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Bovine ocular squamous cellular carcinoma: a report of cases from the Caltagirone area, Italy

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ABSTRACT

Twelve cases of ocular squamous cell carcinoma (OSCC) are reported in the bovine red-pied breed (Simmental), kept in a farm in south Sicily. Lesions showed different clinical aspects (cauliflower-shape masses and/or papilloma-like growths), protruding through the palpebral fissure, and placed at the level of the nictitating membrane or the sclera-conjunctival junction, or by a cutaneous swelling with a central crateriform area and ulcerations on the periorbital region, involving also the eyelids. Histopathological examination revealed a dermic neoplastic growth characterized by the proliferation of invasive squamous cells arranged with a pseudo-cord appearance. The possible relationships were analysed between the high prevalence of the condition and the poorly pigmented skin of this breed, the farming system employed and the exposure of the animals to ultraviolet radiation. Finally, issues related to animal welfare are also considered.

Key words: bovine, eye, carcinoma, animal welfare

Introduction

Ocular squamous cellular carcinoma (OSCC) is one of the most common and important neoplasms of the eye. It occurs frequently in cattle and horses (HYMAN et al., 2002).

Hereditary factors, environmental factors (e.g., latitude, altitude, exposure to sunlight), lack of eyelid pigmentation, age and dietary habits have all been recognized to play a role in the aetiopathogenesis of bovine ocular squamous cellular carcinoma

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(BOSCC) (ANDERSON, 1991; ANDERSON and BADZIOCH, 1991; HEENEY and VALLI, 1985).

In addition, in cattle the aetiology has been linked to a number of viral agents, especially bovine papillomavirus (BPV) (FORD et al., 1982; RUTTEN et al., 1992) and bovine herpes virus type 1 (BHV-1) (TAYLOR and HANKS, 1969) and 5 (BHV-5) (ANSON et al., 1982). Nevertheless, ultraviolet light, viruses and circumocular apigmentation are the major epidemiologic risk factors for the development of the tumour (ANDERSON and BADZIOCH, 1991; KOPECKY et al., 1979)

BOSCC is a disease of high morbidity that results in economic loss through early culling and carcass condemnation at slaughter (RUSSELL et al., 1956).

This paper reports on a preliminary study of ocular neoplasia on a cattle farm in southern Sicily (Caltagirone, Italy) aimed at identifying the factors responsible for it.

Materials and methods

Animals and clinical history. Twelve animals, Simmental Red Pied females aged between 4-12 years, were evaluated, at the farmer's request, because of the occurrence of various lesions involving the ocular globes and eyelids.

The dairy farm was located around the town of Caltagirone (Southern Italy), at approximately 608 metres above sea level. The farm was established in 1998 with 38 animals imported from France. The herd was composed of 110 Red Pied Simmental (75 adults, 15 heifers, 20 calves) registered in the herd book.

The environmental conditions in the areas where the dairy farms are located are warm and dry in summer and autumn, and relatively cold in winter. Fluctuations of temperature of this area are in the range of 0-40 degrees Centigrade. The mean daily sunlight period over the year is 8 to 10 hours.

The animals were kept in a large paddock with a central covering, open on three sides, from which the animals have access to feeding and watering.

There are no specific areas prepared and blankets for rest, and the animals spend the whole day outside, the only covered area being the front where food is administered, which is also the rest area. During the day animals that cannot find space in that area are in the open area of the paddock. In the months of February, March and April the animals are led out to pasture for most of the day. In the remaining months of the year they are constantly maintained in loose housing and fed once a day.

The farmer reported that occasionally, over the last ten years, a dozen of the animals have had the lesions often involving their eyes which evolved slowly over several months leading to serious impairment of vision with frequent generalized complications

No diagnosis had been made regarding these animals, and the treatment (antibiotic eye ointment and/or antibiotic treatment systems had no therapeutic effect.

Sampling. Punch or incisional biopsies of the affected tissues were performed. Samples were fixed in 10% formalin, embedded in paraffin, and 5µ sections were stained for routine histopathological diagnosis with haematoxylin and eosin. All OSCC were classified with regard to macroscopic and microscopic features (Table 1). Differentiation was evaluated according to the presence and intensity of keratinization, squamous differentiation of neoplastic cells, and island formation. The maximal score (3) was attributed to well differentiated neoplasms containing numerous large keratin pearls and large island formation and deep invasion of tissues. The intermediate score (2) referred to poorly differentiated neoplasms with a moderate degree of keratinization and differentiation, exhibiting small keratin pearls and small islands. The minimal score (1) referred to neoplasms with only individual cell keratinization, few small-sized islands, and poor cellular differentiation and with minimum signs of invasion (CARVALHO et al., 2005).

The mitotic index was evaluated as the number of mitotic figures per high-power field, ranging from 0 to 2 (1), 3 to 6 (2), and >6 (3).

Results

Ophthalmological findings. Ophthalmic examination was performed in a dark stable, following prolonged dark adaptation the previous night. The adnexa, anterior, and posterior ocular segments of both eyes were examined with a transilluminator (Heine, Germany), a portable handheld biomicroscope (Portable Slit Lamp SL-14, Kowa - Japan), and a direct ophthalmoscope (Heine BETA 200®, Germany). Intraocular pressure was measured when feasible (TonoPen® XL - Reichert Technologies, USA).

