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CASE REPORT

Food/farmed animals

First case of pithomycotoxicosis in sheep in the Netherlands

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Abstract

Pithomycotoxicosis, commonly known as facial eczema, is a hepatogenous photosensitisation in grazing ruminants caused by intake of sporidesmin-containing spores of the saprophytic fungus *Pithomyces chartarum*. Although this is a significant sheep disease in various countries in the world, it is rarely seen in Europe, and has been reported only once in the Netherlands, but in cattle. In October 2019, both sheep and lambs in a flock of 50 breeding sheep showed clinical signs of photosensitisation, including oedematous facial swelling, reddening of eyelids, ulcerative skin lesions, hyperpigmentation, and in some cases icteric sclerae. The combination of clinical signs, seriously elevated glutamate dehydrogenase, gamma-glutamyl transferase and total bilirubin, necropsy findings, course of events, time of the year, absence of known toxic plants or mycotoxins, strongly suggest that sporidesmin was the most probable cause of this case of hepatogenous photosensitisation, which makes this the first reported case of pithomycotoxicosis in sheep in the Netherlands.

KEYWORDS

hepatic disease, histopathology, mycotoxins, fungal toxins, sheep, toxicology

BACKGROUND

Pithomycotoxicosis, commonly known as facial eczema, is a hepatogenous photosensitisation of ruminants grazing pasture, caused by intake of sporidesmin-containing spores of the saprophytic fungus *Pithomyces chartarum*.[1,2] This fungus grows rapidly on dead litter at the base of pasture, and spores freely in specific weather conditions of high humidity and ambient temperatures above 12°C, in late summer and autumn. Under these conditions, it produces sporidesmin, a hepatotoxic mycotoxin, which in sufficient concentrations is able to cause hepatobiliary and other tissue damage, but its mechanism of action is not precisely known.[3] The pathogenesis of hepatogenous photosensitisation is based on increased circulating plasma concentrations of the photosensitising agent phytoporphyrin, a normal breakdown product of chlorophyll, following impaired hepatobiliary excretion because of hepatic dysfunction or bile duct lesions. Once accumulated in the capillary blood vessels of sun-exposed skin, sufficient plasma levels of phytoporphyrin can cause a phototoxic reaction with daylight, releasing free radicals and causing lesions of unpigmented skin. These lesions do not appear until at least a week after sporidesmin has been ingested.[1]

Facial eczema has been known for over 100 years in New Zealand, where it causes severe problems in sheep, cattle, goats and deer,[1,2] but has also been observed in various other countries in the world. In Europe, however, only very few cases of pithomycotoxicosis have been described in Portugal, Spain, France, Hungary and Italy.[4–7] In 2006, the first cases were reported in the Netherlands in cattle.[8] Until the case reported in this paper, no previous cases in sheep in the Netherlands have been documented despite the fact that this animal species tends to be more sensitive to sporidesmin than cattle.[9] Because the weather conditions necessary for the occurrence of facial eczema may become more common in Western Europe due to climate change, we thought it worthy to publish this first case in sheep in the Netherlands.

CASE PRESENTATION

In a flock of 50 mainly Dutch spotted breeding sheep, kept on a mixed sheep and dairy cattle farm, some sheep and lambs, grazing pasture, developed oedematous facial swelling from the 10th of October 2019 onwards, and their number subsequently increased rapidly. The most obvious clinical signs were oedematous swelling and reddening of eyelids, leading to forced closure of the eyes and heavily droopy ears. The veterinary practitioner visited this farm the same date and advised to house animals with clinical signs and feed them ad libitum hay and some commercially available concentrates. She ruled out hypoalbuminaemia caused by gastrointestinal nematode and liver fluke infections by performing faecal egg counts. After she had revisited the farm on 28 October and had ruled out cobalt or vitamin B12 deficiency, based on clinical signs and results of blood tests (Table 1), she consulted Royal GD (GD) Veekijker, a telephone helpdesk as part of the national animal health monitoring system. A farm visit by one of the GD veterinarians specialised in small ruminant health management took place on 15 November. Until then, around

30 animals, both sheep and lambs, had presented clinical signs in varying degrees of severity. Most of the affected animals were recovering. Six animals had died after presenting clinical signs. In total, 10 severely affected animals had been housed for a longer period and were still kept indoors. After being removed from pasture, most of them had improved quickly and no longer showed oedematous swellings and acute skin lesions. However, according to the farmer, their body condition had deteriorated over the previous weeks, resulting in a very poor condition in some of these sheep.

