Diagnostic Exercise

From The Davis-Thompson Foundation*

Case # **223**; Month: **October**; Year: **2023**

Answer sheet

Title: Purpura hemorrhagica (PH)

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Clinical History: A 15-year-old paint horse gelding was evaluated by the equine medicine service for evaluation of pyrexia and ventral edema in all four limbs. Preliminary blood work revealed normal white blood cell count with mild lymphopenia, moderate hyperglycemia, moderate-to-marked hypomagnesemia, mild hyponatremia, mild hypochloremia, and mild-moderate hyperbilirubinemia. A *Streptococcus equi* SeM protein ELISA was requested. After hospitalization, the horse developed severe ecchymoses on the oral mucosa and hyperemia of the conjunctiva. Thromboelastography revealed a mildly prolonged R time. Imaging revealed moderate comet tails throughout the cranioventral lung fields with regions of consolidation. The horse continued to clinically decline over the next two days despite aggressive treatment, with significant progression of the mucosal ecchymoses and development of significant muzzle edema. The horse also had significant conjunctival edema with hemorrhagic lacrimation. Due to rapid systemic decompensation and poor prognosis, the horse was euthanized.

Autopsy Findings: Bilaterally the palpebral and nictitans conjunctiva were dark red and swollen. The skin of the lips and muzzle had petechiae and fewer ecchymoses, which extended across the mucocutaneous junction along the buccal mucosa and coalesced along the gingival maxillary and mandibular borders, as well as in the caudal buccal mucosa, forming diffusely red-purple zones (Fig. 1). In the maxillary buccal mucosa, there was a 0.2 cm in diameter ulcer surrounded by submucosal hemorrhage. The ventral surface of the tongue had few scattered petechiae and five pinpoint to 0.2 cm in diameter ulcers. The subcutis ventral to the mandible was wet and gelatinous with coalescing petechiae and ecchymoses. Throughout the body, the visceral and peripheral adipose had petechiae and ecchymoses.

Gross and Microscopic Images:

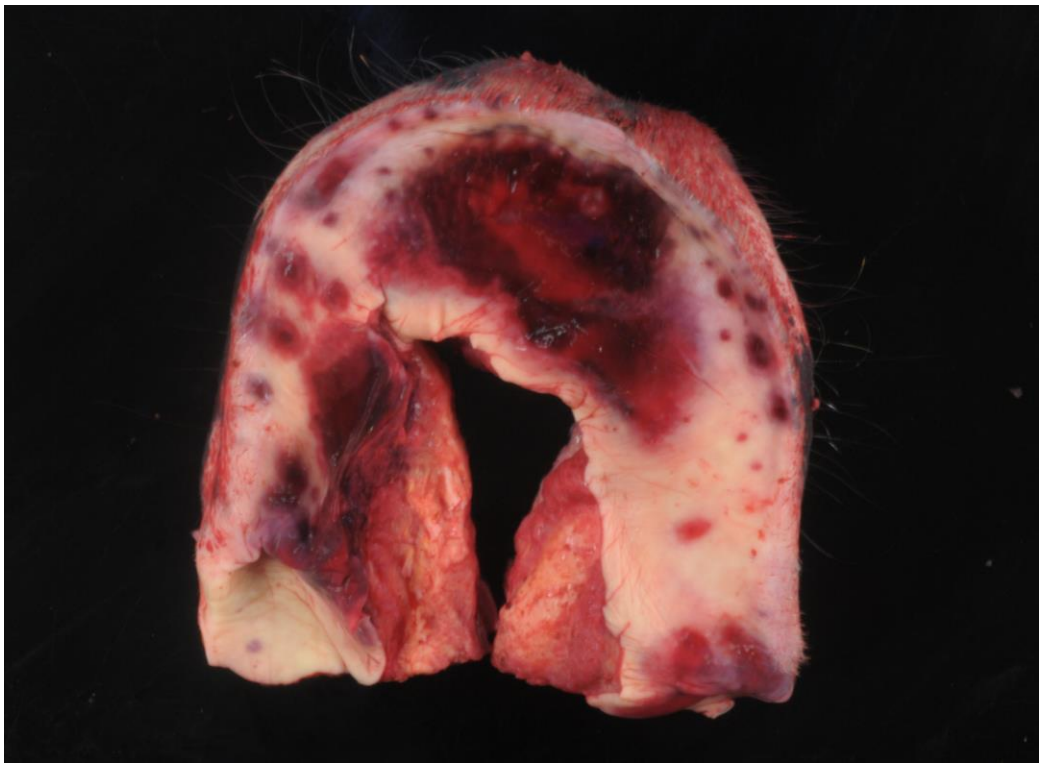

Figure 1. The skin of the lips and muzzle have petechiae and ecchymotic hemorrhages forming mottled red-purple foci.

