Clinical course of sarcoids in 61 Franches-Montagnes horses over a 5–7 year period

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ABSTRACT

Background: The progression of equine sarcoids (ES) is notoriously unpredictable. Making a choice for the appropriate treatment is challenging when dealing with milder manifestations of ES.

Objective: The aim of this study was to investigate the clinical course of ES in young horses.

Animals and methods: A cohort of 61 ES-affected three-year-old Franches-Montagnes horses and a breed-, age- and geographically matched control group of 75 ES-free peers were examined twice over a period of 5–7 years. Owners and caretakers were queried, using a standardized questionnaire.

Results: More than half of the 38/61 (62%) horses that were ES-affected at the age of three, had become ES-free at the time of follow-up. In 29 of 38 horses, representing 48% of the entire study population, ES lesions had spontaneously disappeared without therapy. When differentiating the clinical types of ES lesions, occult ES underwent complete spontaneous regression in 65% (11/17), while verrucous lesions regressed spontaneously in 32% (9/28). None of the evaluated intrinsic or environmental factors showed a significant effect on the risk for development, regression or exacerbation of ES disease.

Conclusions: Our results document a surprisingly high rate of spontaneous ES regression for young horses affected with milder manifestations of ES disease. These findings justify a ‘wait-and-see’ approach in selected cases of occult and verrucous ES, provided that all lesions are closely monitored. Furthermore, results of this study should also be considered when critically assessing treatment effects of therapies directed against ES, especially in the context of uncontrolled studies.

KEYWORDS
Horse; equine; sarcoid; clinical course; spontaneous regression; longitudinal study

1. Introduction

Equine sarcoids (ES) are the most common skin neoplasia in equids, accounting for up to 90% of all cutaneous tumors (Marti et al. 1993; Scott & Miller 2003; Knowles et al. 2015). Sarcoideal tumors invade dermal and/or subcutaneous tissues locally, but true metastatic dissemination does not occur. Although the disease is rarely fatal, tumors may become ulcerated or infected, and recurrence is frequently observed after tumor removal (Knottenbelt 2009). Accordingly, welfare and economic aspects must be considered when treating this disease.

Bovine papilloma virus (BPV-1/-2) has long been recognized as an essential etiologic factor (Olson & Cook 1951; Bogaert et al. 2005; Brandt et al. 2008) and is supposedly transmitted from cattle to horses or from horse to horse, possibly involving biting flies as vectors (Knottenbelt & Kelly 2000; Chambers et al. 2003). Several potential risk factors including the proximity to BPV infected cattle (Bogaert et al. 2005), extensive pasturing times (Mele et al. 2007), or traumatic and surgical skin lesions (Voss 1969; Carr et al. 2001) have been proposed as a part of the multifactorial ES etiopathogenesis.

Evidence for a genetic basis of ES as an important intrinsic factor includes family- (Ragland et al. 1966; James 1968; Stannard 1978) and breed-predispositions (Angelos et al. 1988; Mohammed et al. 1992), associations of ES with certain equine leukocyte antigen alleles (Meredith et al. 1986; Broström et al. 1988; Lazary et al. 1994) and with other genomic loci (Jandova et al. 2012). Furthermore, a recent segregation analysis of ES disease in a large sample of the Franches-Montagnes (FM) horse population revealed an estimated heritability of up to 21% (Christen et al. 2014).

Both spontaneous regressions (Broström 1995; Studer et al. 1997; Knottenbelt & Kelly 2000) and severe exacerbations (Ragland et al. 1970) have been described, and the clinical course of ES is notoriously unpredictable, seemingly irrespective of lesion location, type of lesion, age and environmental factors (Knottenbelt 2009). Surely, there is a scarcity of published evidence on which equine veterinarians can
base their decisions whether or not to treat an ES lesion or recommend purchase of an ES-affected animal. To the authors' knowledge, no longitudinal studies have critically assessed the progression and clinical course of ES over a period of several years.

In the present study, two cohorts, one consisting of ES-affected and the other of ES-free FM horses, were examined at the age of three and again after a 5–7 year period. Our main objective was to determine disease progression with and without therapeutic interventions. We hypothesized that (1) spontaneous regression is rare in ES disease, and that (2) young horses affected with ES disease are at an increased risk of being eliminated, because of ES disease exacerbation.

