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1 **Causes of pleural effusions in horses resident in the United Kingdom**

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## 21 **Summary**

22 Pleural effusions (PE) reportedly occur most commonly secondary to bacterial pneumonia with  
23 neoplastic effusions contributing a minority of cases. The majority of reports originate from America  
24 and Australia, where long distance transport of horses, a recognised risk factor, may occur more  
25 frequently than in the United Kingdom (UK). Anecdotally, a greater proportion of horses with PE are  
26 diagnosed with neoplasia in the UK than has been reported. The aim of this retrospective study was  
27 to describe the causes of PE in horses in the UK, and to identify markers that can help differentiate  
28 between septic and neoplastic causes of PE. Medical records from 4 equine hospitals in the UK were  
29 searched for horses diagnosed with PE. Information recorded included signalment, admission  
30 physical examination and biochemical findings, and characteristics of the effusion (volume, cell  
31 count, total protein (TP) concentration). A total of 69 horses were identified, with 26 (38%)  
32 diagnosed with a neoplastic effusion. The remainder were categorized as septic, including 14/43  
33 (32.5%) that had a history of international transport. Horses with septic effusions were significantly  
34 younger (8 vs 13 years;  $P=0.001$ ) and had significantly smaller volumes of pleural fluid drained at  
35 admission (9.8l vs 32.2l;  $P<0.001$ ). Horses with septic PE had a significantly higher rectal temperature  
36 (38.6 vs 38.2°C;  $P=0.03$ ), fibrinogen concentration (7.8g/l vs 5.3g/l;  $P=0.01$ ) and serum amyloid A  
37 concentration (230mg/l vs 59mg/l;  $P=0.02$ ) than those with neoplastic effusions. A significantly  
38 higher pleural fluid cell count and TP concentration was identified in horses with septic PE  
39 ( $63.9 \times 10^9/l$  vs  $8.6 \times 10^9/l$ ;  $P<0.001$ ; 57.5g/l vs 35.9g/l;  $P=0.04$ ). These results suggest that in the UK  
40 neoplastic effusions account for a greater proportion of PE than previously reported. A large volume  
41 of PE in an older horse with a low cell count and relatively low TP concentration should increase the  
42 index of suspicion of neoplasia.

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44

## 45 **Introduction**

46 The majority of cases of pleural effusion reported in the scientific literature describe horses with  
47 septic pleuropneumonia, resulting from extension of bacterial infection of the lungs in to the pleural  
48 cavity, and most of these studies originate from the United States or Australia. (Smith 1977; Raphel  
49 and Beech 1982; Sweeney 1992; Collins *et al* 1994; Austin *et al* 1995; Racklyeft *et al* 2000; Arroyo *et*  
50 *al* 2015) In the United Kingdom, however, a greater proportion of pleural effusion cases seem to be  
51 caused by neoplasia, although the evidence to support this is scarce. (Mair *et al* 2004; Mair 2012)  
52 Early determination of the cause of a pleural effusion is paramount, so that prompt and appropriate  
53 treatment can be instigated in cases amenable to treatment, or euthanasia be performed in cases  
54 with a hopeless prognosis. The aim of this study was thus to determine whether horses identified  
55 with pleural effusion and which are resident in the UK are more frequently diagnosed with neoplasia  
56 than has been reported in previous studies, and to determine whether factors present at admission  
57 could be used to increase the index of suspicion for a neoplastic pleural effusion.

58

## 59 **Methods**

60 Records of horses presented to four equine referral hospitals in the United Kingdom between 2000  
61 and 2014 were searched for horses in which a pleural effusion had been diagnosed. The cause of the  
62 effusion was then categorised as either neoplastic, septic or 'other' based on information in the  
63 medical records including history, analysis of pleural fluid and tracheal wash characteristics,  
64 ultrasonographic and radiographic findings, and post mortem results as applicable. A history of  
65 travel prior to the development of clinical signs was recorded, as was admission clinical and  
66 clinicopathological data, and outcome. Outcome was recorded as survival to discharge. Clinical data  
67 recorded included signalment, admission heart rate, respiratory rate and rectal temperature, clinical  
68 signs and duration of those signs prior to admission, and volume of pleural fluid drained at

69 admission. Clinicopathological data included admission packed cell volume, total plasma protein  
70 concentration, serum amyloid A and fibrinogen concentrations, pleural fluid nucleated cell count  
71 (NCC) and total protein concentration, results of cytological examination of pleural fluid, and  
72 bacterial culture results of tracheal wash samples, pleural fluid or both. When a sample was  
73 obtained from both sides of the thorax, the mean protein and nucleated cell count was used for  
74 statistical comparisons. Normality of continuous data was assessed utilising the Kolmogorov-  
75 Smirnov statistic, and differences between categories compared as appropriate. No cases of pleural  
76 effusion due to 'other' reasons were identified and thus differences between septic and neoplastic  
77 pleural effusions were compared using either the independent t test or the Mann Whitney U test.  
78 For all tests, the null hypothesis was rejected when  $P < 0.05$ .