Clinical inspection of the sclera revealed a discoloration, varying from off-white to yellow, in a few of these sheep. Some also showed severe corneal oedema and opacity. The facial swelling had developed into skin lesions characterised by exudation, crusts, ulcerative lesions, necrotic tissue, hyperkeratinisation and hyperpigmentation, mostly affecting the periorbital region, ears and bridge of the nose. Some sheep apparently experienced irritation, scratching their head along the fencing. Nonpigmented and hairless or sparsely haired regions of the skin seemed remarkably more affected than the pigmented or more covered regions. Oral inspection revealed no lesions of lips, buccal mucosa and tongue. No increase in body temperature was measured.

Pastures on which the sheep had grazed when they developed clinical signs were scanned for known toxic plants during the farm visit of 15 November, more than a month after the start of the problems, and grass samples were collected to be checked for presence of spores of *P. chartarum*. By this time, regrowth of lush grass had occurred and no dead litter was found in the pasture. No toxic plants were detected. We advised to euthanise one severely affected sheep for postmortem examination.

LEARNING POINTS/TAKE HOME MESSAGES

- Weather conditions favourable for the occurrence of facial eczema may become more common in Western Europe due to climate change. Pithomycotoxicosis should be considered as a differential diagnosis for cases of photosensitisation occurring in autumn.
- Early detection of photosensitisation makes it possible to collect the right samples in time, not only to make a diagnosis but also to learn more about facial eczema in the Netherlands and surrounding countries.
- Additional investigations are the key to differentiate between different types of photosensitisation and help determine the aetiology.
- Collaboration with different veterinary disciplines is essential to quickly gain a better understanding of a hitherto locally unknown disease.

INVESTIGATIONS

Faecal egg counts of samples collected during the farm visit of 10 October were below 500, and no *Fasciola hepatica* eggs were found. During her second farm visit on 28 October, the veterinary practitioner collected jugular blood samples from five housed severely affected sheep, and submitted these to the laboratory of GD to be tested for the following liver function indicators: aspartate aminotransferase (AST), glutamate dehydrogenase (GLDH), gamma-glutamyl transferase (γGT), total bilirubin and albumin. Blood test results are shown in Table 1. The blood sample from sheep 1166 was seronegative for fasciolosis but became haemolytic, and was excluded from further testing. Three of the remaining sheep also tested seronegative for fasciolosis, and one was seropositive. Vitamin B12 concentrations indicated absence of cobalt or vitamin B12 deficiency, although an increase in serum vitamin B12 has been described due to sporidesmin-induced liver damage. Except for a normal AST and bilirubin in one animal, all other liver enzymes and bilirubin were elevated. Albumin levels were normal or close to normal.

Grass samples collected on 15 November were checked for presence of spores of *P. chartarum* using the wash method

TABLE 1 Results of blood tests (references) of jugular blood samples from five severely affected sheep collected during the farm visit of the veterinary practitioner on 28 October (1) and 27 December (2)

		Test											
Animal ID	Date of birth	*F. hepatica* ELISA[a]	Vitamin B12 (pmol/L)[b]	AST (IU/L)[c]		GLDH (IU/L)[d]		γGT (IU/L)[e]		Total bilirubin (μmol/L)[f]		Albumin (g/L)[g]	
				1	2	1	2	1	2	1	2	1	2
1166	27 February 2016	Negative	–	[h]	142	[h]	620.7	[h]	697	[h]	3	[h]	28.4
7973	10 March 2014	Negative	>656	76	57	112.0	53.2	709	146	4	2	22.9	19.8
1281	2 February 2017	Negative	–	179	101	328.8	327.0	833	593	11	4	36.6	34.6
1186	2 March 2016	Positive	>656	581	104	1145.6	611.4	932	556	18	3	24.4	28.2
1207	10 March 2016	Negative	–	193	103	232.2	590.0	1193	1039	17	3	36.3	30.1