2. Materials and methods

Records of 702 FM horses were reviewed, that were clinically examined by one qualified veterinarian in 2004 according to a standardized protocol as described previously (Mele et al. 2007). These examinations including interviews with owners or caretakers using a standardized questionnaire were performed during the yearly official field tests of the three-year-old FM horses, which serve to assess the quality of conformation, gait and behavior. Furthermore, for each horse, date of birth, gender, coat color, pedigree and owner information were recorded.

Of these 702 horses, 115 (16%) were described as ‘ES-affected’ based on gross appearance and localization of skin lesions. In 32 of these 115 records, the examiner denoted the ES lesion as ‘questionable diagnosis’, based on either atypical localization or atypical gross appearance of the lesion observed. Consequently, all 32 horses with a ‘questionable diagnosis’ were excluded from further analyses in the present study, leaving 83 horses, which were unambiguously identified, as ES-affected (Figure 1).

A breed-, age- and geographically matched convenience sample of 100 horses was formed from the 587 horses without any suspicion of ES lesions at the initial examination in 2004. The selection criterion of geographical proximity to ES-affected horses was included in an attempt to control for extrinsic environmental factors that potentially vary with geographic location. Five to seven years after the field test examination, owners of both ES-affected and ES-free horses were again contacted based on information provided by the Swiss Breeding Federation of the FM Horse. Of 83 ES-affected horses and 100 ES-free controls, 11 had since been euthanized or slaughtered (unrelated to ES), and the owners of another 36 could not be contacted, leaving a total of 136 horses (61 in the study group and 75

Figure 1. Flow diagram depicting accrualment of study and control population and progression over the 5–7 year period.
in the control group) available for follow-up (Figure 1). Between 2009 and 2011, these 136 individuals were again examined and their owners or caretakers were again queried by one veterinarian (FB; questionnaire see Supplementary Item 1).

The initial clinical examination, conducted in 2004 and previously described in detail (Mele et al. 2007), included a thorough inspection of the horse’s integument specifically describing the localization, clinical type of ES lesions, as well as affected surface area and number of lesions found in each horse. In 14 horses, however, an unambiguous distinction between occult and verrucous lesions had not been reached by the examiner and could not clearly be made retrospectively based on the examination protocols, although lesion localization and affected surface area were clearly recorded (Table 1).

At the time of follow-up examination, the same protocol was repeated. Moreover, special care was taken to investigate and palpate the localizations for which the presence of ES lesions had previously been described in the records provided of 2004. By comparing the affected surface area, morphological lesion type and number of lesions per horse of the findings from initial and follow-up examination, lesion progression was either defined as ‘unchanged’, ‘partially regressed’ (decrease in number and/or size of the affected surface area) or ‘progressed’ (progression to a more advanced morphological type or a notable increase in number and/or size of the affected surface area). If no ES lesions were found on the entire integument, the horse was classified as ES-free.

The questionnaires were designed to acquire information regarding environmental factors that potentially influence the development or progression of ES disease. Explicitly, questions pertaining to stabling, pasturing (access to pasture, fly vector exposure and contact with cattle or other ES-affected horses) as well as the horses’ medical history (specifically surgical interventions including castrations and lacerations that received medical attention) were investigated. Caretakers were also specifically asked whether or not horses had been treated against ES and, if so, which therapeutic modalities were used.

### 3. Statistical analyses

Data were stored using Microsoft Excel (Microsoft Version 2010). Descriptive statistics were performed using the statistical software package NCSS 2008. The chi-square test or Fisher’s exact test (for small samples) were used to compare the study groups.

