Sporadic, severe bronchointerstitial pneumonia of foals

John F. Prescott, Brian P. Wilcock, P. Suzanne Carman, Andrew M. Hoffman

Abstract

Bronchointerstitial pneumonia was diagnosed postmortem in 19 foals in a 10 year retrospective study of submissions to a diagnostic center in Ontario. Mean age at death was 2.0 ± 0.05 (SEM) mo (range five days to four months). Fourteen of 19 were aged from 1.5 to 2.5 mo. Clinically, the disease was generally characterized by sudden onset of fever and increasingly severe dyspnea which developed into respiratory distress before death. Mean length of illness was 7.0 ± 0.33 days (range 1–21 days). The disease appeared to affect only individual foals on 19 different farms.

At postmortem, lungs were typically diffusely red, wet, firm, and failed to collapse. The major lesion recognized histologically was epithelial necrosis of alveoli and terminal bronchioles. Alveolar lumens contained large epithelioid cells, which were probably macrophages, and multinucleated syncytial cells were present in 16 of the 19 lungs. Inflammatory cells were sparse. Intraalveolar fibrin was prominent in all lungs. Bacteriological examination revealed no significant pathogen in 12 animals, but *Rhodococcus equi* was isolated from seven foals, associated in two animals with extensive abscesses. Viruses were not recovered from eight foals examined.

On the basis of the similarity and severity of lesions, the sporadic nature of the disease, and the similar age at onset which appears to coincide with declining maternally-derived immunoglobulins, we speculate that this disease may be the result of a viral infection.

Résumé

Pneumonie bronchointerstitielle sévère, sporadique chez les poulains

Une pneumonie bronchointerstitielle a été diagnostiquée postmortem chez 19 poulains admis à un centre de référence en Ontario, au cours d'une étude rétrospective sur une période de 10 ans. L'âge moyen lors de la mortalité était de 2,0 ± 0,05 (ESM) mois avec un intervalle variant de cinq jours à quatre mois. Quatorze des 19 animaux étaient âgés entre 1,5 et 2,5 mois. La présentation clinique de la maladie était généralement caractérisée par l'apparition subite de fièvre et une dyspnée sévère progressive évoluant vers une détresse respiratoire précédant la mort. La durée moyenne de la maladie était de 7,0 ± 0,33 jours (avec un intervalle variant de 1 à 21 jours). La maladie semblait affecter seulement des cas individuels répartis sur 19 fermes. Lors de l'examen postmortem, les poumons étaient de coloration diffuse rougeâtre, humide, ferme et n'étaient pas affaissés. Les lésions histologiques prédominantes comportaient une nécrose de l'épithélium alvéolaire et des bronchioles terminales. La lumière alvéolaire contenait de larges cellules épithéloïdes correspondant probablement à des macrophages et à des cellules syncytiales multinucléées chez 16 des 19 poumons atteints. La présence de cellules inflammatoires était rare. Il y avait prédominance de fibrine intraalvéolaire dans tous les poumons. L'examen bactériologique a démontré la présence de *Rhodococcus equi* chez sept poulains associé dans deux cas à la présence d'abcès importants, alors que chez les 12 autres sujets, aucun agent pathogène n'a été isolé de façon significative. La virologie fut négative chez huit sujets examinés.

Considérant la similarité et la sévérité des lésions, la nature sporadique de la maladie et l'âge d'apparition, laquelle semble coïncider avec la diminution d'immunoglobulines d'origine maternelle, les auteurs présument que cette maladie résulte d'une infection virale. (*Traduit par Dr Thérèse Lanthier*)

Can Vet J 1991; 32: 421–425

Introduction

Bronchointerstitial pneumonia of foals is a sporadically-occurring, ill-defined disease of uncertain cause (1,2). The most complete account is given in a retrospective study by Buergelt *et al* (3), who described a proliferative interstitial pneumonia in 20 horses in Florida. Of these, 14 were in foals aged less than six months. No causative agent was identified, and the authors suggested that an ingested toxin might be the cause (3). Our retrospective study was instigated by an apparent increase in the prevalence of this disease in foals in Ontario. We describe the structural, microbiological, and epidemiological findings in 19 foals that died with this distinctive disease.

