Braz J Vet Pathol, 2024, 17(1), 72-75
DOI: https://10.24070/bjvp.1983-0246.v17i1p72-75

BJVP
Brazilian Journal of Veterinary Pathology
ISSN 1983-0246

Diagnostic Exercise from the Latin Comparative Pathology Group and the Davis-Thompson Foundation:

Multisystemic eosinophilic epitheliotropic disease in a horse

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Clinical History: A 16-year-old paint mare presented to the Texas A&M equine emergency medicine service for chronic weight loss despite an adequate appetite, inappropriate mentation, and hair loss. Clinical signs started three months prior with a history of gradual weight loss that did not respond to prophylactic oral deworming, diet change, or dental float. The horse then began displaying signs of pruritus with self-inflicted patchy alopecia primarily localized to the pigmented skin followed by rapid epaxial and gluteal muscle atrophy and fluctuant swelling around the head and neck (Fig. 1). Palpable, firm skin nodules appeared in the cervicothoracic, pectoral, axillary, and inguinal regions (Fig. 2). The mare also began exhibiting signs of colic, decreased borborygmi and dry fecal matter. Despite an initial two-day improvement with gastric decompression, anti-inflammatory medications, and supportive care, the horse became acutely neurologic with abnormal mentation and right front limb lameness/paresis. See video:

https://youtu.be/NbiVcdOOkg0

Neurologic signs significantly worsened over the next three days to pyrexia, weakened tail tone, abnormal right hind stride, generalized ataxia, head pressing, and violent outbursts. Hematology revealed a stress leukogram with a moderate mature neutrophilia (11,537 cells/µL), mild lymphopenia (695 cells/µL), and mild eosinophilia (1,390 cells/µL). Chemistry analysis revealed hyponatremia (128 mmol/L), hyperphosphatemia (5.6 mg/dl), hyperglobulinemia (4.4 g/dl), hyperbilirubinemia (4.9 mg/dl), elevated ALP (534 U/L), elevated AST (722 U/L), elevated lactic acid (32 mg/dl), and elevated creatinine kinase (1293 U/L). Ultrasound evaluation showed pleural effusion, a heterogenous liver, and an enlarged lymph node within the cecal band. Physical exam further revealed multifocal ulcerations on the buccal mucosal surfaces and severe muscle wasting. Due to the diffuse and severe nature of the disease and poor prognosis, the horse was humanely euthanized.

Necropsy Findings: Multiple thickened areas of alopecia with superficial crusting were distributed across the abdomen, pectoral, and inguinal areas, with preference to pigmented skin.

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:// davist- hompsonfoundation.org/diagnostic-exercise/).

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Figure 1. Alopecia on the poll



Figure 2. Abrasions and swelling in pectoral region.

On cut section, these thickened areas were markedly firm, mottled pale tan to red, and extended into the underlying panniculus and skeletal muscle along with expansion by edema and hemorrhage (Fig. 3). The cervical, thoracic, paraspinal, shoulder, and pectoral skeletal muscles were pale and dry (Fig. 4). Additional hemorrhage and ulcerative lesions were within the oral and urinary bladder mucosae. Diffuse lymphadenomegaly was noted throughout the body, and the retroperitoneal and peritoneal space showed marked effusion. Many firm, pale tan, rounded nodules measuring up to 1 cm diameter were found infiltrating the wall of the jejunum, omentum, and on the greater curvature of the stomach. There were 1 mm, pale tan, firm, nodules disseminated throughout the parenchyma of all liver lobes. Histologic lesions were noted in the skin, skeletal muscle (Fig. 5), liver, meninges (Fig. 6), and bone marrow (Fig. 7).

Follow Up Questions:

- *Microscopic description*
- *Morphologic diagnosis*
- *Differential diagnoses*
- *Name of the condition*
- *Diagnosis*



Figure 3. Multifocal tan, firm areas extend from the dermis into the subcutis.