Abbreviations: AST, aspartate aminotransferase; GLDH, glutamate dehydrogenase; γGT, gamma-glutamyl transferase.
[a] *Fasciola hepatica* f2 antigen ELISA (IDEXX Laboratories Pty Ltd, New Zealand).
[b] Vitamin B12 was tested using a chemiluminescence method; reference value >400 pmol/L.
[c] AST was determined using an enzymatic IFCC method at 37°C; reference value 83–137 IU/L.
[d] GLDH was determined using an enzymatic DGKC method at 37°C; reference value 0.0–22.0 IU/L.
[e] γGT was determined using an enzymatic IFCC method at 37°C; reference value 24–50 IU/L.
[f] Total bilirubin was determined using a colorimetric DMSO method; reference value 0–6 μmol/L.
[g] Albumin was determined using a colorimetric BCG method; reference value 25.0–28.0 g/L.
[h] No results are shown for liver function tests of sample 1166, as the sample was too haemolytic to be tested.

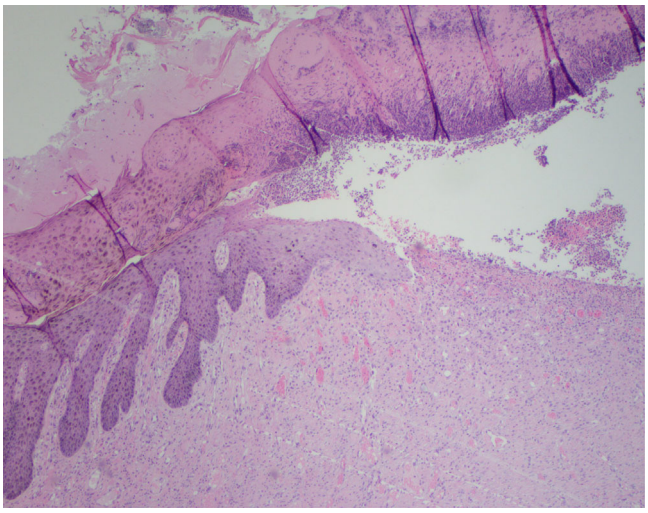

FIGURE 1 Skin of the ear; HE stain; 40× magnification. Ulceration flanked by regenerated hyperplastic epidermis that is covered with remnants of coagulative necrotic epidermis

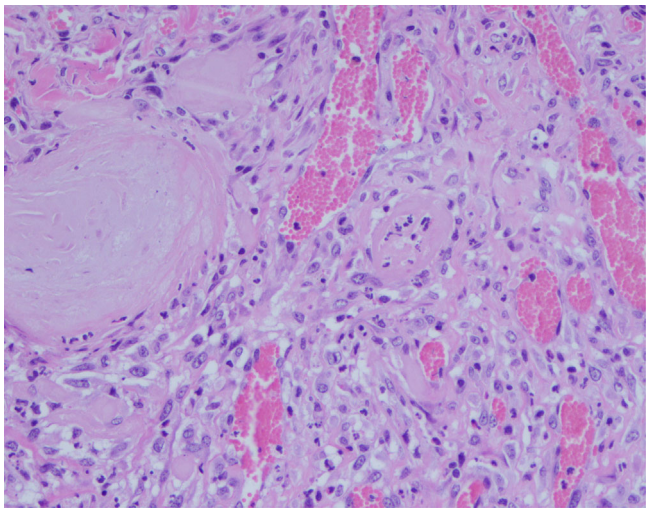

FIGURE 2 Skin, dermal blood vessels; HE stain; 200× magnification. Multiple dermal blood vessels show fibrinoid necrosis of the blood vessel wall and are surrounded by proteinaceous oedema and a mixed inflammatory infiltrate

as described by Thornton and Sinclair (1960),[10] with negative results.

On 19 November, one severely affected sheep with representative symptoms and lesions was euthanased and submitted to GD for necropsy. Routine gross postmortem examination of the euthanased sheep revealed a carcase in moderate body condition with signs of jaundice, bilateral conjunctivitis, a bilateral ulcerative dermatitis on the dorsal side of the pinna and on the top of the head. The liver was pale with an enhanced zonal pattern. The kidneys were autolytic and of normal colour and there were no signs of haemoglobinuric nephrosis.