Materials and methods

Histories and pathological examination

The pathology reports of the Department of Pathology, Ontario Veterinary College, and of the Veterinary Laboratory Services, Ontario Ministry of Agriculture and Food, for 1980–1989, inclusive, were searched for all diagnoses of respiratory disease in foals under the age of six months. From these 115 records, 23 cases diagnosed as bronchointerstitial pneumonia on the basis of characteristic gross and histological changes were selected, and histological sections were reexamined. Histories available from the records included: breed, age, and sex of the foals; approximate duration of clinical signs and date of onset; a brief summary of clinical findings (which sometimes included informa-

Department of Veterinary Microbiology and Immunology (Prescott), Department of Pathology (Wilcock), Department of Clinical Studies (Hoffman), Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1; Veterinary Laboratory Services Branch, Ontario Ministry of Agriculture and Food, Guelph, Ontario N1H 6R8 (Carman).

Table 1. Summary of foals with bronchointerstitial pneumonia

Foal number	Date (mo,yr)	Breed[a]	Age at death	Sex	Length of illness (days)	Bacteriological findings
1	7.81	TB	2.5 mo	M	7	NS[b]
2	6.83	TB	2 mo	F	NR[c]	*R. equi*
3	7.84	Mix	2 mo	F	1	NS
4	4.85	Han	1.5 mo	M	6	NS
5	2.86	SB	1.5 mo	M	14	*Actinobacillus equuli*
6	8.87	TB	4 mo	M	14	NS
7	7.88	TB	2 mo	M	21	*R. equi*
8	5.88	NR	2 mo	M	1	NS
9	6.89	TB	2 mo	F	14	*R. equi*
10	7.89	TB	3 mo	F	1	*R. equi*
11	8.82	Hunt	2 mo	M	7	*R. equi*
12	6.81	NR	3.5 mo	M	4	NS
13	4.87	TB	2 mo	NR	7	*R. equi*
14	6.86	SB	2 mo	M	7	ND[d]
15	6.86	Han	1.5 mo	F	3	ND
16	5.88	TB	2 mo	NR	NR	ND
17	6.89	TB	2 mo	F	2	*R. equi*
18	4.83	SB	7 days	F	7	*Streptococcus zooepidemicus*
19	4.83	SB	5 days	NR	3	*Klebsiella* sp.

[a]TB, Thoroughbred; Mix, mixed; Han, Hanoverian; Hunt, Hunter; NR, not recorded
[b]No significant isolate
[c]Not recorded
[d]Not done

tion on heart and respiratory rates); and the response to treatments used.

A routine postmortem examination had been performed on each foal. Grossly affected regions of lung and other selected tissues had been fixed in 10% buffered formalin, processed, embedded in paraffin, and stained with hematoxylin and eosin. Most sections of lung had also been stained with one or more of periodic acid-Schiff reagent (PAS), Gram's stain, and methenamine silver.

Microbiological examination

Routine aerobic bacteriological examination of lungs of 16 of the 19 foals was performed (4). It was not recorded whether such examination was only of representative areas of grossly affected lung or whether, in the presence of abscesses, only these areas were sampled. No attempt was made to isolate *Mycoplasma* spp. Virological examination, using standard techniques, was performed on lung from 8 of the 19 foals (5). Attempts to isolate viruses from five foals submitted prior to 1987 (Table 1) involved inoculation of embryonic bovine spleen cells and embryonated chicken eggs. Subsequently, for the three foals submitted after 1987, attempted isolation included inoculation of both embryonated eggs and two cell lines: rabbit kidney-13 (RK-13) in combination with either equine dermis or equine ovary. No serological study for neutralizing antibody to common equine respiratory viruses was recorded in these foals.

Results

Epidemiological and clinical findings

Foals that met the pathological criteria described herein for bronchointerstitial pneumonia formed 19 of 115 submissions of foals with respiratory disease and aged six months or less. An additional four cases, originally diagnosed as bronchointerstitial pneumonia, were rejected from this study because autolysis precluded adequate histological evaluation.

Mean age at diagnosis was 2.0 ± 0.05 (SEM) mo, with a range from five days to four months (Table 1). Males and females were approximately equally represented, and breeds correlated well with breeds of horses presented to the Ontario Veterinary College. Illness occurred from February to August, with 10 of 19 animals presented in June and July. Between one and four diagnoses of bronchointerstitial pneumonia were made annually between 1980–1989.