The subjects showed oedematous, thickened raised lesions of different shapes, with irregular surfaces, firm in consistency, distributed over the palpebral conjunctiva, nictitating membrane, and eyelid skin (Table 1).

Ten animals showed lesions over the bulbar conjunctiva, cornea and limbus, two over the palpebral conjunctiva, nictitating membrane and eyelid skin (Table 1).

Seven animals showed plaque lesions deforming the eyelid profile. The skin of the periocular region was soiled by a more or less dense serum-haemorrhagic exudate from the eye, especially when the subject tried to alleviate the discomfort by rubbing the orbital regions on fixed elements (trees, fences, etc.).

Three animals presented sessile or pedunculated papillomatous-like formations (Fig. 1), whereas another two subjects showed a large new-formed growth, exhibiting an invasive tendency.

Histopathological findings. All tumours sampled were diagnosed as OSCC. Their distribution in the above described categories was as follows: three well differentiated, four moderately differentiated, and four poorly differentiated (Table 1, Figs 2-3).

Table 1. Clinical features and histopathological grading

Case No.	Age	Tumour localization	Affected eyes		Surface appearance	Histopathological grading
			right	left		
1	6 y	bulbar conjunctiva, cornea and limbus	X		nodular and hyperemic	2
2	12 y	bulbar conjunctiva, cornea and limbus and eyelid	X		nodular and hyperemic	2
3	11 y	palpebral conjunctiva, nictitating membrane and eyelid skin	X		cauliflowerlike and congested	3
4	12 y	bulbar conjunctiva, cornea and limbus		X	nodular and hemorrhagic (with purulent discharge)	1
5	6 y	bulbar conjunctiva, cornea and limbus		X	nodular and hemorrhagic (with purulent discharge)	2
6	4 y	bulbar conjunctiva, cornea and limbus	X		nodular and hemorrhagic (with purulent discharge)	2
7	4 y	palpebral conjunctiva, nictitating membrane and eyelid skin		X	cauliflowerlike and congested	3
8	8 y	bulbar conjunctiva, cornea and limbus	X		nodular and hyperemic	1
9	12 y	bulbar conjunctiva, cornea and limbus	X		nodular and hyperemic	1
10	8 y	bulbar conjunctiva, cornea and limbus	X		nodular and hyperemic	1
11	7 y	bulbar conjunctiva, cornea and limbus		X	nodular and hemorrhagic (with purulent discharge)	3
12	11 y	bulbar conjunctiva, cornea and limbus	X		Cauliflowerlike and congested	1

Four tumours were classified as grade I SCC (poorly differentiated carcinoma): individually keratinized cells were evident, minimal signs of invasion of the surrounding

tissue were present, and the mitotic index was between 0 to 2 mitotic figures per higher power field.

Fig. 1. Macroscopic appearance of involved periocular tissues

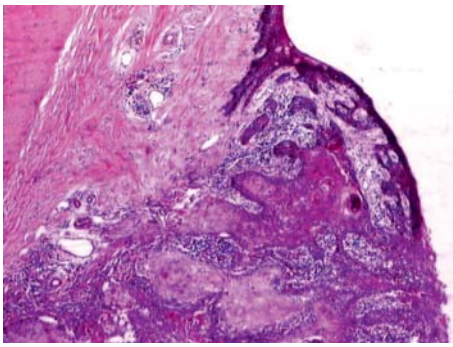

Fig. 2. Histopathological features of the dermic neoplastic growth. H&E, ×2.5.

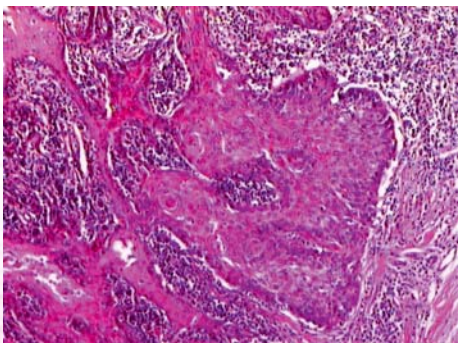

Fig. 3. Pseudo-cordonal growth pattern of invasive squamous cells. H&E, ×10.

Four samples were considered as grade II SCC (moderately differentiated): small keratin pearl formations and small islands were present, the mitotic index was between 3 to 6 mitotic figures per higher power field. Three samples were categorized as grade III SCC (well-differentiated) containing extensive large keratin pearls and large island

formations, with squamous differentiation and a mitotic index of >6 mitotic figures per higher power field.