Factors were screened for their influence on the presence of ES at the time of the initial exam, and on the presence and progression of ES at the time of the follow-up examination using three different logistic regression models (STATA 13 module ‘logit’, StataCorp LP). The first statistical model (M1) tested the influence of the five potential risk factors (Table 2) on the occurrence of ES disease comparing study and control group at the initial examination (2004). The second (M2) and third statistical models (M3) analyzed the influence of seven factors (Table 2) on the outcome variables potentially influencing the outcome variables ‘sarcoid present’ versus ‘sarcoid absent’ in both groups: ES-affected and controls. The outcome variable of M3

| Localization* | Sarcoid lesions at initial exam (2004) (counts and percentages) | Sarcoid lesions at follow-up exam (2009 – 2011) (counts) |
|---------------|---------------------------------------------------------------|------------------------------------------------------|
|               | Unchanged | Partial regression | Complete regression | Progression |
| Head/neck     | 12 (20%)  | 0                   | 0                     | 10          | 2           |
| Trunk/abdomen/extremities | 34 (56%) | 3                   | 6                     | 18          | 7           |
| Paragenital region | 15 (24%) | 0                   | 2                     | 10          | 3           |
| Total         | 61 (100%) | 3                   | 8                     | 38          | 12          |
| Type at initial examb | Occult | 17 (28%) | 0                   | 0                     | 13          | 4           |
|               | Verrucous | 28 (46%) | 2                   | 6                     | 12          | 8           |
|               | No clear distinction between occult and verrucous lesion | 14 (23%) | 1                   | 1                     | 12          | 0           |
| Nodular       | 2 (3%)    | 0                   | 1                     | 1                      | 0           |             |
| Total         | 61 (100%) | 3                   | 8                     | 38          | 12          |
| Therapy       | With therapy | 12 (20%) | 0                   | 2                     | 6          | 4           |
|               | Without therapy | 46 (75%) | 3                   | 6                     | 29         | 8           |
|               | Without information about therapy | 3 (5%) | 0                   | 0                     | 3          | 0           |
| Total         | 61 (100%) | 3                   | 8                     | 38          | 12          |

*If ES lesions were found in multiple localizations, the localization with most lesions or with the most severe lesion was listed.
*bIf multiple lesions were found, the most severe type of lesion was listed.

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Table 1. Clinical course of sarcoid lesions and influence of type, localization and attempted therapy in 61 Franches-Montagnes horses over a 5–7 year period.
Table 2. Results of univariable logistic regression analyses (models 1–3) of potential risk factors for the clinical course of ES.