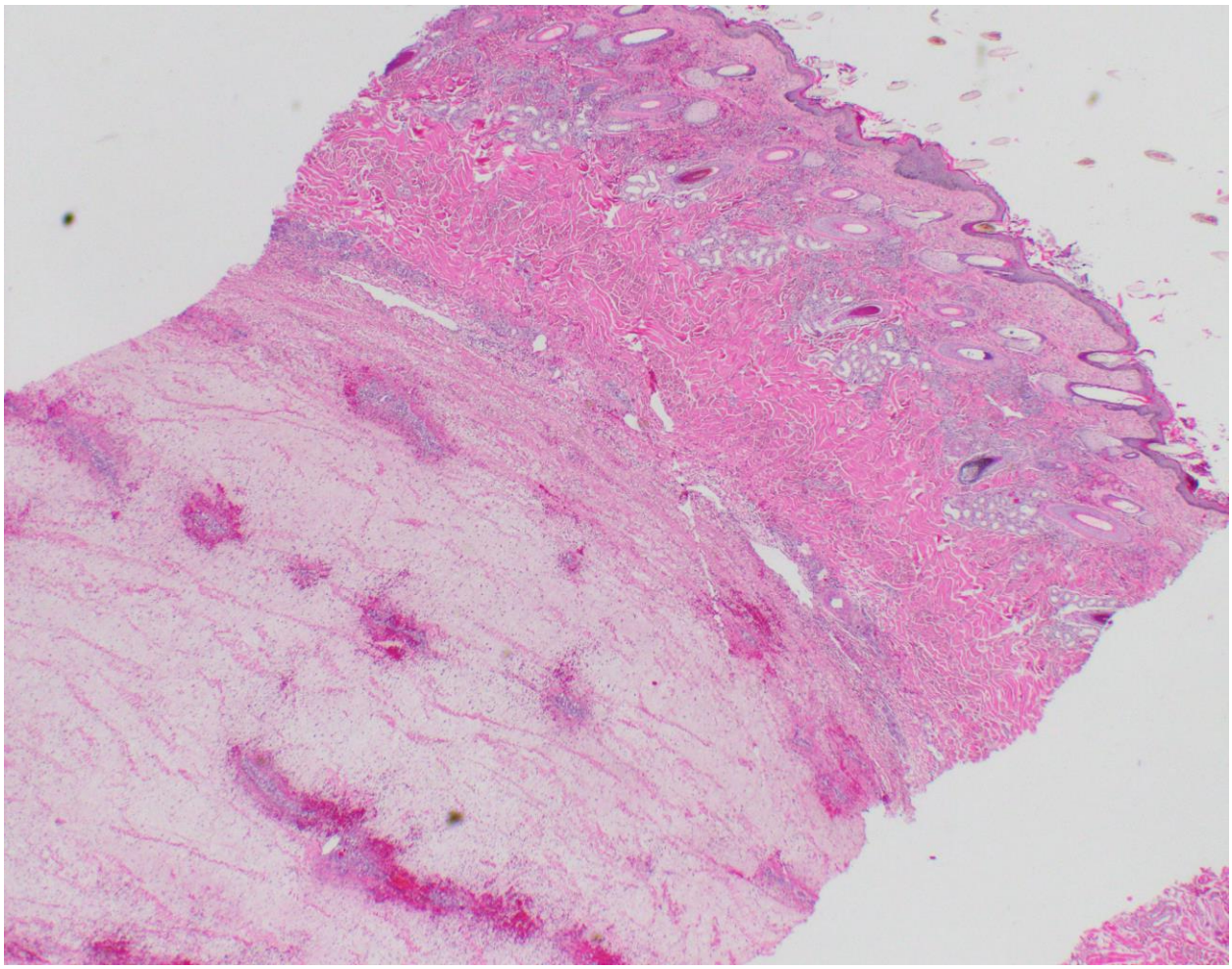

Figure 2. Skin 2x. Horse, skin. There is perivascular hemorrhage and submucosal edema.