## 79 **Results**

80 A total of 69 horses with pleural effusions were identified. Not all data was available for all horses.  
81 The horses ranged in age from 1-28 years ( $n=56$ ; median 10.5 years, interquartile range (IQR) 10  
82 years) and included a variety of breeds, with the largest single group being Thoroughbreds or  
83 Thoroughbred crosses. (24/65; 38%) There were 33 geldings, 23 mares and 5 intact males.. Clinical  
84 signs present at admission were recorded for the majority of horses, and were similar for horses  
85 with either neoplasia or septic causes of effusion. The most common signs included increased  
86 respiratory rate (greater than 15/minute) and/or effort (59/64), tachycardia (heart rate greater than  
87 44 beats per minute; 56/64), depressed mentation (42/59), nasal discharge (27/59), lethargy  
88 (21/59), pyrexia greater than  $38.5^{\circ}\text{C}$  (31/62), cough (15/59) and weight loss (15/59). Peripheral  
89 masses or lymphadenopathy were only identified in 2 horses. The duration of clinical signs was  
90 recorded in 40 horses, and ranged from 1 day to 6 months. (median 7 days)

91 A diagnosis of neoplasia was made in 26/69 (38%) of horses. A definitive diagnosis was made in 23 of  
92 these; the diagnosis was made in 12 horses at post mortem examination and in 11 via cytological  
93 analysis of pleural fluid. In an additional 3 horses a presumptive diagnosis of neoplasia was made. In

94 one of these three horses, thoracic radiographs revealed multifocal rounded radiodense lesions  
95 throughout the lungs and the mediastinum, although cytological or histological confirmation was not  
96 pursued. In the second, a mediastinal mass was identified via ultrasonography, and in the third,  
97 masses within the kidney and pelvic cavity were identified via ultrasonography, in addition to 2  
98 masses within the lungs evident on thoracic radiographs. Lymphoma was diagnosed in 11 horses,  
99 unspecified carcinoma in 3, mesothelioma in 3, melanoma in 2 and for 7 horses a specific type of  
100 neoplasia was not confirmed.

101 Forty three horses were diagnosed with pleural effusions caused by septic causes. Within this  
102 category, 17/43 (39.5%) had a history of international travel; 5 horses had travelled from Ireland to  
103 the UK, 5 from mainland Europe to the UK, 3 from Argentina to the UK, 1 from New Zealand to the  
104 UK. In an additional 3 horses a history of travel was documented but no details provided as to the  
105 duration or distance. For horses with no history of travel, other risk factors identified included  
106 general anaesthesia (n=1) and oesophageal disorders (intra-luminal obstruction n=2; extra-luminal  
107 compressive mass n=1; oesophageal rupture n=2).

108 Table 1 shows admission clinical and clinicopathologic findings. Horses with neoplastic effusions  
109 were significantly older (median 13 years vs 8 years;  $P=0.001$ ), had a significantly lower rectal  
110 temperature (mean  $38.2^{\circ}\text{C}$  vs  $38.6^{\circ}\text{C}$ ;  $P=0.04$ ), and lower acute phase protein concentrations (serum  
111 amyloid A: median  $59\text{mg/l}$  vs  $230\text{mg/l}$ ,  $P=0.02$ ; fibrinogen mean:  $5.3\text{g/l}$  vs  $7.8\text{g/l}$ ,  $P=0.01$ ) versus  
112 horses with septic pleural effusions. No significant differences in heart rate, respiratory rate, packed  
113 cell volume or total plasma protein concentration were identified between horses with neoplastic vs  
114 septic effusions.

115 Pleural fluid analysis was performed in 48 horses. The NCC and total protein concentration of the  
116 pleural fluid were both significantly lower in horses with neoplastic effusions compared to septic  
117 effusions (median NCC  $8.6 \pm 15.3 \times 10^9/\text{l}$  vs  $63.9 \pm 68 \times 10^9/\text{l}$ ;  $P<0.001$ ; median total protein  
118 concentration  $35.9 \pm 16.9\text{g/l}$  vs  $57.5 \pm 43\text{g/l}$ ;  $P=0.04$ ). The mean volume of pleural fluid drained at

119 admission was significantly greater in horses with neoplasia (32.2 +/-17.9l) than those with septic  
120 effusions (9.8 +/-7.6l; P<0.001).