The major clinical manifestation was sudden onset of dyspnea, with tachycardia, that became progressively more severe so that animals sometimes became cyanotic. Foals either died or were euthanized *in extremis*. The mean duration of illness before natural death or euthanasia in 17 foals was 7 ± 0.33 days, with a range from 1–21 days (Table 1). Fever occurred in 13 of 14 foals in which rectal temperature was recorded (mean 40.6 ± 0.09°C, range 40–41.1°C). Neutrophilic leukocytosis occurred in the three foals in which hematology was done. In one foal, the nature of the signs suggested a cardiac anomaly, and a heart murmur was auscultated in a second foal. There was no response to a variety of treatments, including antibiotics, corticosteroids, nonsteroidal anti-inflammatory drugs, antihistamines, and bronchodilators.

Each of the foals came from a different farm but only scanty histories were included in the records. On one farm, a foal developed bronchointerstitial pneumonia and severe respiratory distress following an outbreak of mild, nonfebrile respiratory disease in two-

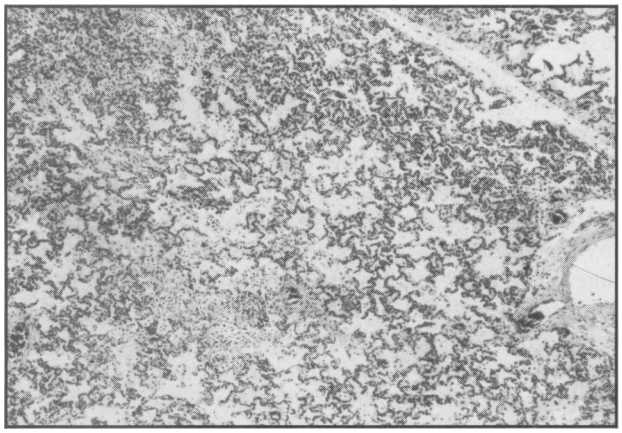

Figure 1. Affected lung is hyperemic, edematous, and appears hypercellular, the last because of the presence of numerous intraalveolar macrophages. The apparent absence of bronchioles in this large lung field is probably the result of necrosis of bronchiolar epithelium, rendering the bronchioles almost invisible at this magnification. H & E.

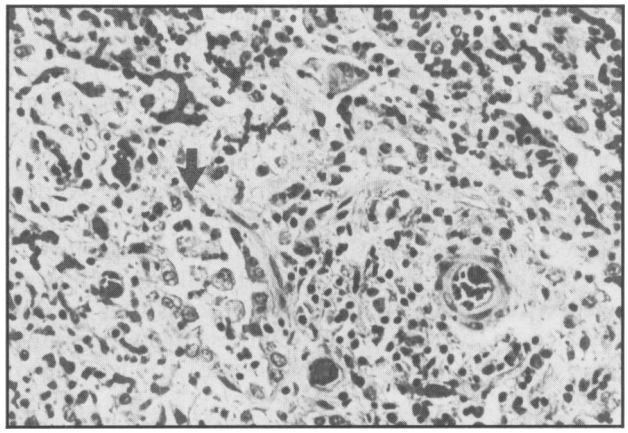

Figure 2. Necrosis of bronchiolar epithelium (arrow) was a prominent feature in all lungs of this series. H & E.

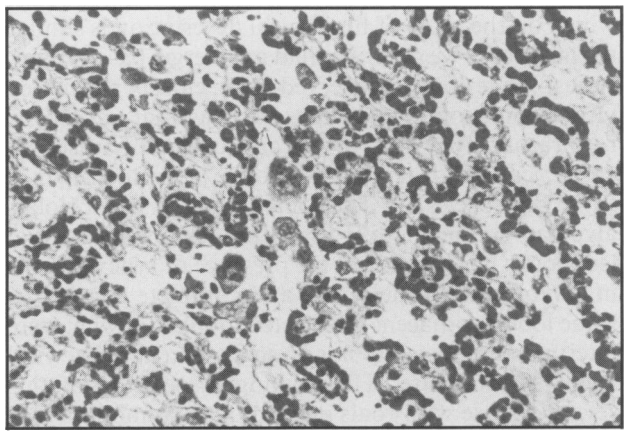

Figure 3. Formation of multinucleated giant cells (arrow) within bronchiolar and alveolar lumens. Such cells are suggestive of viral infections. H & E.

to-four-month-old foals. No similar association with an outbreak of respiratory disease was recorded for the other foals, although in one animal a history of *Rhodococcus equi* infection on the farm was described.

Pathological findings

Typically affected lungs were diffusely red, wet, firm, and failed to collapse when the thorax was opened for examination. No exudate could be detected macroscopically. Occasional small regions of normal color and consistency were found in many affected lungs. Seven lungs had scattered caseous or liquefactive foci typical of *R. equi* infection and, in two of these lungs, there was consolidation and suppuration affecting 20–25% of the anterior lung.

