovine prenatal lethal chondrodysplasia. Hereditary Genet. 2014;3(132):1-5.
19. Muscatello MLV, Benazzi C, Dittmer KE, Thompson KG, Murgiano L, Drogemuller C, Avallone G, Gentile A, Edwards JF, Piffer C, Bolcato B, Brunetti B. Ellis–van Creveld Syndrome in Grey Alpine cattle: morphologic, immunophenotypic, and molecular characterization. Vet Pathol. 2015;52(5):957-66.
20. Pavarini SP, Sonne L, Antoniassi NAB, Santos AS, Pescador CA, Corbellini LG, Driemeier D. Anomalias congênitas em fetos bovinos abortados no Sul do Brasil. Pesq Vet Bras. 2008;28(3):149-54.
21. Ribble CS, Janzen ED, Proulx JG. Congenital joint laxity and dwarfism: A feed-associated congenital anomaly of beef calves in Canada. Can Vet J. 1989;30(4):331-8.
22. Serakides R. Ossos e Articulações. In: Santos RL, Alessi AC, editors. Patologia Veterinária. Rio de Janeiro: Roca; 2016. p. 619-661.
23. Stringam EW. Dwarfism in beef cattle. Can J Comp Med Vet Sci. 1958;22(11):400-3.
24. Struck K, Dierks C, Braun M, Hellige M, Wagner A, Oelmaier B, Beineke A, Metzger J, Distl O. A recessive lethal chondrodysplasia in a miniature zebu Family results from an insertion affecting the chondroitin sulfate domain off aggrecan. BMC Genet. 2018;19(1):91.
25. Tokarnia CH. Plantas que causam malformações congênitas. In: Tokarnia CH, Brito MF, Barbosa JD, Peixoto PV, Dobereiner J. Plantas tóxicas do Brasil para Animais de Produção. Rio de Janeiro: Editora Helianthus; 2007. p. 392-395.
26. Uzal FA, Plattner BL, Hostetter JM. Alimentary System 1. In: Maxie MG, editor. Jubb, Kennedy & Palmer's Pathology of Domestic Animals. Missouri: Elsevier; 2016. p. 1-257.
27. Wurster F, Bassuino DM, Juff GD, Boos GS, Boabaid FM, Antoniassi NAB, Driemeier D. Chondrodysplasia Dexter type in aborted bovine fetuses. Acta Sci Vet. 2012;40(3):1060.