Idiopathic Systemic Granulomatous Disease

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ABSTRACT: Idiopathic systemic granulomatous disease in horses is characterized by exfoliative dermatitis, severe wasting, and granulomatous inflammation of multiple organ systems. More common causes of scaling and crusting dermatoses (e.g., dermatophilosis, dermatophytosis) must be ruled out in making the diagnosis. Skin and peripheral lymph node biopsies have the greatest value in confirming the diagnosis because of the ease of collection and likelihood of showing granulomatous changes. The cause of the disease in horses is unknown but is likely an abnormal host immune response to an antigen trigger. The preferred treatment is administration of corticosteroids, but the relative benefits and risks must be weighed in horses with only cutaneous involvement. This article describes two horses with primarily cutaneous manifestations of idiopathic systemic granulomatous disease. One horse’s disease resolved after a short course of corticosteroid administration, but the other horse died from suspected therapy-associated complications.

Idiopathic systemic granulomatous disease is uncommon in horses. The disease is often called sarcoidosis, as is human systemic granulomatous disease, which has clinical and histopathologic similarities to the equine disorder. However, the term idiopathic systemic granulomatous disease is more accurate and avoids confusion with equine sarcoids.1 Equine idiopathic systemic granulomatous disease is characterized by exfoliative dermatitis, severe wasting, and granulomatous inflammation of multiple organ systems.2 Skin lesions take two forms, with the more common being scaling, crusting, and alopecia.3 The lesions usually start on the face or legs before progressing to generalized disease. Affected horses may have bilaterally symmetric lesions over the jugular furrow.4 Skin lesions may rarely include nodules or large tumor-like masses.3,4 Most affected horses develop exercise intolerance, weight loss, and a low-grade fever.2 Many affected horses also have internal organ involve-
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**Key Points**

- Idiopathic systemic granulomatous disease causes scaling and crusting that is often called sarcoidosis.
- Idiopathic systemic granulomatous disease likely occurs as a result of an abnormal host immune response to an antigen trigger.
- Horses with only cutaneous involvement may have a better prognosis, although aggressive treatment using corticosteroids can have severe adverse effects.

without signs of wasting and systemic disease. Common infectious diseases, such as dermatophilosis and dermatophytosis, should be ruled out. Less common diagnostic differentials include idiopathic seborrhea, drug reaction, contact dermatitis, pemphigus foliaceus, cutaneous and systemic lupus erythematosus, epitheliotropic lymphoma, multisystemic eosinophilic epitheliotropic disease, and toxicoses caused by arsenic, mercury, selenium, or iodide.

**DIAGNOSIS**

The diagnostic workup should include a complete blood count (CBC), fibrinogen level testing, a serum chemistry profile, and either radiography or abdominal ultrasonography, depending on the clinical signs. The CBC and serum chemistry profile results may be normal, although some affected horses have leukocytosis, mild nonregenerative anemia, hyperfibrinogenemia, hyperglobulinemia, and hypoalbuminemia. Thoracic radiography, abdominal ultrasonography, and percutaneous needle biopsies of the lungs and/or liver may be helpful in determining the presence and extent of systemic involvement. In horses with lung involvement, findings on thoracic radiographs may include interstitial infiltration.

Multiple, full-thickness punch biopsies of the affected skin and peripheral lymph nodes should be performed. Biopsy specimens should be examined by a pathologist experienced in interpreting equine skin biopsy results. The major histologic changes are aggregates of epithelioid cells and multinucleated giant cells (i.e., sarcoidal granulomas). Granulomas in the skin tend to be in the superficial and perifollicular dermis.

A diagnosis of idiopathic systemic granulomatous disease is confirmed when typical granulomatous changes are found on biopsy and other granulomatous diseases caused by fungal or bacterial agents are ruled out by culture or special stains.