| Statistical model | Variable | Cases, n (%) | Controls, n (%) | Odds ratio | 95% Confidence interval | P-value |
|-------------------|----------|--------------|----------------|------------|-------------------------|---------|
| **Model 1**       |          |              |                |            |                         |         |
| At the time of initial exam (age 3); presence of ES vs. absence of ES | Coat color | Bay | 30 (38.0) | 49 (62.0) | 1.9 | 0.9–3.8 | 0.07 |
| | Chestnut | 29 (53.7) | 25 (46.3) | 1.7 | 0.8–3.6 | 0.2 |
| | Grey | 2 (66.7) | 1 (33.3) | 3.3 | 0.3–37.6 | 0.3 |
| | Gender | Female | 42 (41.6) | 59 (58.4) | 0.9 | 0.4–2.2 | 0.3 |
| | | Male | 19 (54.3) | 16 (45.7) | 0.7 | 0.3–2.2 | 0.3 |
| | Stabling | Inside | 45 (45.9) | 53 (48.1) | 1.4 | 0.8–2.4 | 0.1 |
| | | Outside | 11 (37.1) | 19 (62.9) | 2.8 | 1.0–7.9 | 0.03 |
| | Significant wound | No | 52 (44.4) | 65 (55.6) | 0.6 | 0.4–0.9 | 0.02 |
| | | Yes | 4 (30.8) | 9 (69.2) | 0.6 | 0.2–2.1 | 0.3 |
| | Surgery other than ES excision | No | 54 (43.2) | 71 (56.8) | 1.3 | 0.9–1.9 | 0.03 |
| | | Yes | 2 (50.0) | 2 (50.0) | 1.3 | 0.2–6.6 | 0.3 |
| **Model 2**       |          |              |                |            |                         |         |
| At the time of follow-up exam (age 8–11); ES-affected group only; lesion progression (progression vs. unchanged, partial regression, complete regression) | Coat color | Bay | 7 (23.3) | 23 (76.7) | 0.7 | 0.4–1.3 | 0.3 |
| | Chestnut | 5 (17.2) | 24 (82.8) | 0.7 | 0.4–1.3 | 0.3 |
| | Grey | 0 (0.0) | 2 (100.0) | 1.3 | 0.0–18.1 | 0.3 |
| | Gender | Female | 7 (16.7) | 35 (83.3) | 0.5 | 0.2–1.4 | 0.4 |
| | | Male | 5 (28.3) | 14 (73.7) | 1.8 | 0.5–6.6 | 0.4 |
| | Stabling | Inside | 6 (17.6) | 28 (82.4) | 0.9 | 0.2–3.7 | 0.9 |
| | | Outside | 4 (16.7) | 20 (83.3) | 0.9 | 0.2–3.7 | 0.9 |
| | Significant wound | No | 10 (18.5) | 44 (81.5) | 1.5 | 0.7–3.1 | 0.3 |
| | | Yes | 0 (0.0) | 2 (100.0) | 0.3 | 0.0–1.0 | 0.3 |
| | Surgery other than ES excision | No | 5 (11.6) | 38 (88.4) | 0.5 | 0.2–1.2 | 0.05 |
| | | Yes | 6 (40.0) | 9 (60.0) | 5.1 | 1.3–20.4 | 0.02 |
| | ES localization | Head, neck | 2 (16.7) | 10 (83.3) | 0.3 | 0.1–1.0 | 0.05 |
| | | Trunk, abdomen, extremities | 7 (20.6) | 27 (79.4) | 0.9 | 0.5–1.7 | 0.05 |
| | | Paragenital region | 3 (20.0) | 12 (80.0) | 2.0 | 0.8–5.1 | 0.05 |
| | ES type | Occult | 4 (23.5) | 13 (76.5) | 0.3 | 0.1–0.9 | 0.03 |
| | | Verrucous | 8 (28.6) | 20 (71.4) | 0.7 | 0.3–1.7 | 0.05 |
| | | Nodular | 0 (0.0) | 2 (100.0) | 0.3 | 0.0–1.0 | 0.05 |
| | | Unknown | 0 (0.0) | 14 (100.0) | 0.3 | 0.0–1.0 | 0.05 |
| | Contact with cattle | No | 2 (11.8) | 15 (88.2) | 1.3 | 0.5–3.8 | 0.03 |
| | | Yes | 8 (19.0) | 34 (81.0) | 1.8 | 0.6–5.1 | 0.03 |
| | Contact with other ES-affected horses | No | 1 (33.3) | 2 (66.7) | 0.3 | 0.1–1.0 | 0.05 |
| | | Yes | 0 (0.0) | 2 (100.0) | 0.3 | 0.0–1.0 | 0.05 |
| | ES therapy | No | 8 (17.3) | 38 (82.6) | 0.6 | 0.3–1.7 | 0.05 |
| | | Yes | 4 (33.3) | 8 (66.7) | 2.4 | 0.6–9.8 | 0.02 |
| **Model 3**       |          |              |                |            |                         |         |
| At the time of follow-up exam (age 8–11); presence of ES vs. absence of ES; corrected for the presence or absence of an ES lesion at the initial examination | Coat color | Bay | 30 (38.0) | 49 (62.0) | 1.4 | 0.6–3.5 | 0.4 |
| | Chestnut | 29 (53.7) | 26 (46.3) | 1.4 | 0.6–3.5 | 0.4 |
| | Grey | 0 (0.0) | 3 (100.0) | 1.4 | 0.6–3.5 | 0.4 |
| | Gender | Female | 42 (41.6) | 59 (58.4) | 1.6 | 0.8–3.3 | 0.1 |
| | | Male | 19 (54.3) | 16 (45.7) | 1.8 | 0.7–4.7 | 0.2 |
| | Stabling | Inside | 34 (40.5) | 50 (59.5) | 1.8 | 0.7–4.7 | 0.2 |
| | | Outside | 24 (50.0) | 24 (50.0) | 1.6 | 0.8–3.3 | 0.1 |
| | Significant wound | No | 53 (42.1) | 73 (57.9) | 1.6 | 0.8–3.3 | 0.1 |
| | | Yes | 2 (100.0) | 0 (0.0) | 0.3 | 0.0–1.0 | 0.05 |
| | Surgery other than ES excision | No | 43 (42.2) | 59 (57.8) | 1.0 | 0.6–1.8 | 0.05 |
| | | Yes | 15 (50.0) | 15 (50.0) | 3.3 | 1.2–9.1 | 0.02 |
| | Contact with cattle | No | 17 (53.1) | 15 (46.9) | 0.6 | 0.3–1.3 | 0.05 |
| | | Yes | 42 (42.4) | 57 (56.7) | 0.4 | 0.2–1.2 | 0.09 |
| | Contact with other ES-affected horses | No | 3 (23.1) | 10 (76.9) | 1.0 | 0.4–2.9 | 0.05 |
| | | Yes | 2 (100.0) | 0 (0.0) | 0.3 | 0.0–1.0 | 0.05 |

