Congenital Hypotrichosis with Thymus Hypoplasia in a Female German Holstein Calf

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Abstract: The present case was a nearly complete hairless female German Holstein calf. Clinical examination and necropsy were performed when the calf was six weeks old. The calf had conjunctivitis in both eyes, injuries, ulcer and edema at limb joints. Histopathological findings of the present case confirmed a general hypotrichosis, a segmental atrichosis and dermatitis. Further findings were hyperkeratosis, pneumonia, splenitis, glycogen storage in liver and hypoplasia of the thymus. The virological results were negative for bovine viral diarrhea (BVD) virus and antibody. The inbreeding coefficient for the affected calf was 1.074%, chromosomal anomalies were not found in the metaphases of the affected calf (2n=60,XX). The congenital hypotrichosis/atrichosis described herein shows similarities with the nude/severe combined immunodeficiency (SCID) caused by *Forkhead-box n1* (FOXN1) phenotype in humans inherited as an autosomal recessive disorder. Further research has to clarify whether FOXN1 plays a pivotal role for this disease in calves.
***Keywords**: Congenital anomaly, Hypotrichosis, Thymus hypoplasia, Cattle*

Dişi Bir Alman Holstein Buzağıda Timus Hipoplazisi ile Beraber Seyreden Konjenital Hipotrikoz

Özet: Sunulan olgu vücudunun neredeyse tamamı tüysüz olan dişi bir Alman Holstein buzağıdır. Klinik ve nekropsi muayenesi buzağı altı haftalıkken gerçekleşmiştir. Buzağıda gözün kornea tabakasında yangı ve ön bacaklarda ise ülser, ödem ve yaralanmalar tespit edildi. Histopatolojik incelemede ise; genel bir hipotrikoz, segmentalatrikoz ve dermatit gözlemlendi. Diğer bulgular ise; hyperkeratoz, pnömoni, splenitis, karaciğerde glikojen odakları ve timus hipoplazisi olarak tespit edildi. Virolojik muayene sonucunda Bovine Viral Diarrhea (BVD) virusa rastlanılmadı. Akrabalık katsayısı % 1.074 olarak bulundu ve herhangi bir kromozomal anomaliye rastlanılmadı. Hastalığın semptomları, insanlarda görülen *Forkhead-box n1* (FOXN1) gen mutasyonu sonucu oluşan sistemik yalın ya da şiddetli seyreden kombine immundefekte (SCID) fenotipik olarak çok benzediğinden, sığırlarda timus hipoplazisi ile karakterize konjenital hipotrikoz nedenine bu buzağıda yapılacak genetik analizler ile çözüm bulacağı kanısına varılmıştır.
***Anahtar Kelimeler**: Konjenitalanomali, Hipotrikoz, Timushipoplazisi, Sığır*

Introduction

Bovine hypotrichosis is a congenital disease characterized by partial or complete absence of hair coat, with or without accompanying developmental defects (Jayasekara et al., 1979). At least six different forms of congenital hypotrichosis are distinguished including lethal (semi-lethal), partialisvitalis (viable), areata, semi-hairlessness, streaked hairlessness, and X-linked hypotrichosis (Hutt, 1963). Cases were reported for several breeds (Distl et al., 2000; Hanna and Ogilvie, 1989). The lethal (semi-lethal) hairless condition causes stillbirth or death shortly after birth. Affected animals have hair on the eyelids, ears, navel, genital, tail end and pasterns (Herzog, 2001). This hairless form occurs frequently with hypoplasia of the thyroid or thymus, sometimes associated with corneal opacity. This form is lethal for male Holstein calves and semilethal for female Holstein calves (Herzog, 2001). Other malformations may occur together with lethal hairlessness (Herzog, 2001). Animals with semi-hypotrichosis show a thin, short curled hair at birth, besides that also circumscribed hairless areas (ears, abdomen, extremities inner surfaces, tail) (Herzog, 2001; Hutt, 1963). Lethal hairlessness and semi-hairlessness are assumed to be simple autosomal recessive traits (Leipold et al., 1983). X-linked anhidrotic ectodermal dysplasia (ED1) is characterized by hypotrichosis, missing teeth and missing eccrine sweat glands. Several mutations responsible for this condition have been identified in the EDA gene (Drögemüller et al., 2002; Drögemüller et al., 2006; Ogino et al., 2011). The objective of the present study was to analyze a case of congenital hypotrichosis with thymus hypoplasia in a female German Holstein calf using clinical, pathological, histopathological, virological and cytogenetic examinations as well as pedigree analysis.