Representative samples of liver, skin and eye were collected for histopathology, fixed in 10% neutral-buffered formalin, routinely processed, paraffin embedded and stained with haematoxylin and eosin. The skin lesions on the ears and the head were characterised by thick serocellular crusting and multifocal ulceration, bordered by hyperplastic regenerating epidermis that was covered with some desquamated remnants of coagulative necrotic epidermis. Remnants of necrotic hair follicles were scattered throughout the skin. The dermis showed variable oedema, fibrovascular proliferation, mild lymphohistiocytic and neutrophilic perivascular inflammation (Figure 1). Some of the dermal blood vessels were affected by segmental fibrinoid necrosis of the vascular wall with occasional thrombosis (Figure 2). The combination of blood vessel damage, oedema and coagulative necrosis of epidermis and hair follicles is consistent with photosensitisation dermatitis.

Lesions were also observed in the cornea where hyperplasia of the corneal epithelium with mild intracorneal proliferation of capillary blood vessels and mild perivascular to interstitial infiltration of neutrophils were observed.

Histopathologic examination of the liver revealed centrilobular hepatocellular degeneration with hepatocellular dissociation (Figure 3). Centrilobular hepatocytes and sinusoidal macrophages contained intracytoplasmic yellow to orange pigment. Randomly scattered within the parenchyma, small neutrophilic and granulomatous inflammatory foci and a few bile lakes occurred. The portal tracts showed variable fibrosis with moderate lymphoplasmacytic and histiocytic inflammation, multifocal degeneration and necrosis

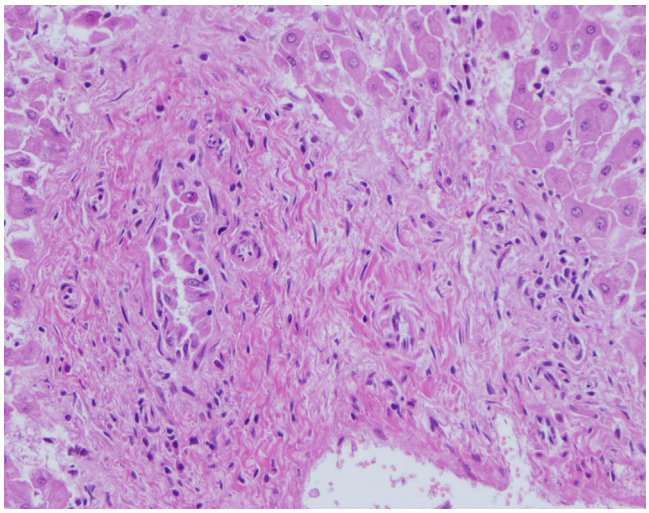

FIGURE 3 Liver, portal area; HE stain; 200× magnification. The portal triad is expanded by fibrosis with mild lymphohistiocytic inflammation. There is epithelial damage in the bile duct, characterised by variable attenuation, karyopyknosis and karyolysis

of bile duct epithelium and mild ductular proliferation. An additional rhodanin stain for copper-binding proteins was negative.

DIFFERENTIAL DIAGNOSIS

Based on the above-mentioned information, sheep and lambs in this case suffered from photosensitisation, which can be classified into three main categories based on aetiology; namely, primary (type I), endogenous (type II) and hepatogenous or secondary (type III).[11] In this case, clinical signs, seriously elevated GLDH and γGT levels, increased total bilirubin levels and necropsy findings strongly indicate hepatogenous photosensitisation.

Many aetiological agents have been reported to cause hepatogenous photosensitisation in sheep, and although some of these agents can be excluded mainly based on histopatho-

logical findings, others are more complex to distinguish. In addition, synergistic or additive effects caused by different aetiologies have been reported.

The presented clinical signs, histopathological findings, results of additional investigations and conditions in this particular case are most consistent with hepatogenous photosensitisation induced by sporidesmin, which is therefore the most plausible aetiology.[7–13] Nevertheless, other causes that potentially could lead to the observed clinical signs have been discussed and excluded. Cobalt or vitamin B12 deficiency is an important cause of photosensitisation in the Netherlands.[14–17] Adult sheep, however, practically never show clinical signs as a consequence of this deficiency, and combined with necropsy findings and normal vitamin B12 serum levels, this deficiency was excluded. Of the extensive list of plant species that are associated with hepatogenous photosensitisation, only a small selection naturally occurs in the country. *Narthecium ossifragum* is known to flourish in certain geographical regions of the Netherlands, however, is uncommon in this particular area. As for other plant species, like *Brassica napus*, *Trifolium pratense*, *Medicago sativa* and *Ranunculus* spp., it seemed unlikely that sheep got access to the required toxic quantity, as they were kept on restricted grass sown pastures. Also, pasture inspection revealed no further indications. In addition, many plant-induced hepatogenous photosensitivity disorders are associated with the ingestion of steroidal saponins; however, no accumulation of saponin crystals in the bile duct and bile duct epithelium was noticed.[2] *Hypericum perforatum* can cause primary photosensitisation, but this plant was not found on this farm.