121 Bacterial culture of either tracheal wash samples, pleural fluid aspirates or both was performed in 34  
122 cases with a final diagnosis of septic pleural effusion. No growth was obtained in 6/34 (17.6%), a  
123 single isolate was obtained in 10/34 cases (29%) and a mixed bacterial population in 18/34 (52.9%).  
124 The most common isolates were *Streptococcus* spp. (16 isolates), *Escherichia coli* (12), *Enterococcus*  
125 *faecalis* (6) and anaerobes (6; including *Bacteroides* spp (3), *Fusobacterium necrophorum* (2) and  
126 *Clostridium perfringens* (1)). Other isolates included *Actinobacillus* spp, *Corynebacterium* spp and  
127 *Klebsiella* spp (all single isolates).

128 Details of diagnostic imaging results, including radiographic and ultrasonographic findings, were not  
129 recorded in sufficient detail in most cases to allow for meaningful analysis. For example, the  
130 presence or absence of pleural fluid on ultrasonographic examination was noted, but  
131 characterisation of pulmonary parenchymal changes, fibrin accumulation or presence of gas bubbles  
132 within pleural fluid was not consistently reported.

133 Outcome was recorded as survival to discharge. Overall, there were 43 non-survivors, 24 survivors  
134 and 2 horses in which outcome was not recorded. For horses with septic pleural effusions, survival  
135 rate was 47.6% (20/42). All horses with septic pleural effusions secondary to an oesophageal  
136 disorder died or were euthanased. Six horses with neoplastic effusions were discharged from the  
137 hospital, presumably for either palliative treatment or euthanasia at home, although this was not  
138 recorded.

139

## 140 **Discussion**

141 The findings of this study support the clinical impression that in the UK, pleural effusions secondary  
142 to neoplasia occur relatively more frequently than has been previously described in reports from

143 other countries. Although direct comparisons are difficult due to differing study designs, one similar  
144 study from the United States of America reported neoplasia as a cause of pleural effusion in only  
145 11% of 37 horses. (Smith 1977) A second study, also from the USA, identified 32/122 (26%) of horses  
146 with effusion caused by 'non-infectious' causes, although these were not further categorised.  
147 (Raphel and Beech 1982) Long distance transport is a recognised risk factor for the development of  
148 pleuropneumonia and septic pleural effusion. (Raphel and Beech 1982; Austin *et al* 1995) Head  
149 elevation during transportation minimizes a horse's ability to clear lower respiratory tract (LRT)  
150 secretions and inhaled bacteria. (Norton *et al* 2013) Combined with the physiologic stress associated  
151 with travelling, the defence mechanisms of the LRT such as mucociliary transport, pulmonary  
152 alveolar macrophages and neutrophils can become overwhelmed. (Smith 1996; Oikawa *et al* 1995;  
153 Norton *et al* 2013) Establishment of infection within the lungs results in increased capillary  
154 permeability of the inflamed lung and visceral pleura, resulting in the accumulation of a sterile  
155 transudate within the pleural cavity. Bacteria from the infected lung rapidly invade the pleural space,  
156 resulting in the accumulation of a large volume of fluid packed with inflammatory cells, cellular  
157 debris and bacteria. (Oikawa *et al* 1995; Reuss and Giguère 2015) Most studies define long distance  
158 transport as over 500 miles, and as such, it is possible that the relatively short distances that horses  
159 travel within the UK, as compared to countries like the USA and Australia, may contribute to the  
160 lower proportion of septic pleural effusions. Interestingly, in the current study, 40.5% of horses with  
161 septic pleural effusions had a history of long distance travel (in 14/17, known international  
162 transport) in comparison to 24.4% reported by Raphel and Beech (1982). Thus, long distance  
163 transport is a consistent risk factor for the development of pleuropneumonia, regardless of  
164 geographic location.

165 In this study, horses with neoplasia were significantly older than those with septic pleural effusions.  
166 Horses with pleuropneumonia are typically young, with mean ages of 3.6 years and 2.5 years in 2  
167 studies. (Collins *et al* 1994; Arroyo *et al* 2015) Presumably, this is associated with an increased  
168 likelihood for younger horses to be transported long distances for competitive reasons, or to



169 undertake high intensity exercise. In the current study, horses with septic pleural effusions were  
170 older than in other reports with a median age of 8 years, suggesting that age in itself may not be a  
171 specific risk factor, more that factors which increase the risk of developing septic pleural effusions  
172 are more likely to occur in younger horses. Whilst horses with neoplasia were older than those with  
173 septic pleural effusions in the current study, neoplasia can affect any age of horse. (Taintor and  
174 Schleis 2011) Lymphoma is typically identified in horses aged 4-10 years, with a mean age of 7 years  
175 in one study (Mair *et al* 1985; Taintor and Schleis 2011) As such, although there was a statistically  
176 significant difference between the age of both groups, young age in itself should not be relied on to  
177 rule out neoplasia as a cause of pleural effusion.