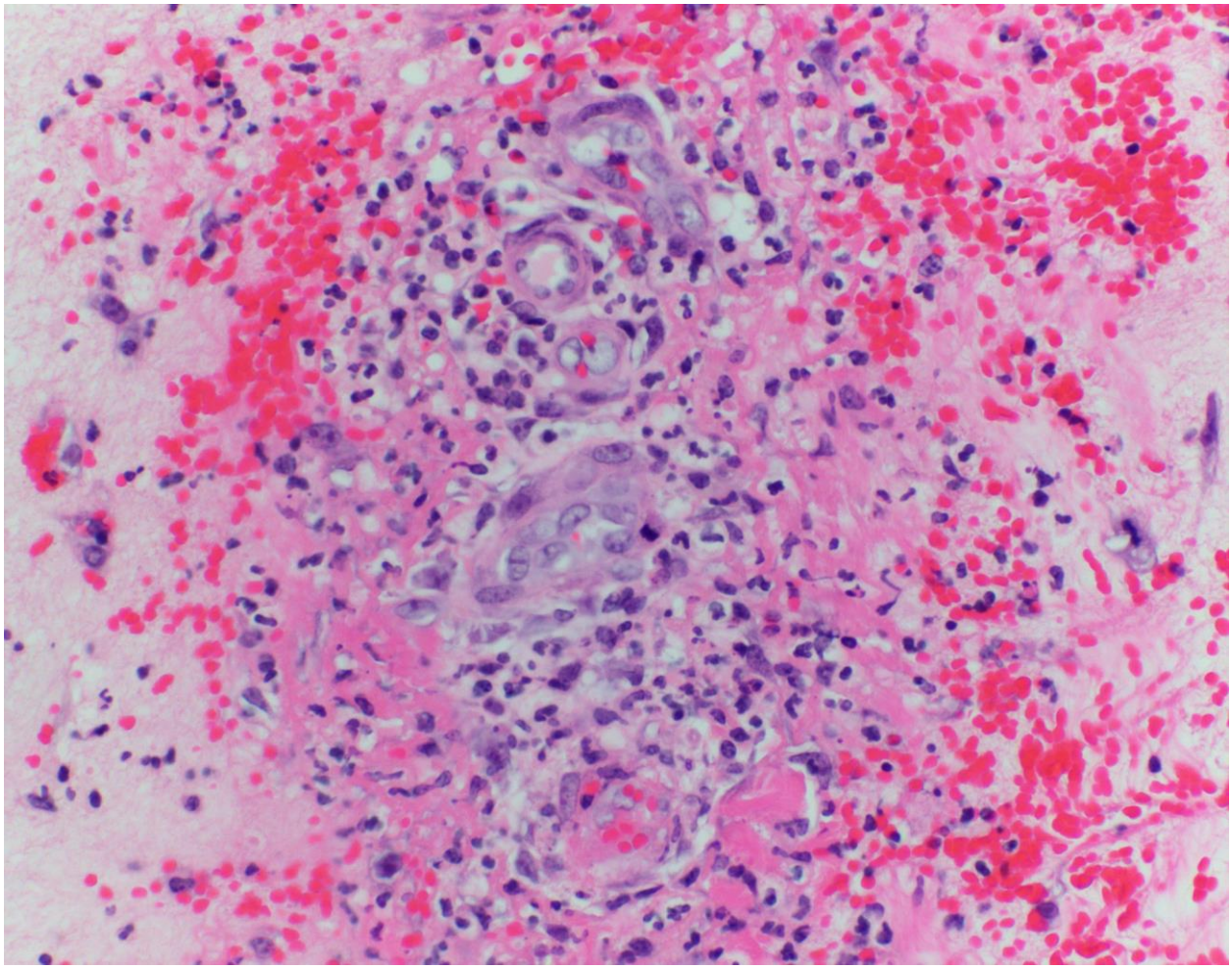

Figure 3. Horse, skin. Vascular walls are distorted by viable and necrotic neutrophils mixed with fibrin and karyorrhectic debris. There is perivascular hemorrhage and edema.