Although intoxication due to cyanobacteriae cannot be excluded based on histopathological examination of the liver, it is thought to be unlikely given the moment of occurrence, as well as the absence of invaded water sources.

In cases where sheep farmers ask for advice because some animals show swelling of the head, it is necessary to distinguish between the location and type of the swelling, which means distinguishing between hypoalbuminaemia, locally increased blood pressure, blood vessel lesions and photosensitisation. In this case, hypoalbuminaemia as a consequence of severe gastrointestinal nematode or *Fasciola hepatica* infection was excluded. In rare cases, orf virus infections can result in severe lesions of the oral cavity, oesophagus and rumen, and an accompanying swelling of the retropharyngeal lymph nodes may result in locally increased blood pressure and facial oedema.[18] Clinical inspection did not reveal any of these clinical signs, and orf was excluded. Pathological lesions of bluetongue virus (BTV) infection are associated with primary vascular damage, leading to oedema and haemorrhage.[19] Except for facial swelling, no other clinical signs characteristic for BTV infection were present, and, combined with the BTV-free status of the country, bluetongue was excluded. Copper intoxication is reported as a cause of photosensitivity only sporadically, but absence of haemoglobinuric nephrosis, results of pathological examination and a negative rhodanin stain for copper-binding proteins ruled out this cause.

TREATMENT

Sheep and lambs on this farm had not received any treatment during the weeks preceding the first cases of photosensitisation, and no changes in pasture management had been implemented over the past few years. Between the occurrence of the first clinical cases and the farm visit on 15 November, sheep had been moved to another pasture, after which no subsequent cases followed. Clinically affected animals had been continuously housed aiming at avoiding exposure to sunlight. Treatment other than supportive care was not carried out. This intervention proved successful, as most of the affected animals had recuperated quickly afterwards, although the body condition of some sheep had decreased significantly, according to the farmer.

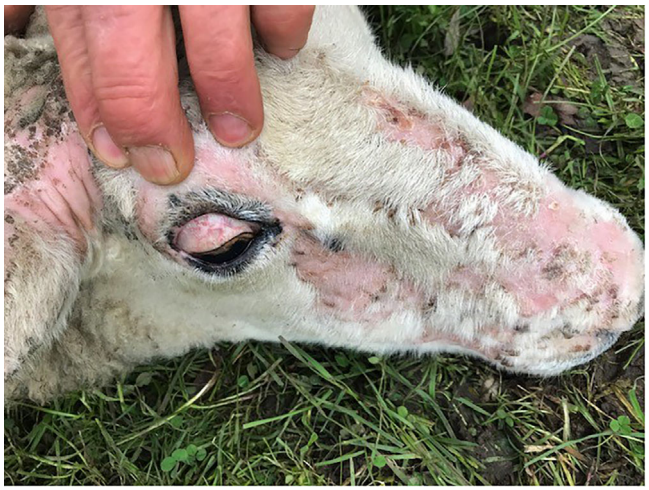

FIGURE 4 One of the recovering sheep with an almost healed facial skin

OUTCOME AND FOLLOW-UP

Clinically affected sheep remained housed until skin lesions had fully recovered; an example of which can be seen in Figure 4. However, to be able to monitor hepatic recovery, a second series of blood serum samples was collected on 27 December, and tested for liver function, 8 weeks after the initial samples were taken (Table 1). With the exception of two, all sheep were back on pasture when samples were taken. Compared to previous results, AST, total bilirubin and albumin were within or almost within reference values, but GLDH and γGT were still clearly elevated, as has been described in sheep with facial eczema.[12]