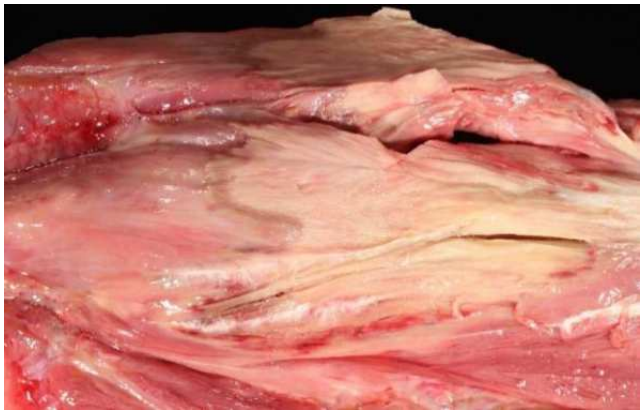


Figure 4. Multiple skeletal muscle fascicles are pale yellow and dry.

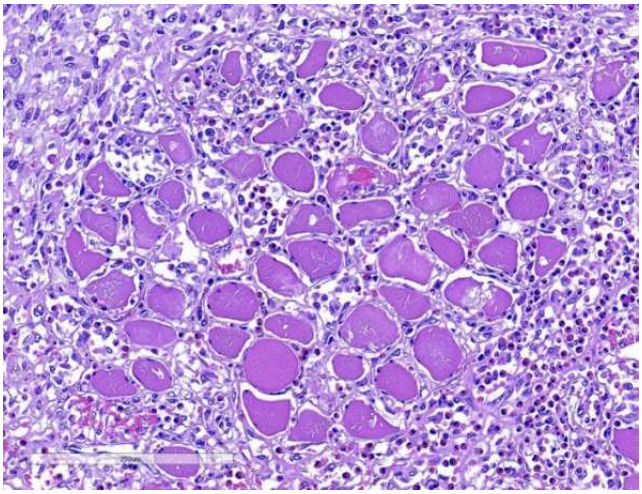


Figure 5. Skeletal muscle, H&E, 200x: myofibers are necrotic and surrounded by numerous eosinophils and macrophages.

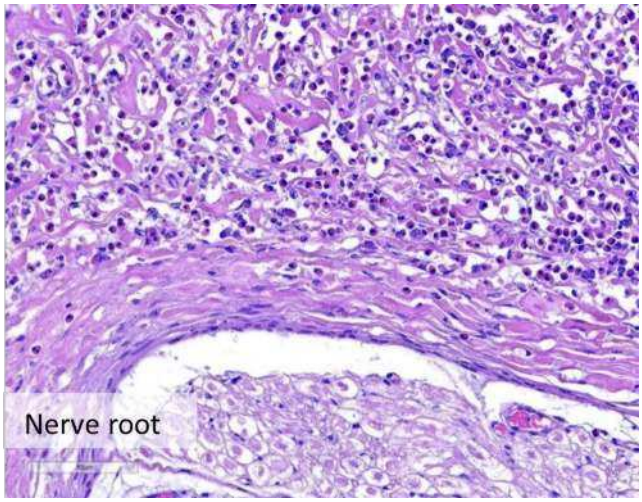


Figure 6. Spinal cord meninges, H&E, 200x: Eosinophils and macrophages are dispersed throughout the meninges and around nerve roots.

ANSWERS

Microscopic description:

Haired skin: Markedly infiltrating the dermis, deep dermis, panniculus, and skeletal muscle are numerous eosinophils, macrophages, lymphocytes, and plasma cells along with large amounts of serum protein (edema), hemorrhage, and pyknotic and karyorrhectic debris (necrosis).

Skeletal muscle: Numerous eosinophils and macrophages surround and replace skeletal myofibers in multiple muscles. Myofibers within this area often exhibit one of the following: swollen with loss of cross striation (degeneration) with increased variability in size and shape, shrunken with pyknotic nuclei and fragmented sarcoplasm (necrosis), or sarcoplasmic basophilia with internalized nuclei and rowing (regeneration).

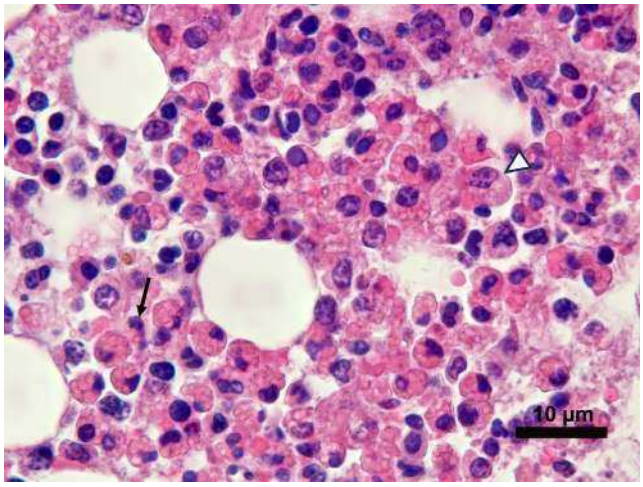


Figure 7. Bone marrow, H&E, 1000x: Numerous mature eosinophils (arrow) efface the marrow and macrophages occasionally contain erythrocytes (arrowhead).