**CAUSE**

The cause of the disease in horses is unknown. Many similarities to human sarcoidosis can be found. Human sarcoidosis occurs worldwide and more frequently in women and some ethnic groups. Variation of prevalence in geographic locations and populations suggests that ethnic susceptibility factors and environmental factors underlie human sarcoidosis. In humans, surgical or posttraumatic scars and tattoos many years old may develop granulomatous reactions.
Clinical Cases

Case One

A 24-year-old Thoroughbred gelding presented with a several-month history of nonpruritic skin lesions. When the horse was purchased, patchy alopecia and scaling were present on the jugular furrows and face. The lesions subsequently spread to the neck underneath the mane, dorsal rump, lateral thorax, and abdomen. The horse’s attitude, appetite, and activity level were normal, and routine vaccinations were up to date.

During examination, the gelding had a normal body condition and appeared alert with no abnormalities other than skin disease and mild lymphadenopathy of both subiliac lymph nodes. Bilaterally symmetric, multifocal, patchy alopecia with lichenification, scales, and crusts were found along both jugular furrows, the lateral thorax, the dorsal rump, and the dorsal neck beneath the mane (A–D).

Surface cytology of samples from under crusts on the rump revealed many rods, cocci, and neutrophils, whereas skin cytology results from other sites were unremarkable. Multiple deep and superficial skin scrapings tested negative for ectoparasites. Results of a fungal culture were negative. Multiple punch biopsies of affected areas were obtained.

The CBC findings, serum chemistry profile results, and electrolyte and fibrinogen levels were within normal limits. Chest radiographs showed a focal heavy bronchointerstitial pulmonary infiltrate within the caudoventral lung and two mineralized opacities within the caudodorsal thorax. Ultrasonography of the liver revealed a mild increase in echogenicity of the left lobe.
of the liver compared with that of the spleen, suggesting possible cellular infiltrates. The changes could have been age related but could also have been an indication of bacterial infection, toxic insult, or chronic inflammation. Results were negative for the following: aerobic, fungal, and mycobacterial culture as well as PCR analysis for mycobacterial DNA in the skin, liver, and lymph nodes. Fresh tissue collected and submitted to the University of California, Davis for immunohistochemistry failed to determine the lineage of the histiocytic cells in the dermis. Skin biopsies revealed moderate infiltrates of macrophages with lesser lymphocytes and occasional multinucleated giant cells in the dermis and around hair follicles and adnexal structures (E, F). The diagnosis was severe diffuse superficial and perifollicular granulomatous dermatitis. Biopsy of the liver showed diffuse, neutrophilic portal hepatitis; diffuse, moderate to marked periductular fibrosis; mild bridging fibrosis; and bile duct hyperplasia with evidence of individual hepatocellular regeneration. Moderate to marked lymphoid hyperplasia was found in the lymph node biopsy specimen. Accumulations of moderate numbers of epithelioid macrophages and multinucleated giant cells were present in the lymph node, resulting in a diagnosis of moderate granulomatous lymphadenitis and lymphoid hyperplasia (G). A diagnosis of idiopathic systemic granulomatous disease was made based on the granulomatous changes found in the skin and lymph nodes.

Therapy with dexamethasone (0.1 mg/kg PO q24h) using the 2-mg/ml injectable form was dispensed. At the 2-week recheck, the exfoliative dermatitis had markedly improved, with hair regrowth present in several areas of former alopecia (H, I). The lymph nodes were not palpable, and the rest of the physical examination results were within normal limits. The owner was told to treat the patient until clinical resolution before slowly tapering administration of dexamethasone, and a 1-month recheck was recommended.

After 27 days of dexamethasone therapy, the owner called to report that the horse had been acutely ill for less than 24 hours before being found dead in the stall.

During gross examination at necropsy, there was further improvement in the skin lesions with only mild alopecia and hyperpigmentation remaining. There was no microscopic evidence of granulomatous disease in the skin, suggesting a positive response to therapy. Bacterial and fungal pneumonia and bacterial pyelonephritis were found. A meningioma was also found and was considered an incidental finding.