Multiple sections of lung selected for histopathological examination from each foal had similar lesions of bronchointerstitial pneumonia. The major lesion was necrosis of the epithelium of alveoli and terminal bronchioles. Larger bronchioles and bronchi were unaffected. Alveolar and bronchiolar lumens contained fibrin mixed with debris from the necrotic epithelium, and few leukocytes. Alveolar lumens usually contained large epithelioid cells which could sometimes be identified as sloughed pneumocytes. In many cases, however, it was not possible to determine whether these cells were pneumocytes or alveolar macrophages. Multinucleated syncytial cells were seen in alveoli and bronchioles in 16 of the 19 lungs, with reparative proliferation of pneumocytes observed in seven animals (Figures 1–3).

Intraalveolar fibrin, either mingled with intraluminal debris or, in seven lungs, as hyaline membranes, was a prominent feature in all lungs. Leukocytes other than alveolar macrophages were sparse, and the few identified cells were usually lymphocytes or plasma cells. One foal had suppurative exudate within one section from a cranial lobe, a finding that was interpreted as a secondary bacterial bronchopneumonia.

Although the lesion in most lungs was diffuse and affected all terminal bronchioles and alveoli, in some sections from three foals there was a patchy lesion which appeared to be an earlier stage of the diffuse disease. In these sections, there was necrosis of bronchiolar epithelium and that of adjacent alveoli, with scant fibrin and no proliferation of pneumocytes. Affected lobules were bordered by unaffected lobules. No causative agent was detected in sections stained with PAS, Gram's stain or with methenamine silver, except in foal 6 in which intracellular bodies typical of *Pneumocystis carinii* were identified in sections from anterior lobes.

Microbiological findings

Bacteria isolated were *R. equi* from seven foals, and *Streptococcus zooepidemicus*, *Klebsiella* spp., and *Actinobacillus equuli* in moderate numbers from one foal each. No isolate was recorded from six foals, and cultures were not performed on three foals (Table 1).

No virus was isolated from eight foals examined. Virological examination was not performed on tissues from the other 11 foals.

Discussion

The similarities in age (14 of 19 were 1.5–2.5 mo), clinical signs of sudden onset of dyspnea which failed to respond to treatment, and macroscopic and microscopic pathological changes in affected foals suggest

that these cases represented a distinct entity of foals. Our findings were similar to those described previously from a series of 20 horses from Florida (3). The only substantial difference between the lesions in the Florida study and those reported here is our description of epithelial necrosis in the terminal bronchioles. The authors of the Florida series did, however, report terminal bronchiolar epithelial hyperplasia, which not infrequently occurs as a result of previous injury to the epithelium. They also reported alveolar fibrosis, which we did not see, suggesting to us that the differences in the lesions between these two series might be related to chronicity of lesions at the time of necropsy.

Buergelt *et al* (3) considered toxic insult from a poisonous plant or chemical to be more likely than an infectious agent as the cause of the interstitial pneumonia they described. Zent (1) suggested that the disease he described as interstitial pneumonia in foals, which on the basis of his clinical description is similar to the disease we describe, had an allergic basis. In our series, the lesion we observed more closely resembled viral bronchiolitis-alveolitis, such as that caused by respiratory syncytial or parainfluenza-3 viruses of cattle, canine distemper of dogs, or influenza in a variety of species (2). The combination of bronchiolar-alveolar epithelial necrosis, the lack of substantial leukocytic inflammation, the presence of syncytial cells in alveoli and bronchioles, and complete sparing of some lobules adjacent to affected lobules (in what were interpreted as the early stages) suggest an airborne viral agent as the cause. The striking association of this severe disease with foals aged about two months suggests an infectious cause which occurred at a time when maternally-derived immunity is expected to be declining, and before the foals had mounted their own immune response. The immunoglobulin status of the two neonates which died (Table 1, foals 18 and 19) was not determined. The sporadic nature of the disease and its apparent restriction to individual foals on several farms also suggests that the putative viral agent is widespread among horses. Zent (1) also observed that most cases of "interstitial pneumonia" were sporadic, but recognized that several foals might be affected at the same time on a farm.

Two cases in our series occurred in foals aged five and seven days, whereas the majority were found in foals aged between 1.5 and 2.5 mo. These findings are similar to those described by Buergelt *et al* (3) who found that 10 of 14 affected foals were aged between one and four months and only three foals were aged less than nine days. The peak incidence in June and July probably reflects the seasonal pattern of foaling in Ontario.