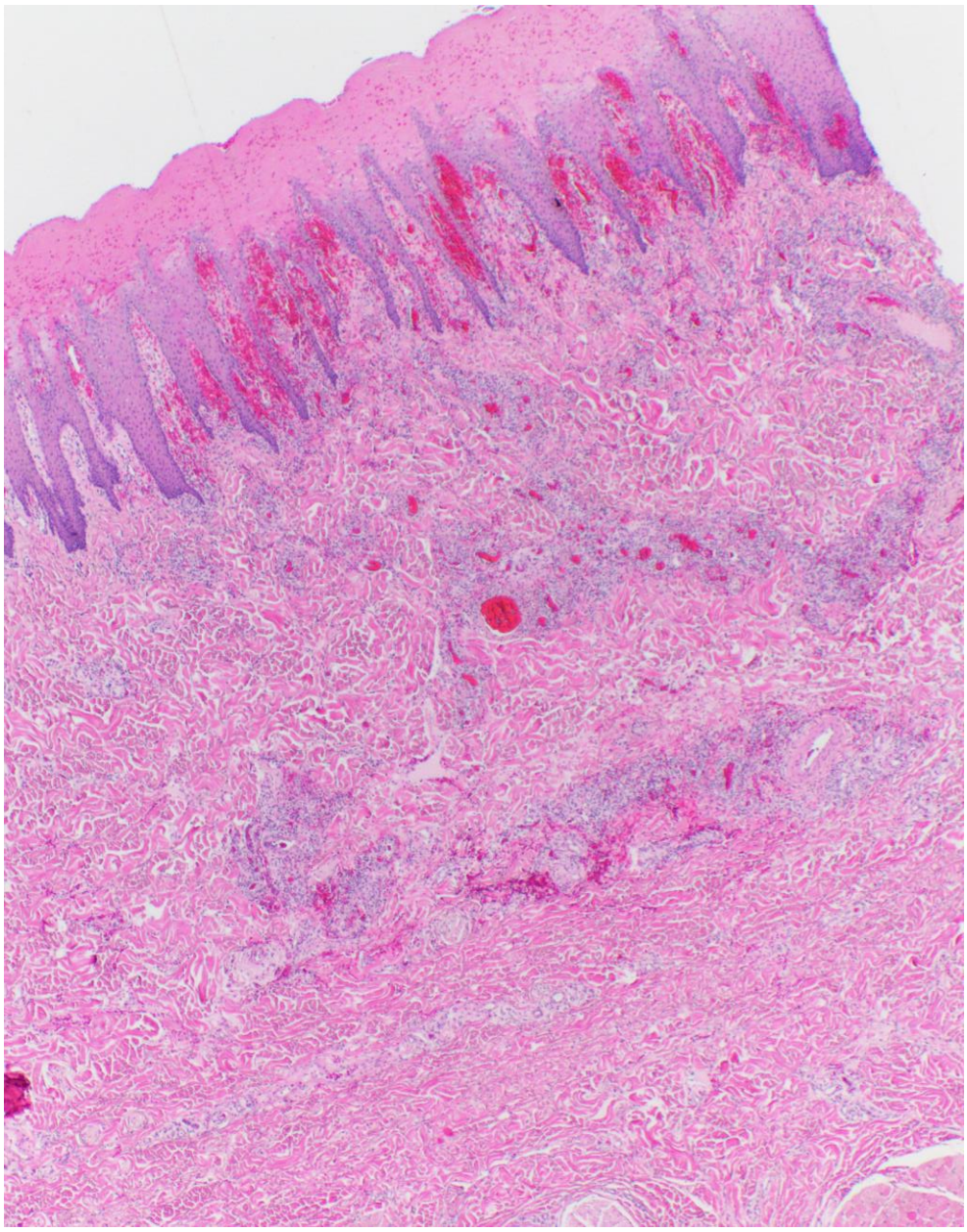

Figure 4. Horse, tongue. There is perivascular hemorrhage and inflammation.