178 Consistent with previous reports, neoplasia in this study was associated with large volume  
179 accumulation of pleural fluid, with up to 55l drained in several horses. (Figure 1) (Mair *et al* 1985;  
180 Mair *et al* 2004) The development of such large volume effusions is presumed to occur due to  
181 decreased lymphatic drainage, especially when mediastinal masses are present, and/or to increased  
182 fluid production, when the neoplasm affects the pleural surfaces. (De Heer *et al* 2002; Mair *et al*  
183 2004) In most horses with neoplasia in the current report, the pleural fluid was described as a  
184 modified transudate, with a relatively low NCC and moderately increased total protein  
185 concentration. As would be expected, both the NCC and the total protein concentration were  
186 significantly higher in horses with septic causes of pleural effusion.

187

188 A definitive diagnosis of neoplasia can be made if cytologic evaluation of the fluid identifies  
189 neoplastic cells or if masses are accessible for biopsy. (Figures 2 and 3) (Sweeney and Gillette 1989;  
190 Mair *et al* 2004) Lymphoma is believed commonly to result in exfoliation of neoplastic cells into the  
191 pleural fluid and in two reports up to 40% of cases were diagnosed ante-mortem via cytologic  
192 analysis of pleural fluid. (Mair *et al* 2004; Lee *et al* 2013) Similarly, in the current study, a diagnosis of  
193 neoplasia was made in 38% of horses via cytologic examination of pleural fluid. As has been

194 previously described, most cases in the current series did not present with a peripheral  
195 lymphadenopathy or visible mass that would be amenable to biopsy for histological analysis. (Mair  
196 *et al* 2004) A recent report described biopsy of intrathoracic masses in 2 horses via thoracoscopy,  
197 allowing the authors to confirm a diagnosis of neoplasia in each case, suggesting that in selected  
198 cases, this may be an appropriate and effective diagnostic tool. (Lee *et al* 2013)

199 The prognosis for horses with septic pleural effusion in the current series was relatively poor, with  
200 only 47% of horses surviving to discharge. From the records available, it was not possible to  
201 determine whether horses were euthanased due to poor prognosis and failure to respond to  
202 treatment, or whether euthanasia was elected for financial reasons. Previous reports have similarly  
203 identified overall survival rates of approximately 50% (Racklyeft *et al* 2000) although more recent  
204 reports suggest that with early identification and treatment, outcomes can be much improved.  
205 (Arroyo *et al* 2015; Tomlinson *et al* 2015) Factors associated with failure to survive in previous  
206 studies have included infection caused by anaerobic bacteria, a larger volume of pleural fluid and the  
207 presence of fibrinous effusions. (Figures 4 and 5) (Sweeney *et al* 1991; Racklyeft and Love 2000;  
208 Tomlinson *et al* 2015) Anaerobic bacteria were only identified in 6 horses in the current study,  
209 making correlations between their presence and survival difficult to interpret. Consistency in  
210 reporting fibrinous effusions precluded analysis of this characteristic. Pleural fluid drainage (as  
211 compared to thoracocentesis for sampling) was only performed in 13 horses with septic PE; although  
212 not recorded, it may be that, in the remaining horses, the volume of effusion did not warrant  
213 drainage, although this is a presumption as accurate measurements of ultrasonographic dimensions  
214 of visible pleural fluid were not recorded in most cases. In the current report, all cases with septic  
215 effusions secondary to oesophageal disorders did not survive. Two horses developed aspiration  
216 pneumonia secondary to oesophageal obstruction, two developed oesophageal rupture of unknown  
217 cause, and one had an extra-luminal mass compressing the oesophagus, resulting in aspiration. Five  
218 cases of intrathoracic oesophageal perforations with resultant septic pleural effusions have recently  
219 been reported, all with a similarly grave outcome. (Hepworth-Warren *et al* 2015) Aspiration of feed

220 material and subsequent pneumonia following oesophageal obstruction was not reported in 60  
221 horses treated in a primary care setting. (Duncanson 2006) In comparison, 8/34 horses presented to  
222 a referral hospital developed pneumonia, which was significantly associated with duration of clinical  
223 signs. (Feige *et al* 2000) Interestingly, the degree of feed material contamination of the trachea  
224 (assessed endoscopically) was not associated with the development of pneumonia, suggesting that  
225 this may not be a sensitive tool in the assessment of whether aspiration has occurred or not.  
226 Considering the poor outcome in horses with oesophageal disorders, close monitoring of animals  
227 with oesophageal obstruction, and prompt evaluation and treatment of those suspected of having  
228 aspiration is warranted. (Feige *et al* 2000)