Discussion

Ocular squamous cell carcinoma (OSCC) or "cancer eye" is the most common malignant neoplasm of epithelial origin affecting cattle and is responsible for significant economic losses. In the United States, the prevalence of OSCC varies geographically and is higher in the south-western region and in lower latitudes with higher levels of sunlight (TSUJITA and PLUMMER, 2010). Different factors are believed to contribute to the development of OSCC, and treatment options that have been proposed. ANDERSON and SKINNER (1961) showed that the incidence of OSCC increased significantly with increasing altitude and mean hours of sunlight, and with decreases in latitude. Other studies have confirmed these observations of an increased risk of OSCC with an increased level of solar radiation (ANDERSON and BADZIOCH, 1991). In our study the possible relationships were analysed between the high prevalence of the condition and the poorly pigmented skin of this breed, the extensive farming system employed and the exposure of the animals to ultraviolet radiation. Ultraviolet radiation (UVR) has numerous effects on the skin, including photoaging (SEITÉ et al, 2010), immune suppression, DNA damage and tanning. Its role as a carcinogen in the development of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and cutaneous malignant melanoma (CMM) (KRICKER et al., 1994 a; KRICKER et al., 1994b; ENGLISH et al., 1998) has been reviewed in human medicine (GILCHREST et al., 1999; GALLAGHER and LEE, 2006; GARLAND et al., 2003; MOAN et al., 1999; MOAN et al., 2008; TRAN et al., 2008). As with other carcinogens, UV radiation causes mutation in oncogenes and tumour-suppressor genes, and specific *p53* mutations have been detected in UV light-induced cutaneous squamous cell carcinoma (COULTER et al.,1995; GAMBLIN et al., 1997; GOLDSMITH et al., 1998). This gene functions in the control of the cell cycle, DNA repair, and apoptotic pathway (ROSENAU et al., 2002) giving rise to a nuclear phosphoprotein that serves as a negative regulator of cell proliferation (COULTER et al.,1995; GAMBLIN et al., 1997; ORAM et al., 1994). As in human squamous cell carcinoma, p53 overexpression is frequent in bovine OSCC, providing support for the possible role of the protein in the pathogenesis of this neoplasia (CARVALHO et al., 2005). Numerous phenotypic features are well-known risk factors for skin cancer, including several related to pigmentation. Studies involving the precise signaling network from DNA damage to tanning have been presented (NARAYANAN et al., 2010), as many of the aforementioned pigmentation loci are present in a tightly regulated signaling cascade, which appears to govern response to UVR and dictates skin cancer susceptibility. There is considerable evidence suggestive of the genetic basis of OSCC, as indicated by variable morbidity rates among various breeds of cattle, lines of sires, and increased rates in the progeny of those affected compared with that of unaffected parents. Lesion

development is not heritable, but indirectly, the genetic effect on periocular pigmentation to a large extent determines the degree to which the eye is susceptible to a carcinogenic agent. OSCC should be important both in terms of animal welfare and as a cause of lost production. In fact, cattle afflicted with ocular neoplasia represent a management challenge from both an economic and animal care/welfare perspective. Failure to deal with cows with ocular neoplasia in a timely manner can result in economic loss to the owner, unnecessary suffering for the animal, and negative public perceptions. This type of poor management is inconsistent with sound quality assurance. Clearly, it is in the cattlemen's best interest from an economic, humane, and public perception standpoint to treat or market cattle with ocular neoplasia as soon as practical. An animal suffering from ocular neoplasia is less able to graze and compete for feed. The consequences of OSCC include: *i)* decline in body condition; *ii)* lower calf birth weight; *iii)* reduced growth rate in calf; *iv)* reduced milk production; *v)* lower fertility in bulls; and, subsequently, *vi*) a lack of animal welfare. It should be necessary to encourage all those who care for farm bovines to adopt the highest standards of husbandry, according to Directive 98/58/EC (EC, 1998) that includes general previsions on the care and treatment of animals. Without good stockman-ship, animal welfare can never be adequately protected.

Finally, we believe that the farm examined, where we found the lesion described, should be more careful in the future, investigating other aspects such as epidemiology, genetics and various hereditary mechanisms of disease. Studies in experimental animals have shown that elevated temperatures may contribute to skin carcinogenesis by generating DNA damage via the same indirect oxidative stress pathway (CERUTTI et al., 1990). So, new approaches to the prevention of skin damage are important, especially for specific groups of photosensitive animals and patients on immunosuppressive therapy.

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SAŽETAK

Prikazano je 12 slučajeva skvamocelularnog karcinoma u goveda simentalske pasmine držanih na jednoj farmi na jugu Sicilije. Oštećenja su se klinički očitovala u obliku cvjetače i/ili rasta nalik na papilom, izbočujući se kroz naprslinu na vjeđi sa smještajem u području treće vjeđe ili na spoju bjeloočnice i spojnice, ili oteklinom kože sa središnjim uvrnućem i ulceracijama u periorbitalnom području zahvaćajući i vjeđe. Patohistološkom pretragom ustanovljena je kožna novotvorina koja se očitovala proliferacijom invazivnih skvamoznih užolikih stanica. Analizirani su mogući odnosi između visoke prevalencije karcinoma te slabe pigmentiranosti kože simentalske pasmine, načina držanja i izloženosti goveda ultraljubičastom zračenju. Razmatrani su i neki čimbenici dobrobiti životinja.

Ključne riječi: govedo, oko, karcinom, dobrobit životinja