*aNo assessable result due to insufficient case number.

bCases.

cControls.

dReference category.
referred to the observed disease status at the time of the follow-up examination and was, hence, corrected for the presence or absence of an ES lesion at the initial examination (i.e. ES status at time of first examination kept in the model).

The overall level for statistical significance was set to 0.05. Please refer to supplementary material (Appendix A) for a detailed description of the multivariable statistical analyses.

4. Results

The group of 61 ES-affected horses contained 42 mares, 14 geldings and 5 stallions. Thirty horses were bay, 29 chestnuts and 2 greys. The control group of 75 horses included 59 mares, 13 geldings and 3 stallions of which 49 horses were bay, 25 chestnuts and 1 grey. At the time of follow-up examination, six horses of the control group had acquired ES lesions.

The proportion of horses lost to follow-up in the study group (22/83; 27%) and the control group (25/100; 25%) did not differ significantly (P = 0.8), neither did gender proportions differ between the groups (P = 0.2).

4.1. Clinical progression of ES disease

At the time of the follow-up examination, 38 of the 61 (62%) ES-affected horses of the study group had become free of ES lesions during the 5–7 year follow-up period (Figure 1). Comprehensive information pertaining to therapy attempts and responses was available for 35 of the 38 horses. In 29 (48% out of 61) horses, lesions had disappeared without treatment and they were consequently considered as cases of ‘spontaneous regression’ (Table 1).

Twenty-three out of 61 (38%) horses still had ES at the time of follow-up (Figure 1). Following treatment, two cases underwent partial regression, but in four of the treated horses, ES lesions had taken an unfavorable clinical course, affecting a larger surface area or forming new, additional lesions. One of these four horses had been euthanized by the time of the follow-up examination due to severe exacerbation of ES disease.

Upon re-evaluation of the 61 horses that had ES lesions as three-year-olds, ES lesions had progressed to more severe clinical forms in 12 horses (Table 1). Four of these 12 horses had occult lesions at the initial exam. These progressed to verrucous (1), nodular (1), fibroblastic (1) and mixed (verrucous and fibroblastic; 1) lesions. In the remaining 8 of 12 horses that had verrucous lesions at the initial exam, lesions remained of the verrucous type in 3 horses (but increased in surface area or number), in another 4 horses, nodular lesions had developed, and in 1 horse, a mixed lesion was present at the time of follow-up.

Of the 12 horses, which received specific treatment for ES disease (Figure 1), therapy was successful in eliminating the ES lesions in half of them. In one of these six horses, the ES tumor had been surgically excised, another horse was medicated with mistletoe-extract injections (Iscador-P4, Weleda AG), two horses were treated with other forms of complementary or alternative medicine (CAM) and two horses received topical chemotherapy of unknown composition. In the six other horses, treatment attempts explicitly aimed at the ES lesion were unsuccessful in eliminating the tumors or were succeeded by tumor recurrences within the follow-up period. In two of these horses lesions underwent only partial regression following a mixed application of a topical chemotherapeutic agent (XX-Terra, Larson Labs and toothpaste), or a CAM therapy approach, respectively. Lesions progressed in 4/12 (33%) of the treated horses: one horse had a recurrence after surgical excision with exacerbation of ES disease and was consequently euthanized, two horses received CAM treatment and another horse had been treated topically with a chemotherapeutic agent of unknown composition.