In our foals, the clinical description of a rapidly progressive, severe respiratory disease with apparent lack of response to various treatments was similar to that described for "interstitial pneumonia" by Zent (1). The signs of severe impairment of gaseous exchange in these foals can be explained by the loss of ventilatory units and reduced compliance of the edematous and necrotic lung. It is not clear whether this disease predisposed foals to pneumonia caused by *R. equi*. Selection bias in tissue sampling may have given the erroneous impression that *R. equi* was more significantly associated than it was in reality. In five of the seven foals in which abscesses caused by *R. equi* were present, the lesions were sparse; in two foals, the lesions were severe. Since most pneumonia caused by *R. equi* occurs in foals aged between one and four months, and in association with declining maternally-derived immunity (6,7), incidental lesions of pneumonia caused by *R. equi* might be expected in foals that died at this age. Such foals might indeed be misdiagnosed as dying of infection caused by *R. equi*. The absence of *R. equi* from 12 of these foals eliminates this organism as the cause of bronchointerstitial pneumonia in these animals. Nevertheless, the strikingly large number of lesions associated with *R. equi* suggests either that bronchointerstitial pneumonia might predispose some foals to secondary pneumonia caused by *R. equi*, or that a postulated immaturity or defect in pulmonary defense which predisposes foals to this bacterial pneumonia (8), might also make some animals susceptible to severe, infectious, bronchointerstitial pneumonia. It is interesting, however, that Buergelt *et al* (3) did not report the isolation of *R. equi*. Our study examined only foals under the age of six months, because it was below this age that the condition was recognized clinically. An interstitial pneumonia was described in six adult horses (3) and has been described in an adult by others (8), but its relation to the disease that we describe in foals in unclear.

No attempt was made to isolate *Mycoplasma* spp. However, there is one suggestion in the literature that, following aerosol challenge, an unidentified *Mycoplasma* spp. induced a lymphocyte- and histiocyte-rich interstitial pneumonia in foals (10).

No virus was isolated from the lungs of eight foals sent for viral isolation. Methods of viral isolation used prior to 1987 would have been adequate to isolate only influenza, equine herpesvirus type 1 (subtype 1), and, possibly, equine adenovirus. After 1987, methods of isolation might be expected to have isolated both of the viruses of equine influenza (H7N7, H3N8), and those of equine herpesvirus type 1 (subtype 1 and subtype 2), equine herpesvirus type 2 (EHV-2), equine rhinovirus type 1 and type 2, equine adenovirus, and equine arteritis virus. It is possible that the isolation of equine herpesvirus type 2 might have required more passages in cell culture before a cytopathic effect was observed and therefore might have been missed in the procedure used here (11). However Fu *et al* (12) were regularly successful in isolating EHV-2 in RK-13 cells after 14 days of culture from the nasal swabs of clinically-affected foals. Another reason for failure of viral isolation might have been the presence of neutralizing antibody in the tissues of foals with terminal disease. The methods used would not have isolated bovine respiratory syncytial virus, and an as yet unrecognized respiratory syncytial viral infection of horses cannot be discounted. In the study by Buergelt *et al* (3), no antibody to BSRV was detected in three foals examined.

Equine herpesvirus type 2 (equine cytomegalovirus) is a possible candidate as the agent of this disease. In humans, cytomegalovirus causes a variety of diseases including interstitial pneumonia in immunosuppressed

patients (13). Establishing a role for EHV-2 in disease is clouded by the widespread nature of the infection in horses, in which antibody is widespread and the fact that subclinical systemic infection may occur (11,14–16). Most foals are infected by two months of age (12,14). Once infected, horses appear to be life-long carriers and shedders of the virus (14). Descriptions of pathological changes in two-month-old foals alleged to have died of EHV-2 pneumonia are scanty (11). Palfi *et al* (15) described epidemics of respiratory disease in six-to-ten-week-old foals in which they associated the infection with EHV-2 by nasal isolation and serological studies. These epidemics had a biphasic clinical course, in which a mild episode of pyrexia and serous nasal discharge was followed within two to three weeks by the development of severe pneumonia caused by *R. equi* in about one-third of the foals. Since this second phase of the disease was prevented in subsequent years by the administration of antibiotics, a severe bronchointerstitial pneumonia of the type we describe here was not a sequel to the syndrome they recognized. Ames *et al* (17) described the isolation of EHV-2 from pneumonic foals from a farm on which several foals died. In the one foal examined post-mortem, lungs were grossly firm and failed to collapse. Histologically, there was extensive proliferation of alveolar lining cells, similar to that seen in some foals in our series; we interpreted this lesion to be a sequel to alveolar epithelial necrosis. Experimentally, EHV-2 infection may cause mild conjunctivitis, rhinitis, and chronic follicular pharyngitis (16,18). No description of experimental EHV-2 infection of foals deprived of maternal antibody has been published. Since foals acquire infection within the first few months of life (11,14), it would be difficult to find conventionally-reared foals that are free of EHV-2 infection.