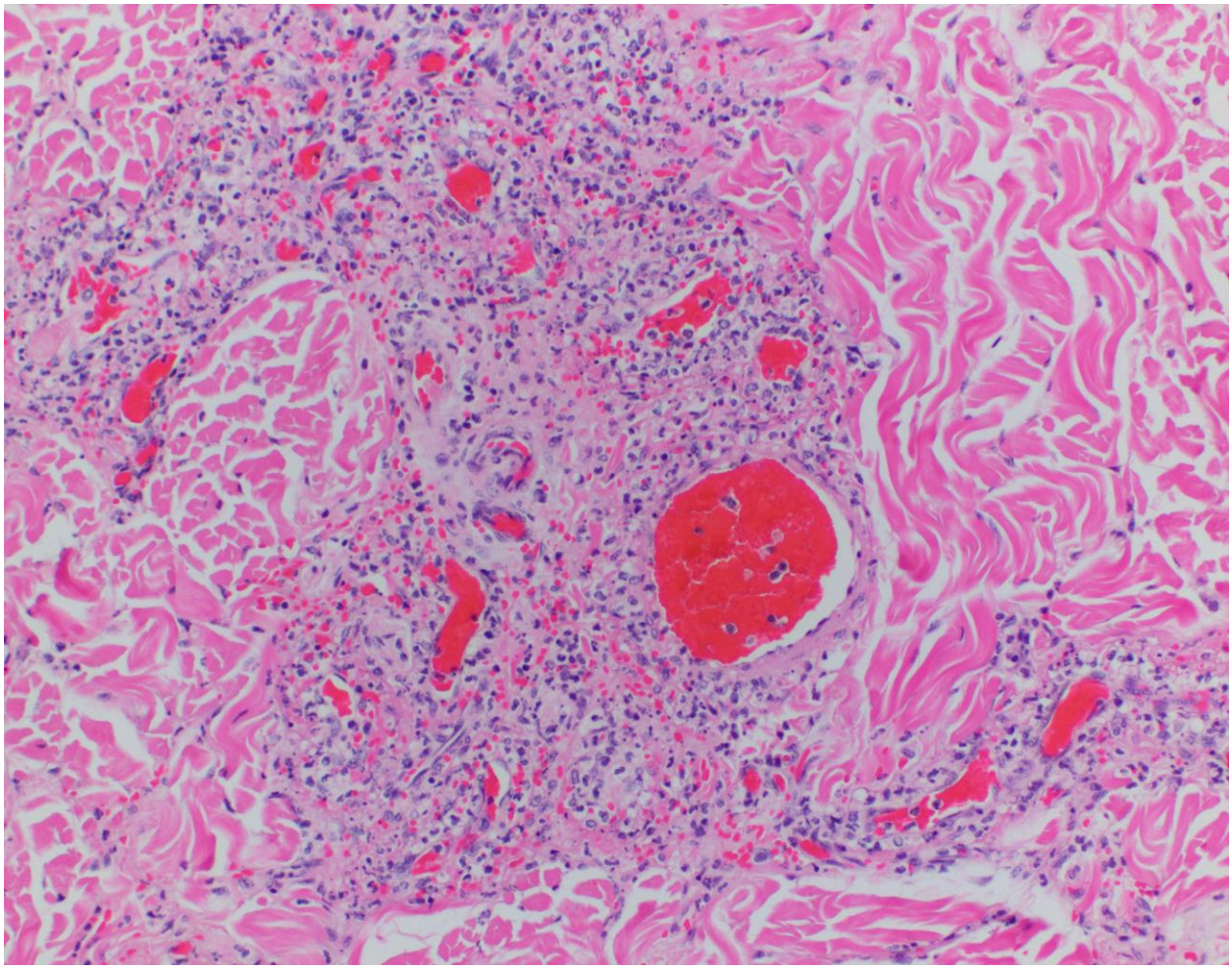

Figure 5. Horse, tongue. Vascular walls are distorted by neutrophils admixed with fibrin and karyorrhectic debris. There is minimal perivascular hemorrhage.

Follow up question #1: Microscopic description

Skin, tongue: Within the epidermis and oral mucosa, the vascular walls are expanded and distorted by intramural viable and necrotic neutrophils admixed with fibrin and karyorrhectic debris (leukocytoclastic vasculitis). Thrombi are present within affected vessels (not shown). Within the skin, the panniculus is markedly expanded by edema and moderate perivascular to interstitial hemorrhage. Within the tongue, the subepithelial stroma contains mild perivascular hemorrhage. The overlying superficial stroma and epithelium are variably necrotic with occasional loss of the surface epithelium (ulceration).