Disease progression over the 5–7 year follow-up period differed with regard to the clinical type of ES lesion present upon the initial examination but not lesion localization (Table 1). Significantly, more occult lesions (13/17; 77%) in comparison with verrucous (12/28; 43%) had entirely regressed or been treated successfully (P = 0.03). Of the 13 occult lesions that regressed during the follow-up period, 11 (65%) regressed spontaneously. Of the remaining two horses, one had been treated with CAM, and information toward a possible therapy was missing for the other horse. Of the 12 verrucous lesions that regressed during the follow-up period, 9 (32% of 28) underwent spontaneous regression and 3 horses had been treated: 1 horse with mistletoe-extract injections, 1 with CAM and another with a therapeutic agent of unknown nature.

4.2. Potential risk factors for the occurrence and progression of ES

None of the tested multivariable logistic regression models had a significantly better fit than the simple univariable model (likely due to the low number of variables and cases). Results of the latter are presented in Table 2. The analysis of potential risk factors revealed no significant effect on the development of ES lesions when comparing the study and control group at the age of three (M1, Table 2).

When screening for potential risk factors again at age 8–10, having been subject to a surgical intervention (excluding surgical excision of ES lesions) significantly increased the risk for ES disease to occur (M3; odds ratio...
(OR) = 3.3, confidence interval (CI): 1.2–9.1, P = 0.02) and to progress (M2; OR = 5.1, CI: 1.3–20.4, P = 0.02).

5. Discussion
To our knowledge, this is the first study focusing on the clinical course of ES disease in horses over a follow-up period of 5 years and more. Although most horses were affected with milder forms of ES disease (Figure 2), with occult and verrucous ES lesions predominating in the study population, it is still remarkable that over 60% of horses diagnosed with ES at the age of three were free of ES, 5–7 years later. Moreover, in a clear majority (76%) of these 38 horses, ES lesions had healed without therapeutic intervention, resulting in an overall spontaneous regression rate of 48% of all ES-affected horses.

Few, mainly anecdotal reports and studies with ill-defined, small cohorts have described low spontaneous regression rates from 5.6% to 15% for ES (Broström 1995; Knottenbelt et al. 1995; Studer et al. 1997). Our present findings, however, do not support the main hypothesis that spontaneous regression is a rare phenomenon in ES disease, at least in young FM horses affected with occult and verrucous ES lesions almost half of the cases showed no more sarcomas after 5–7 years.

This is valuable information for owners, breeders and veterinarians alike, who are involved in the decision process of addressing ES therapeutically and judging the risk of disease exacerbation, for example in sale situations. These results are also relevant to studies assessing treatment effects in ES disease, since the large proportions of observed spontaneous regressions may explain some therapeutic successes in anecdotal reports and uncontrolled studies. In the present study population of young adult FM horses in Switzerland, we observed that nearly half of all ES-affected horses underwent spontaneous regression of their ES lesions without any specific treatment directed at these ES lesions. However, three specific characteristics of the present study population need careful consideration: all horses were screened at the age of three, belonged to the FM breed and were affected with milder manifestations of ES disease.

Epidemiological data from referral hospital populations or diagnostic laboratory data bases suggest that ES is a ‘disease of young horses’, at least when compared with the age of horses diagnosed with other skin tumors (Miller & Campbell 1982; Torrontegui & Reid 1994; Broström 1995; Foy et al. 2002; Bogaert et al. 2005). More specifically, a large study of ES in Western Canada reported a median age of five for fibroblastic tumors and of seven for other types of ES lesions (Wobeser et al. 2010). Hence, a large proportion of horses develop ES lesions and receive veterinary medical attention for such, during the age period which was followed in the subjects of this longitudinal study.

Although the present study population is exclusively comprised of FM horses, a breed indigenous to Switzerland, we argue that results can be translated to other, genetically closely related breeds, in particular European Warmbloods. The reported prevalence of ES lesions, for instance, in three-year-old FM horses and three-year-old Swiss Warmblood horses is similar, with 11.9% and 11.5%, respectively (Mele et al. 2007; Studer et al. 2007).

Exactly which processes underlie spontaneous regression and result in a ‘healing process’ remains unclear. It has been proposed that spontaneous regression of ES lesions is accompanied by an acquired immunity to the disease (Broström 1995; Knottenbelt et al. 1995).

Unfortunately, the present data is not conclusive as to whether or not a long-lasting immunity against ES is acquired with a documented spontaneous regression of ES lesions.