Spinal cord and meninges: At the level of T3, the meninges and surrounding adipose tissue are infiltrated by numerous eosinophils and macrophages. The spinal cord segments at the level of T14-17 and L3-6 have axonal degeneration with digestion chambers.

Bone marrow: Distributed throughout the bone marrow is marked eosinophilic hyperplasia. Approximately 95% of the marrow space is effaced by large numbers of mature eosinophils, with loss of erythroid, myeloid, and megakaryocytic precursors. Eosinophils exhibit mild anisocytosis and anisokaryosis, with segmentation.

Special stains: The intracytoplasmic granules of most of the inflammatory cells were bright red with Luna stain and did not stain with Toluidine blue, suggesting eosinophilic origin.

Immunohistochemistry: A few CD3+ T lymphocytes and IBA-1+ macrophages were interspersed among the eosinophilic inflammation.

Morphologic diagnosis:

1. Moderate to marked, multifocal to diffuse, chronic eosinophilic and histiocytic dermatitis, panniculitis, myositis, and meningitis.
2. Moderate bone marrow myeloid hyperplasia with increased eosinophils and erythrophagocytosis.

Differential diagnoses: Differentials for eosinophilic inflammation in horses are multisystemic eosinophilic epitheliotropic disease (MEED), disseminated mast cell tumor, *Heterobilharzia americana* infection, *Pythium insidiosum* infection, or habronemiasis (1). Additional considerations for chronic, progressive exfoliative dermatitis include paraneoplastic syndrome from lymphoma (2), pemphigus foliaceus, and photosensitization from pyrrolizidine alkaloid toxins (3). Eosinophilic leukemia was excluded due to lack of immature circulating eosinophils and normal bone marrow maturation.

Name of the condition: Clinically, this horse was suspected to have an infectious or neoplastic process, such as lymphoma. However, the gross and microscopic lesions were consistent with an extensive infiltration of eosinophils in multiple organs. These findings fall within the spectrum described in multisystemic eosinophilic epitheliotropic disease (MEED).

The **diagnosis** of multisystemic eosinophilic epitheliotropic disease (MEED) relies on a process of exclusion (1,6). In this case, no identifiable etiologic agent was found on histologic examination, therefore reducing the suspicion of *Pythium insidiosum*, *Habronema* sp. or *Heterobilharzia americana*. Toluidine blue was performed, and evidence of mast cell tumor was absent. Because of the multi-organ involvement, primary dermatologic disease was deemed less likely. Immunohistochemistry for CD3 and Iba-1 were also performed to exclude lymphoma and histiocytic sarcoma.

Discussion:

Multisystemic eosinophilic epitheliotropic disease is an uncommon disease in horses that can be difficult to diagnose ante-mortem due to its unpredictable multi-organ involvement (5,6). The etiology for this condition is not yet fully established (1,3,5).

Clinical presentations of MEED, depending on organ infiltration, can vary widely. Documented cases with this disease have most reliably shown signs of chronic weight loss and frequent dermatologic abnormalities (1,3,5,6,7). Inconsistent features include pyrexia, respiratory distress, pancreatitis, coronitis, hepatitis, recurrent colic, oral ulceration, and a change in appetite (1,6,7). When eosinophils permeate the gastrointestinal tract, this condition is considered a subcategory of inflammatory bowel disease (1,4,6,7). Chemistry findings may show elevated liver and pancreatic enzymes, hypoalbuminemia, and curiously, rare eosinophilia (1,3,4). Younger, adult horses have been more frequently noted with this disease, thus suggesting a possible age predilection (2,4). Although standardbreds seem to be an overrepresented population, MEED is not limited to a specific breed (1,7).

In a live patient, skin and rectal biopsies may prove beneficial towards establishing a diagnosis. The prognosis of MEED is grave and does not respond to treatment therapy (1,3). Corticosteroids and hydroxyurea have been used to alleviate clinical signs, but lasting improvement has proved unfruitful (2,4,5).

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