229 This study is limited by its retrospective nature; not all data was available for all horses. A definitive  
230 diagnosis of the type of neoplasia was not obtained in all horses, making a more detailed assessment  
231 of characteristics of individual tumour types impossible. Survival was based solely on survival to  
232 hospital discharge, which is likely to have skewed the data as several horses with neoplasia were  
233 classified as survivors due to the fact that they went home, presumably for euthanasia or palliative  
234 therapy. Although successful treatment of thoracic neoplasia has been reported, the prognosis is still  
235 considered hopeless. (Mair *et al* 2004; Saulez *et al* 2004)

236 Pleural effusions can develop for a number of reasons, the two most common being  
237 pleuropneumonia (septic) and neoplasia. In this study, horses with septic pleural effusions were  
238 younger than those with neoplasia, had significantly higher acute phase protein concentrations at  
239 admission, and had a smaller volume of pleural effusion with a higher NCC and total protein  
240 concentration. Of the 26 horses with confirmed or suspected neoplasia, the diagnosis was confirmed  
241 at post mortem in 12 horses, although in some cases a high index of suspicion existed without  
242 confirmation via cytological analysis of pleural fluid or lymph node aspirate. In 11 horses, a diagnosis  
243 was made ante-mortem using cytological analysis of pleural fluid, and in 3 horses, masses evident on  
244 ultrasound or radiography were consistent with neoplasia but cytological confirmation was not

245 pursued. This information may be helpful in making a prompt diagnosis when the clinician is  
246 presented with a horse with pleural effusion.

247

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- 313

314 **Table 1: Clinical and clinicopathologic findings in horses with septic and neoplastic pleural**  
 315 **effusion. <sup>a</sup>median (Interquartile range (IQR)); <sup>b</sup>mean (standard deviation) \*Significant difference**  
 316 **between septic and neoplastic groups**

PARAMETER	SEPTIC GROUP	NEOPLASTIC GROUP	P
<b>Age<sup>a</sup></b> (years; n=55)	<b>8</b> (9)	<b>13</b> (12)	<b>0.001*</b>
<b>Heart Rate<sup>a</sup></b> (bpm; n=64)	<b>56</b> (15)	<b>60</b> (16)	<b>0.8</b>
<b>Respiratory rate<sup>a</sup></b> (/min; n=65)	<b>29</b> (21)	<b>36</b> (21)	<b>0.9</b>
<b>Temperature<sup>b</sup></b> (°C; n=63)	<b>38.6</b> (0.89)	<b>38.2</b> (0.74)	<b>0.04*</b>
<b>Packed cell volume<sup>b</sup></b> (%; n=67)	<b>36.5</b> (11.8)	<b>36.9</b> (12.2)	<b>0.9</b>
<b>Total plasma protein concentration<sup>b</sup></b> (g/l; 62)	<b>66.8</b> (11.95)	<b>63.71</b> (17.99)	<b>0.4</b>
<b>Fibrinogen concentration<sup>b</sup></b> (g/l; n=56)	<b>7.8</b> (3.3)	<b>5.3</b> (2.9)	<b>0.01*</b>
<b>Serum amyloid A concentration<sup>b</sup></b> (mg/l; n=49)	<b>230</b> (200)	<b>59</b> (238)	<b>0.02*</b>
<b>Total volume of pleural fluid<sup>b</sup></b> (l; n=28)	<b>9.8</b> (7.6)	<b>32.2</b> (17.9)	<b>&lt;0.001*</b>
<b>Pleural fluid nucleated cell count<sup>a</sup></b> (x10 <sup>9</sup> /l; n=48)	<b>63.9</b> (68.0)	<b>8.6</b> (15.3)	<b>&lt;0.001*</b>
<b>Pleural fluid total protein concentration<sup>a</sup></b> (g/l; n=47)	<b>57.5</b> (43.0)	<b>35.9</b> (16.9)	<b>0.04*</b>