Follow up question #2: Morphologic diagnosis

Gross diagnoses:

(1) Skin (muzzle, limbs, ventrum): Severe, acute, multifocal to coalescing subcutaneous hemorrhage and edema.

(2) Mucous membranes (oral cavity, conjunctiva): Moderate to severe, acute, multifocal to coalescing submucosal hemorrhage and focal ulcer (oral cavity).

(3) Tongue: Subacute, multifocal ulcers and acute petechiae.

Microscopic diagnoses:
(1) Skin, oral mucosa, tongue: Severe, acute, diffuse leukocytoclastic vasculitis with fibrinoid necrosis, moderate to severe hemorrhage and edema, and thrombi.
(2) Tongue, oral mucosa: Acute, multifocal mucosal and submucosal necrosis with ulcers (secondary to vasculitis).

Follow up question #3: Name the condition.
Purpura hemorrhagica (PH).

Follow up question #4: Associated etiologic agent and pathogenesis.
Streptococcus equi subspecies *equi*, a gram-positive beta-haemolytic bacterium of Lancefield group C. Strangles is one of the most common bacterial infections of horses and primarily targets the upper respiratory system. Purpura hemorrhagica (PH) is a potential immune-mediated complication to exposure of *S. equi*.

Discussion:
The clinical signs in our case were attributed to the development of purpura hemorrhagica (PH), a type III hypersensitivity as a sequela to exposure to *S. equi* subsp. *equi.* Serum samples submitted for *S. equi* SeM protein ELISA were positive (1:800), consistent with a 2–3-week post exposure. Though other pathogens can be associated with similar vasculitis, the positive intermediate titer is most supportive of streptococcal-associated PH. Gross and histologic findings were also consistent with the diagnosis of PH. Grossly, the skin, oral mucosa and conjunctiva had petechiae and ecchymoses, which correlated with the mildly prolonged R time and rapid systemic decline. The R time (or reaction time) on thromboelastography correlates with the time for a fibrin clot to form; prolonged R times reflect a hypocoagulable state, often associated with clotting factor deficiencies. In our case, the prolonged R time may reflect consumption/exhaustion of available clotting factors (1).

Histologically, the generalized leukocytoclastic vasculitis within the skin and oral mucosa were a characteristic finding associated with PH. Skeletal muscle involvement may be reported in cases of PH, resulting in regional ischemic skeletal muscle necrosis, a finding that is referred to as infarctive purpura hemorrhagica (IPH). These patients can have firm and painful muscle swellings in the acute stages, which can progress to asymmetric skeletal muscle atrophy (2). IPH was not a gross or histologic feature in our case. The gastrointestinal tract was also affected in our case. Although not clinically evident, previous reports have indicated that patients with gastrointestinal tract involvement may have with colic as the chief clinical complaint (3).

PH is an immune-mediated vasculitis, a type III hypersensitivity, that leads to deposition of immune complexes in the walls of small blood vessels with consequent complement activation. The activated complement components drive the recruitment, activation, and ultimately the degranulation of peripheral blood granulocytes with subsequent generalized vascular damage and increased vascular permeability (3). PH has been commonly associated with exposure to *S. equi*, but can also be caused by other non-*S. equi* antigens, which can include bacterial

infections with organisms such as *Rhodococcus equi* and *Corynebacterium pseudotuberculosis*, or viral infections with equine influenza virus and herpesviruses (3). Clinical signs of PH are associated with vasculitis include subcutaneous edema of the head, trunk and/or extremities and petechial or ecchymotic hemorrhages of the mucous membranes, with the severity of clinical signs varying from a mild, transient reaction to a more severe, fatal disease. The risk of developing PH after exposure to *S. equi* through infection or vaccination is currently not known, but a preexisting high serum antibody titer to *S. equi* antigens or an exaggerated immunological response to infection with *S.equi* may be a predisposing factor to the development of PH (4).

References:

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*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation (DTF). These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the DTF website. (https://davisthompsonfoundation.org/diagnostic-exercise/)

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