Case History

Case description: A German Holstein cow gave birth to female twins whereof one calf was normal and

the other calf was hairless. Gestation length was 265 days. The normal female calf had a normal body size and weight with four weeks of age, whereas the hairless calf showed a reduced body weight and size (Fig. 1A). Similar cases had not been known as this form. The farm was free of bovine viral diarrhea (BVD) virus and bovine herpes virus type 1 (BHV1).

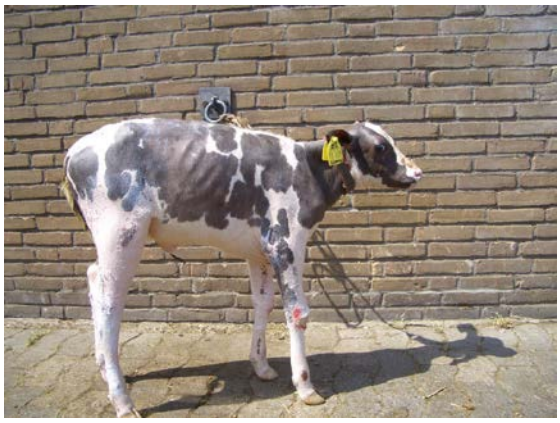

Figure 1. Female German Holstein calf showing an inborn nearly complete hairlessness.

Figure 2. A: Inflammation and ulceration of the carpal joint of the Holstein calf. B: Normally developed incisivi and premolar teeth of the present case.

Clinical findings: The female calf was almost hairless at birth (Fig. 1A). However, a few hairs on the tail and the middle of the back were found (Fig. 1B). Hair fibers were dry, thin and slightly curled. The skin was dry and scurfy (Fig. 1C). The muzzle was completely dry and crusty (Fig. 1D). The calf showed lameness. The joints of the calf were swollen and signs of inflammation were evident. At both carpal joints lesions with ulcer were present (Fig. 2A). The incisive and premolar teeth were normally developed (Fig. 2B, 2C). Appetite was normal but body size and weight were too small for its age. Body weight was 26.2 kg, internal body temperature 38.1 °C, heart rate 98 beats per minute and respiratory rate 24 per minute. Due to the severe pneumonia and the persistent ulcerative inflammation of the carpal joints, the calf had to be euthanized at the age of six weeks.

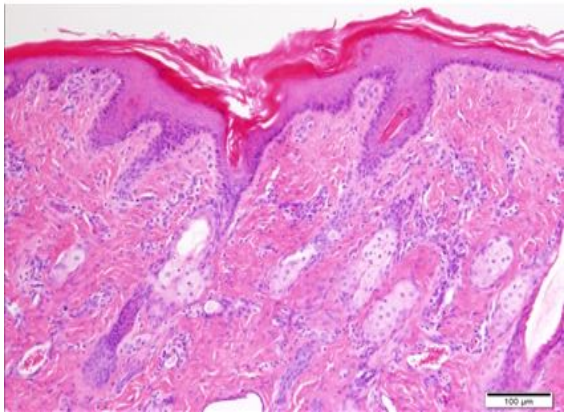

Figure 3. Haematoxylin and eosin-stained skin section from the shoulder region of a fore leg with hyperkeratosis and other dermathopathological changes.

Necropsy findings: A generalized hypotrichosis with a moderate multifocal and erosive dermatitis were identified. A moderate subcutaneous edema was seen in the hind limbs. The muscles appeared anemic. All limb joints were filled with clear synovia. Postmortem examination explains a remarkable hypoplasia of thymus, the weight of thymus of the calf examined 36 g, but the normal weight of thymus of 250 to 400 g. In addition, atelectatic areas in lungs and a hyperemic spleen and liver were found.

Histopathological findings: After necropsy, tissue samples were fixed for histopathological analysis in 10% buffered formalin, and the tissues were dehydrated in an alcohol series and embedded in paraffin paraplast mixture. The paraffin block sections (2-3µm) were prepared using a rotary microtome with integrated Super frost/Plus slides and stained with hemotoxylin-eosin (HE). Histopathological sections from grossly affected skin regions revealed a variety of dermatopathological changes. Skin samples of the present case nursed a subacute purulent and ulcerative dermatitis. In addition, sero-cellular crusts and hyperkeratosis were observed. The hair follicles and their appendices of the complete body

were hypoplastic and in some segments areas completely missing. A mild subacute multifocal, partly lymphohistiocytic and acute purulent pneumonia was found. The spleen showed a moderately acute purulent inflammation. The liver showed moderately diffuse glycogen storage. In eyes, mild acute multifocal purulent conjunctivitis was observed.