Although the first signs of photosensitisation had been noticed just after the start of the breeding season, it seemingly did not have major influence on pregnancy outcome, as birth rates were as expected. All of the examined sheep delivered one or multiple lambs in January or early February; however, one of them died a few months later in May. A larger yearling group had their lambs in May, again with expected lambing rates. Six sheep were sent for slaughter in July, selected on disappointing reproduction, mastitis and poor body condition; however, this number was comparable to previous years. Over the months, despite heightened awareness, no abnormalities were reported. Financial implications in this case were not part of this study but consisted of the value of at least six animals that had died in the acute phase of the disease, extra labour for the farmer, increased costs for feeding and hous-

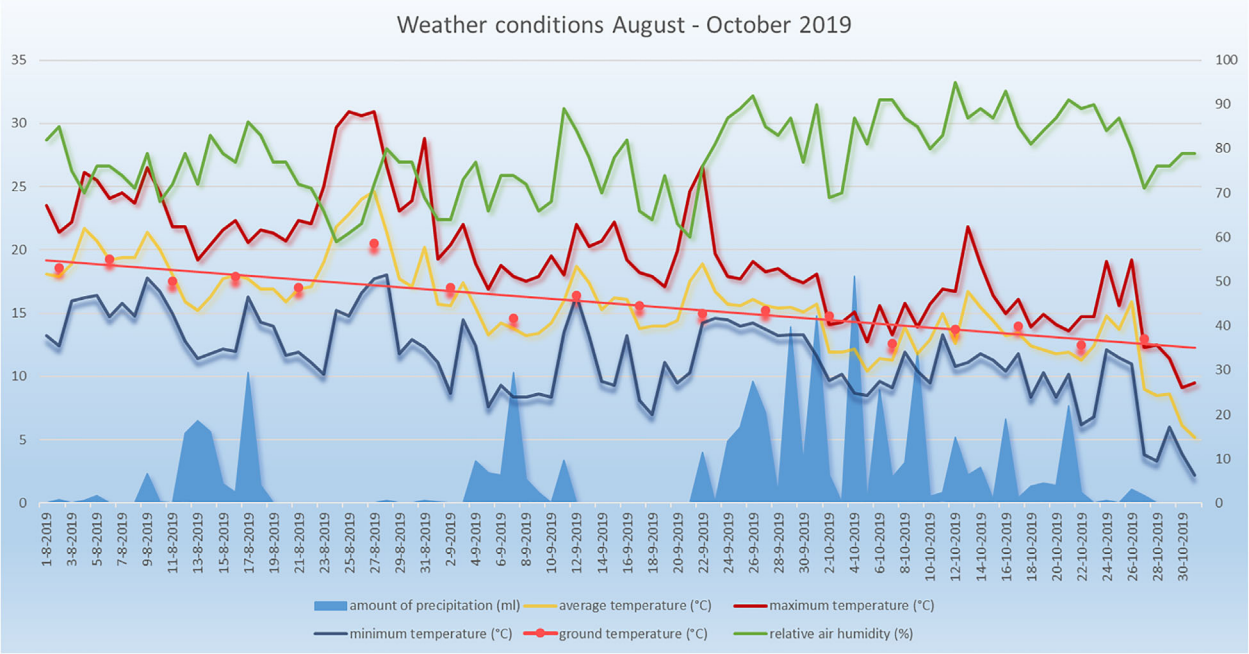

FIGURE 5 Weather conditions recorded by the Royal Netherlands Meteorological Institute from 1 August to 31 October 2019

ing and costs for veterinary care, laboratory investigations and postmortem examination.

DISCUSSION

Pithomycotoxicosis is a hepatogenous photosensitisation of grazing ruminants caused by intake of sporidesmin-containing spores of the saprophytic fungus *P. chartarum*, which grows rapidly on dead litter under specific weather conditions in late summer and autumn.[1,2] Clinical signs, seriously elevated GLDH, γGT and bilirubin levels, and necropsy findings indicated hepatogenous photosensitisation in this case. Pasture inspection took place during the farm visit on 15 November, more than a month after the start of the clinical signs. Regrowth of lush grass had occurred, no dead litter and none of the plants that are known to cause hepatogenous photosensitisation in the Netherlands were noticed. As Figure 5 shows,[20–22] weather conditions in late summer of 2019 have been appropriate for growth of *P. chartarum* with high temperatures and drought at the end of August, alternating with significant rainfall in short periods of time and high humidity above 90% in late September and early October. The recorded ground temperatures remained above 12°C until the end of October. The fact that minimum ambient temperatures dropped significantly at the end of October, combined with regrowth of lush grass, might explain that mid-November dead litter no longer was available, and no spores were detected in collected grass samples. In New Zealand, cases of pithomycotoxicosis occur from February to the beginning of May, comparable to the period from August to the beginning of November in the Netherlands, in which period hepatogenous photosensitisation in this case occurred.