At the time of the initial examination, 97% of the ES lesions within the three-year-old cohort of the study group were occult or verrucous (Figures 2 and 3; Table 1) and had presumably not been treated. Both of these factors, milder clinical forms and lack of previous treatment attempts, are assumed to reduce the risk for further disease progression (Broström 1995; Knottenbelt et al. 1995; Studer et al. 1997; Knottenbelt & Kelly 2000; Knottenbelt 2009). The remaining 3% were nodular sarcomas. More severe forms of ES disease, i.e. fibroblastic or malignant ES types, were not recognized at the time of the initial examination in the present study. Both fibroblastic and malignant ES lesions are characterized by their locally aggressive growth behavior.
The predominant proportion of mild ES lesions in our study population is likely due to the selective nature of the field tests for young individuals that are supposed to be healthy. Hence, owners of horses with large, more advanced and severe lesions may have refrained from showing them at the field tests.

Nonetheless, based on our findings, the hypothesis that young horses affected with ES disease are at an increased risk of becoming unsuitable for their designated use due to disease exacerbation and consequently being eliminated was not confirmed: only one horse of the ES-affected study population was euthanized during the follow-up period due to exacerbation of ES disease. All other ES-affected horses available for follow-up were recorded as active and in use at their designated purpose.

Two principle limitations need to be pointed out: the lack of histopathological confirmation of the diagnosis, and that initial and follow-up examination were not carried out by the same investigator.

Although the protocol of the initial examination was not solely focused on ES, both veterinarians conducting the exams had received similar training (they graduated from the same veterinary school and worked at the same institution during the study) with a special focus on ES lesions, both were equally experienced, and closely adhered to the same, standardized examination protocol. Another limitation is that all data regarding therapy were based on information provided by owners and caretakers. This obviously limits information regarding treatment protocols used, and reported treatment success rates must be interpreted with caution.

In the context of this clinical study on milder forms of ES disease, the diagnoses of ES are based solely on clinical findings and misdiagnoses cannot be ruled out, even though ‘questionable diagnoses’ were not included for further analyses in this study. Possible differential diagnoses that could possibly be mistaken for occult or verrucous sarcoid lesions include fungal and parasitic lesions or rub marks and other circumscribed traumatic skin wounds (Knottenbelt 2009). Nonetheless, a strong agreement between clinical diagnosis and histopathology has been reported (Lazary et al. 1994; Jandova et al. 2012). However, neither of these studies focused on this relevant subject and the statement most likely cannot be extrapolated to all morphological sarcoid types. Last but not least, limitations of histopathology as a gold standard have also been pointed out (Vanselow et al. 1989).

It is well accepted that taking biopsies, especially of occult and verrucous ES, carries a significant risk of disease exacerbation (Ragland et al. 1970; Pascoe & Summers 1981; Howarth 1990; Knottenbelt 2009; Jandova et al. 2012). With that in mind, it can be argued that most equine veterinarians if asked to assess and potentially treat the lesions seen in this study, would have refrained from taking a biopsy and most likely considered a treatment strategy against presumptive ES lesions. This reflects that this study is addressing a real clinical question and a situation many equine practitioners are facing on regular basis. Therefore, we feel that taking skin biopsies of these lesions was neither ethically justifiable nor truly relevant in the context of this study. Moreover, owner compliance in this population or any other clinical study of this scale would likely be minimal.

6. Conclusions

The present study provides valuable information regarding ES disease progression in a well-defined study population. Our results indicate a surprisingly high rate of spontaneous ES regression for young adult FM horses affected with milder clinical types of ES. Nonetheless, making the appropriate decision regarding when and how aggressively milder clinical types of ES are treated remains difficult for equine veterinarians. Considering the present evidence indicating both high spontaneous regression rates and a risk of exacerbation following surgical excision, a cautious observational rather than an aggressive interventional approach may be justified in milder forms of ES, as long as lesion progression is closely monitored and appropriate treatment can be pursued without delay as soon as exacerbation is observed. Future research efforts should be aimed at unraveling potential extrinsic factors as well as inherent genetic differences between horses that manage to overcome ES disease by means of spontaneous regression and those suffering from inexorable disease progression.
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Disclosure statement

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