Virological findings: Tests for BHV1, BVD, bluetongue virus 8, and parainfluenza virus 3 were negative.

Chromosomal findings: We were not able to detect a chromosomal abnormality in the karyotype of present case (2n=60,XX).

Pedigree analysis: The present case was a twin from the second calving of a normal cow. The other calves of this dam showed no congenital abnormalities. The sire of the affected German Holstein calf had been used in artificial insemination. The inbreeding coefficient for the affected calf was 1.074%.

Discussion

Normal hair follicle development in the bovine fetus extends from about day 77 to day 166 of gestation. Most follicles develop hairs by day 220 of gestation and all follicles are mature by birth (Hanna and Ogilvie, 1989). Thus, a reduced number of hair follicles in a fully developed neonate qualifies congenital hypotrichosis. In this study, in a female German Holstein calf with a generalized nearly complete hypotrichosis and atrichosis at some areas, thymus hypoplasia conjunctivitis and joint lesions is presented. Histological sections from grossly affected skin regions revealed a variety of dermatopathological changes. Non-Adnexal changes included subacute purulent and ulcerative dermatitis, sero-cellular crusts and hyperkeratosis and hypoplasia of hair follicles were consistent previous reports.

Takasu et al. (2008) reported calves with hypoplasia of the thymus which were stillborn or thymic hypoplasia may be caused by intrauterine infections during the fetal period (Bauer et al., 2003; Takasu et al., 2008). An intrauterine infection can be excluded for the present case because the tests for BVD virus, BHV1, Bluetongue virus 8 and parainfluenza virus 3 were negative and the twin was not affected as well. Otherwise, in human, DiGeorge syndrome is also known as 22q11.2 deletion syndrome, DiGeorge anomaly, congenital thymic aplasia, and thymic hypoplasia (McDonald-McGinn 2011; Swillen et al., 1999). This syndrome is caused by the deletion of a small piece of human chromosome 22. Clinical symptoms of DiGeorge syndrome are congenital heart disease (40% of individuals), cyanosis, palatal abnormalities (50%), learning difficulties (90%), hypocalcemia (50%) (due to hypoparathyroidism), significant feeding problems (30%), renal anomalies (37%), hearing loss, garyngotracheoesophageal anomalies, growth hormone deficiency, autoimmune disorders, immune disorders due to reduced T cell numbers, seizures (with or without hypocalcemia), skeletal abnormalities, psychiatric disorders. In the present case parallel clinical signs were deficiency of body weight and size, persistent and ulcerative inflammation of the carpal joints. In contrast to previous studies, congenital hypotrichosis or atrichosis associated with thymus hypoplasia was not yet reported. In the liver of the present case, a moderately diffuse glycogen storage was found. Glycogen storage disease (GSD, also glycogenosis and dextrinosis) is the result of defects in the processing of glycogen synthesis or breakdown within muscles, liver, and other cell types. GSD has two classes of cause: genetic and acquired. Genetic GSD is caused by any inborn error of metabolism (genetically defective enzymes) involved in these processes. In livestock, acquired GSD is caused by intoxication with the alkaloid castanospermine (Stegelmeier et al., 1995). In contrast to previous studies, glycogen storage associated with congenital hypotrichosis has not been described before. BVD virus seemed unlikely to play a role in this case as this calf was negative for BVD antigen and cases of congenital hypotrichosis due to BVD virus infections have not been reported. An EDA mutation can be excluded as teeth were normally developed and nasolabial eccrine glands were present (Drögemüller et al., 2002).

In conclusion, the congenital hypotrichosis /atrichosis described herein shows similarities with the nude/severe combined immunodeficiency (SCID) phenotype in humans characterized by congenital alopecia of the scalp, eyebrows, and eyelashes, nail dystrophy, and a severe T cell immunodeficiency, inherited as an autosomal recessive disorder (Romano et al., 2013). Further research has to clarify whether FOXN1 plays a pivotal role for this disease in calves.

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