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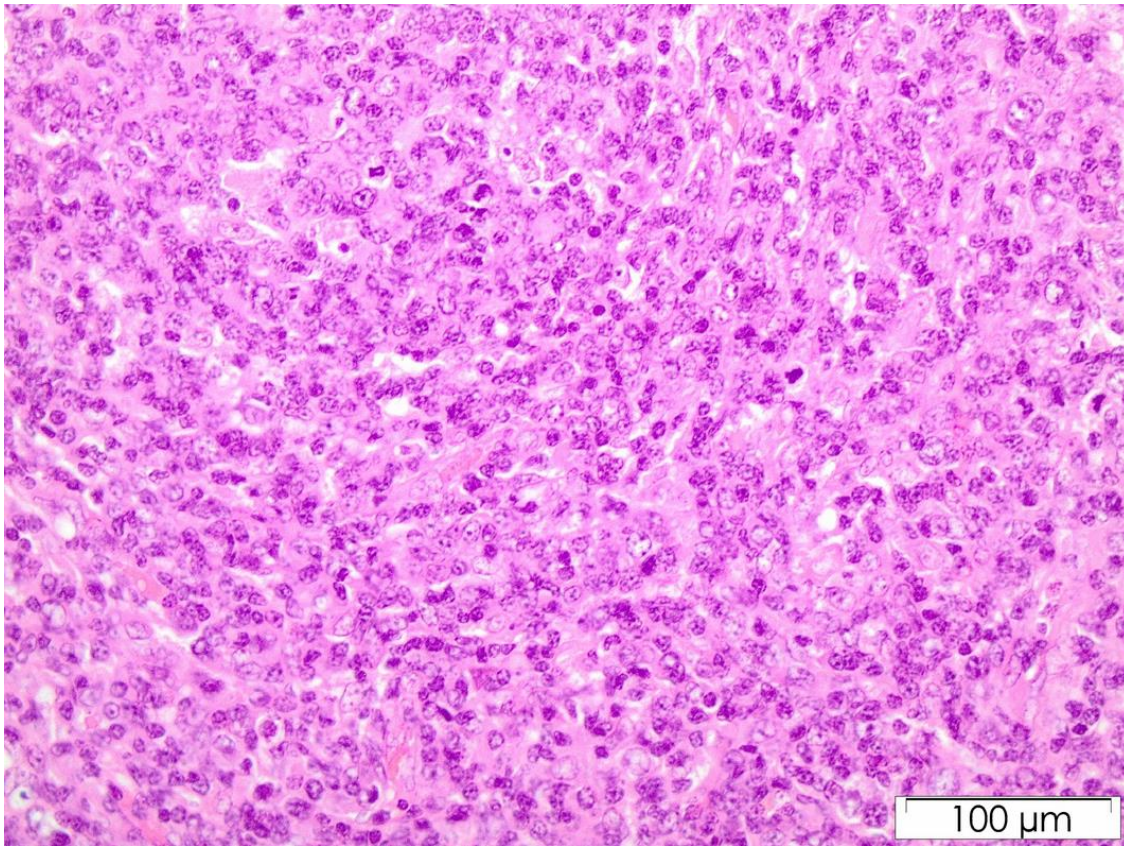
319 **Figure 1:** Large volume effusion drained from the pleural cavity of a horse with lymphoma.



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322 **Figure 2:** Histopathology from a lymph node obtained at post mortem examination in a horse with  
323 lymphoma. Sheets of immature and mitotically active lymphomatous cells are noted throughout the  
324 section.