Further studies are required to establish the cause of this severe disease of foals.

Acknowledgments

We thank Dr. C. D. Buergelt for useful discussion when we started this study, the staff of Veterinary Laboratory Services, Ontario Ministry of Agriculture and Food for making their material cases available, and Dr. M. Hazlett and Ms. K. M. Yielding for help with the record searches. CVJ

References

1. Zent WW. Foal pneumonia. Proc Am Assoc Equine Pract 1987; 32: 269–275.
2. Dungworth DL. The respiratory system. In: Jubb KVF, Kennedy PC, Palmer N, eds. Pathology of Domestic Animals. 3rd ed. Vol 2. Toronto: Academic Press, 1985: 414–456.
3. Buergelt CD, Hines SA, Cantor G, Stirk A, Wilson JH. A retrospective study of proliferative interstitial lung disease of horses in Florida. Vet Pathol 1986; 23: 750–756.
4. Carter GR. Diagnostic Procedures in Veterinary Bacteriology and Mycology. 4th ed. Springfield, Illinois: CC Thomas, 1984: 19–39.
5. Hsuing GD. Diagnostic Virology. New Haven: Yale University Press, 1982.
6. Hietala SK, Ardans AA, Sansome A. Detection of *Corynebacterium equi*-specific antibody in horses by enzyme-linked immunosorbent assay. Am J Vet Res 1985; 43: 13–15.
7. Martens RJ, Martens JG, Fiske RA, Hietala SK. *Rhodococcus equi* foal pneumonia: protective effects of immune plasma in experimentally infected foals. Equine Vet J 1989; 21: 249–255.
8. Yager JA. The pathogenesis of *Rhodococcus equi* pneumonia in foals. Vet Microbiol 1987; 14: 225–232.
9. Turk JR, Brown CM, Johnson GC. Diffuse alveolar damage with fibrosing alveolitis in a horse. Vet Pathol 1981; 18: 560–563.
10. Stipkovits L, Antal T, Szabo I, Antal V, Szollar I, Laber G, Glavits R. Clinical, epidemiological and pathological findings in horses associated in isolation of Mycoplasmas. Abstract, Proc 7th Int Congr Int Org Mycoplasmology, Vienna, Austria, 1988.
11. Sugiura T, Fukuzawa Y, Kamada M, Ando Y, Hirasawa K. Isolation of equine herpesvirus type 2 from foals with pneumonitis. Bull Equine Rest Inst 1983; 20: 148–153.
12. Fu Z, Robinson AJ, Horner GW, Dickinson LG, Grimmett JB, Marshall RB. Respiratory disease in foals and the epizootiology of equine herpesvirus type 2 infection. NZ Vet J 1986; 34: 152–155.
13. Griffiths PD, Grundy JE. The status of CMV as a human pathogen. Epidemiol Infect 1988; 110: 1–15.
14. Studdert MJ. Comparative aspects of equine herpesviruses. Cornell Vet 1974; 64: 94–122.
15. Palfi V, Molnar T, Belak S. Viral (EHV 2) respiratory disease in foals. Magy Allatorv Lap 1979; 34: 687–690.
16. Blakelee JR, Olsen RG, McAllister ES, Fassbender J, Dennis R. Evidence of respiratory tract infection induced by equine herpesvirus, type 2, in the horse. Can J Microbiol 1975; 21: 1940–1946.
17. Ames TR, O'Leary TP, Johnston GR. Isolation of equine herpesvirus type 2 from foals with respiratory disease. Compend Contin Educ Pract Vet 1986; 8: 664–670.
18. Bryans JT, Allen GP. Herpes viral diseases of the horse. In: Wittman G, ed. Herpes Virus Diseases of Cattle, Horses, and Pigs. Boston: Kluwer Academic Publishers, 1989: 176–229.