Based on the above-mentioned information, sporidesmin was thought to be a possible cause. This hepatotoxic mycotoxin is produced by certain strains of the fungus *P. chartarum*, and in sufficient concentrations, it is able to cause tissue necrosis, particularly in bile ducts and blood vessel walls, and also in the adjacent hepatic parenchyma and portal tracts. Photosensitisation dermatitis becomes apparent from Day 10 onwards after ingestion of sporidesmin. By Day 14 after sporidesmin exposure, there is distension and plugging of bile canaliculi, with bile-stained areas of hepatocellular necrosis. After Day 14, marked ductular proliferation with progressive portal tract fibrosis and obliteration of bile ducts by scar tissue is present.[9] Comparable lesions were seen in the sheep submitted for postmortem examination.

The combination of skin lesions around the eyes, and oedema and opacity of the cornea, has not been observed in lambs with vitamin B12 deficiency-related photosensitisation.[14,17] This raises the question whether these lesions can be caused by blood phytoporphyrin accumulation alone, or whether there might be a contributory effect of the circulating mycotoxin sporidesmin. Experimental intoxications of sheep with sporidesmin have demonstrated not only lesions in the hepatobiliary system and skin, but also in the kidneys, particularly the collecting ductules and urinary bladder.[9] The lesions in the kidneys and urinary bladder are attributed to the direct cytotoxic effect of sporidesmin, as mild renal lesions have been observed before the onset of biliary obstruction, and sporidesmin excretion was demonstrated in the urine. Cytotoxic activity has been demonstrated to be greatest in bile, followed by urine and was lower in serum.[3] This might be explained by excretion and concentration of sporidesmin in bile and urine. To what extent sporidesmin leads to corneal oedema remains uncertain; however, hypothetically accumulation of sporidesmin in the aqueous fluid might cause intraocular tissue damage. As sporidesmin is a direct necrotising toxin, accumulation of sporidesmin in skin and cornea or aqueous fluid could contribute to the lesions and partly explain skin lesions around the eyes, and oedema and opacity of the cornea, as seen in the sheep and lambs in this case.

We advised the farmer and veterinary practitioner to keep the more severely affected sheep indoors until their skin lesions had largely healed and other clinical signs had disappeared. It is not sure whether this was necessary, but we know from experience that in individual cases of hepatogenous photosensitisation, clinical signs can recur if animals go outside too quickly.

The presented case shows a potentially high impact of this disease on both economics and animal welfare. Although most animals appeared clinically well recovered within a short period of time, repeated blood test results demonstrated that at the end of December 2019, serum enzyme activities had not returned to normal and liver damage still existed, and this also is a typical feature of pithomycotoxicosis.[12]

Unanswered questions remain. Why has facial eczema been found earlier in cattle in the Netherlands and not in sheep, while sheep are more sensitive than cattle, or have we missed it in sheep? Does climate change play a role and are we going to see more cases in the near future? We have communicated our findings to sheep farmers and veterinary practitioners and asked them to report comparable cases.

Although a few unanswered questions remain, the combination of clinical signs, seriously elevated GLDH and γGT levels, increased total bilirubin levels, necropsy findings, course of events, time of the year, absence of known plants or mycotoxins strongly suggest that sporidesmin was the most probable cause of this case of hepatogenous photosensitisation, which makes this the first reported case of pithomycotoxicosis in sheep in the Netherlands.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

This field study was conducted in compliance with legislation on animal use and practising veterinary medicine in the Netherlands, and used common sampling methods for routine diagnostic purposes. All animals in this study were examined with the consent of their owner. According to Dutch legislation, such studies do not require official or institutional ethical approval as 'non-experimental clinical veterinary practices' are specifically excluded, but they need to be performed according to the Dutch Veterinary Practice Act.

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