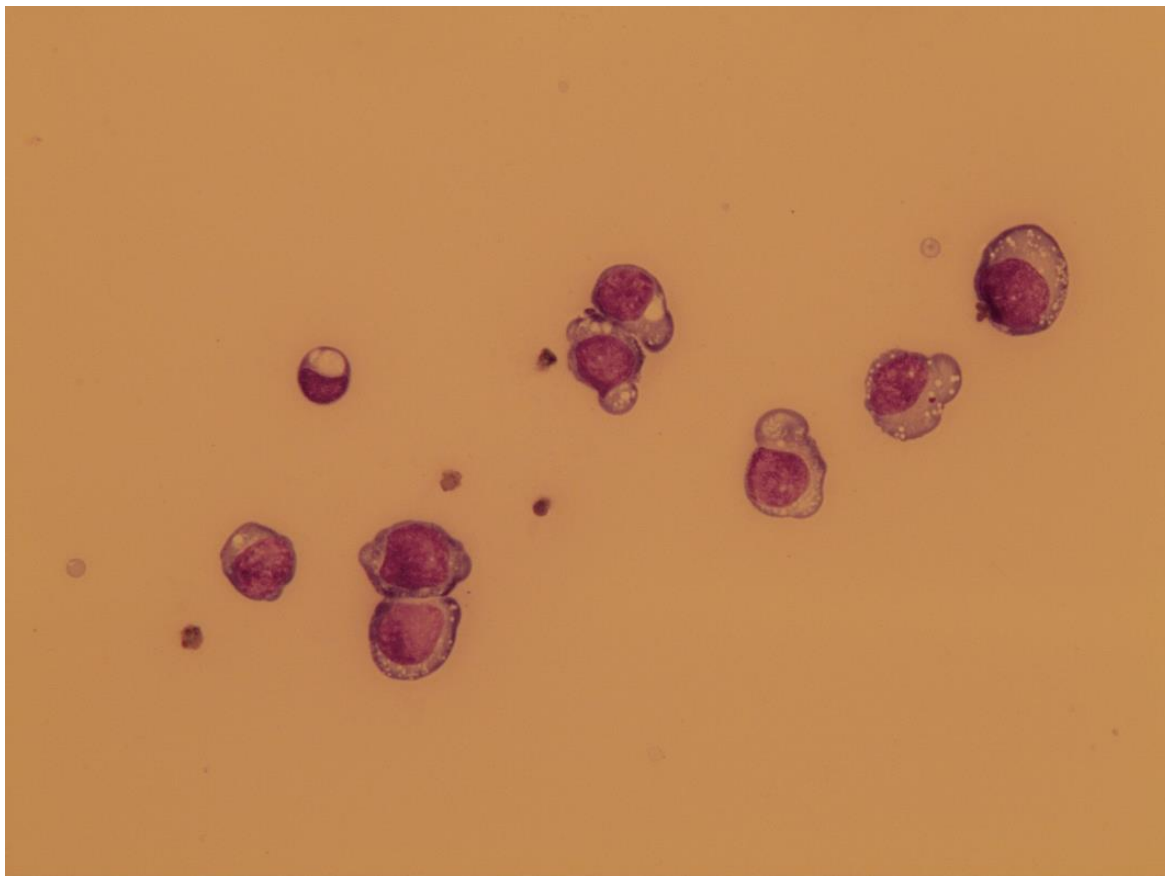


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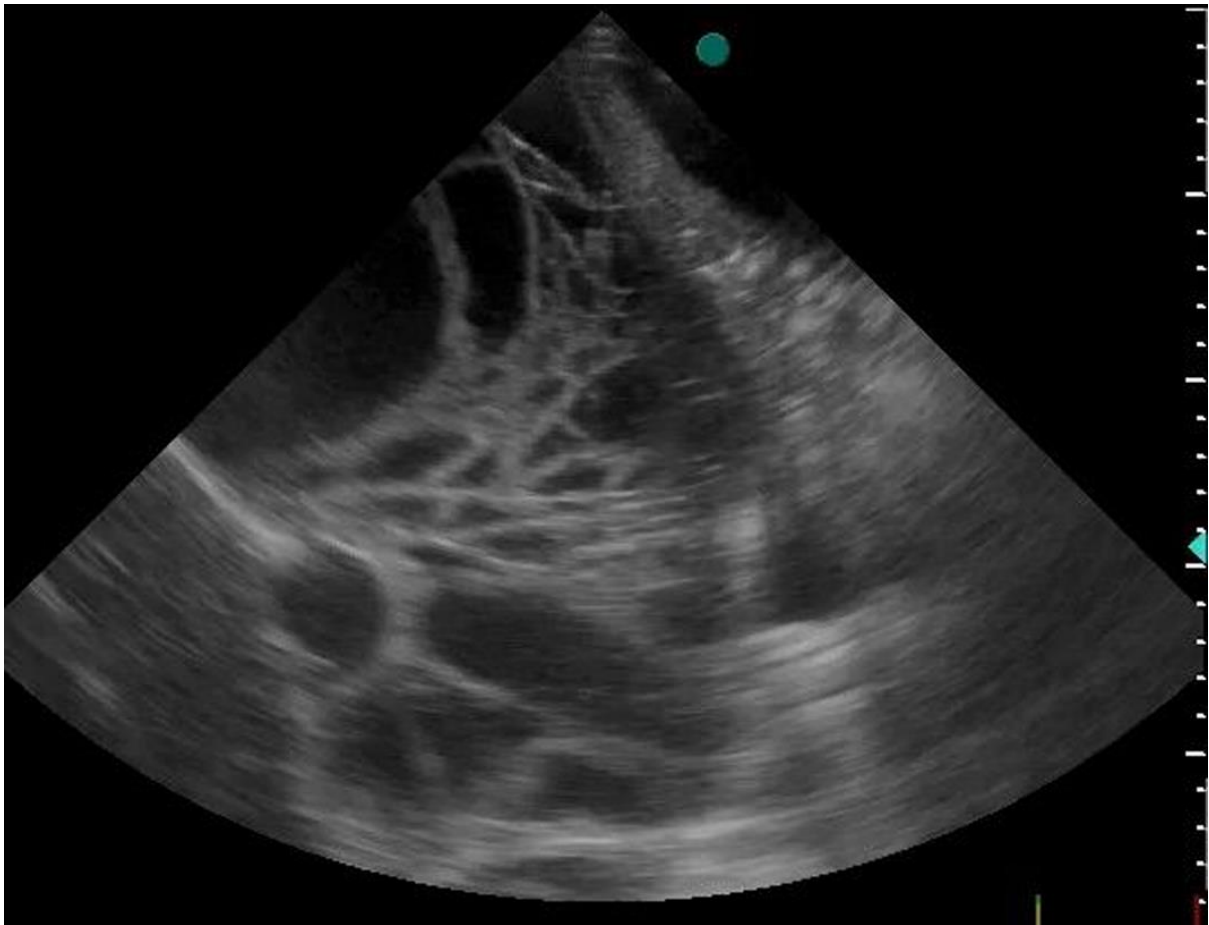
328 **Figure 3:** Pleural effusion from a horse with neoplasia, identifying large round cells with eccentric  
329 nucleus.



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332 **Figure 4:** Ultrasonographic image of a horse with fibrinous pleuropneumonia.

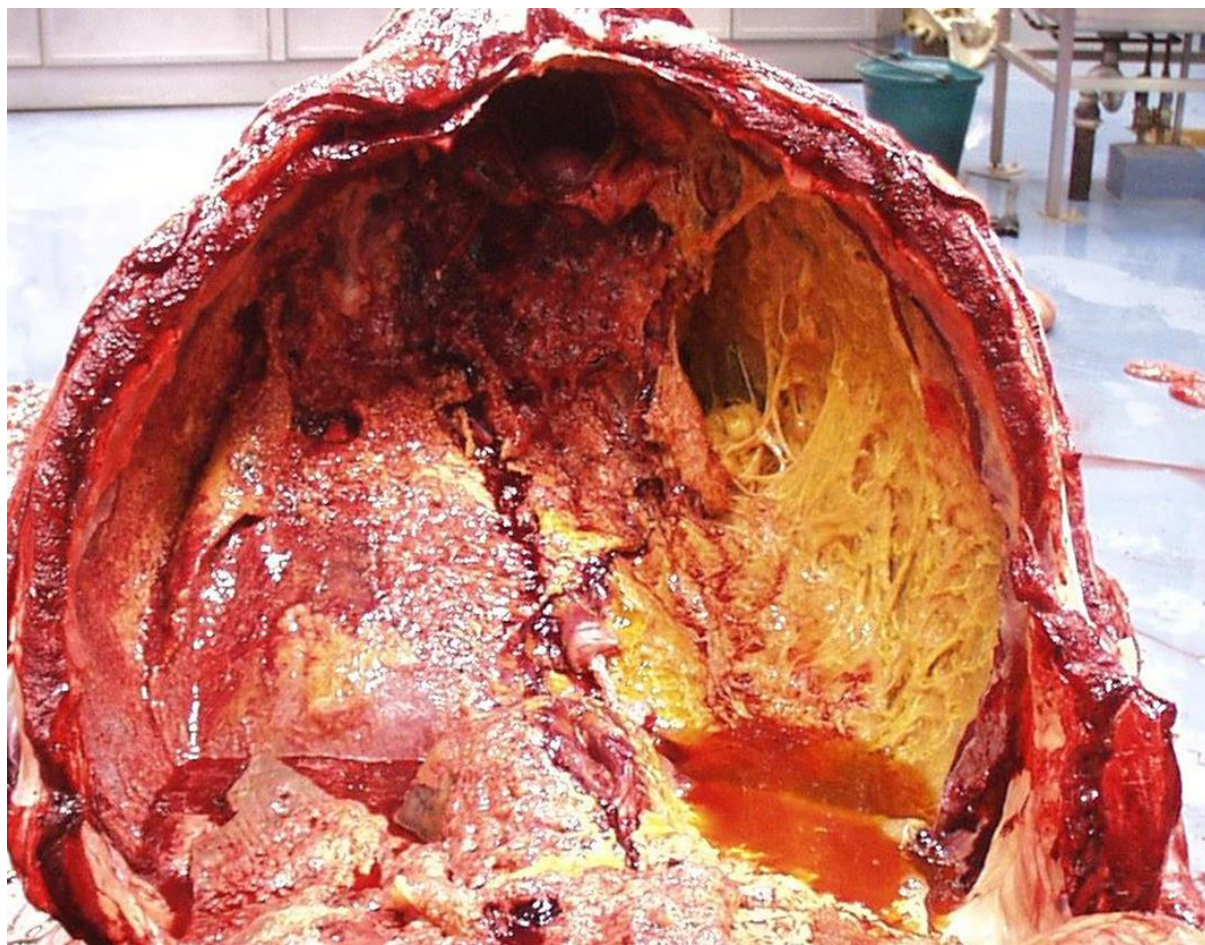


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335 **Figure 5:** Post mortem image of horse with severe fibrinous pleuropneumonia, markedly worse on  
336 the left.



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