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Clinical Cases (continued)

of the liver compared with that of the spleen, suggesting possible cellular infiltrates. The changes could have been age related but could also have been an indication of bacterial infection, toxic insult, or chronic inflammation. Results were negative for the following: aerobic, fungal, and mycobacterial culture as well as PCR analysis for mycobacterial DNA in the skin, liver, and lymph nodes. Fresh tissue collected and submitted to the University of California, Davis for immunohistochemistry failed to determine the lineage of the histiocytic cells in the dermis. Skin biopsies revealed moderate infiltrates of macrophages with lesser lymphocytes and occasional multinucleated giant cells in the dermis and around hair follicles and adnexal structures (E, F). The diagnosis was severe diffuse superficial and perifollicular granulomatous dermatitis. Biopsy of the liver showed diffuse, neutrophilic portal hepatitis; diffuse, moderate to marked periductular fibrosis; mild bridging fibrosis; and bile duct hyperplasia with evidence of individual hepatocellular regeneration. Moderate to marked lymphoid hyperplasia was found in the lymph node biopsy specimen. Accumulations of moderate numbers of epithelioid macrophages and multinucleated giant cells were present in the lymph node, resulting in a diagnosis of moderate granulomatous lymphadenitis and lymphoid hyperplasia (G). A diagnosis of idiopathic systemic granulomatous disease was made based on the granulomatous changes found in the skin and lymph nodes.

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Case Two
A 12-year-old Tennessee walking horse stallion was referred with a history of recent weight loss, decreased appetite, nonpruritic skin lesions, and ventral edema. The owner reported the onset of generalized papules and crusts 1 to 2 weeks after annual vaccination for Venezuelan, Eastern, and Western equine encephalomyelitis as well as tetanus. Scars from wounds that had occurred more than 2 years earlier had recently become more prominent with crusts and scales on the surface. A weight loss of 50 to 70 lb (22.7 to 31.8 kg) had occurred over the previous 2 months. A noticeable decrease in appetite had also occurred over the previous 2 weeks, with the onset of ventral abdominal and scrotal edema. The referring veterinarian had treated the patient with ceftiofur and methylprednisolone acetate injections, and improvements in the appetite and skin lesions were noted by the owner.

At presentation, the horse was in good body condition with no abnormalities other than skin disease and moderately severe pitting edema of the ventral abdomen. Multifocal areas of alopecia, crusts, and scales consistent with exfoliative dermatitis were especially severe along the ventral abdomen, on the neck along the mane, and over the dorsal rump.

Results of a CBC, serum chemistry profile, and fibrinogen level testing were within normal limits. Results of multiple skin scrapings as well as bacterial and fungal skin cultures were negative. During gastric endoscopy, one healed lesion consistent with a previous gastric ulcer was seen. Ultrasonography of the scrotum showed only edema with no evidence of herniation. A herpesvirus titer was positive at 1:640, with a fourfold rise demonstrated over a period of 7 days. An equine viral arteritis titer was negative at less than 1:4.

Multiple punch biopsy specimens of affected skin showed moderate to severe infiltrates of macrophages with lesser lymphocytes and moderate numbers of multinucleated giant cells in the dermis and around hair follicles and adnexal structures. Focal replacement of sebaceous glands by macrophages and multinucleated giant cells with necrotic sebocytes at the center of the inflammation were seen. A diagnosis of severe granulomatous dermatitis consistent with idiopathic systemic granulomatous disease was made. No biopsy specimens of other organs were obtained, so a diagnosis of systemic involvement could not be confirmed.

Treatment with oral prednisolone at 2 mg/kg/day was initiated. During a follow-up telephone conversation, the owner reported that the skin lesions and edema had resolved after 2 weeks of therapy and that administration of prednisolone was slowly tapered over another 2 weeks before being discontinued. Skin lesions had not recurred, and the patient’s attitude, appetite, and activity level were normal at follow-up 8 months after initial presentation.

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The underlying trigger for idiopathic systemic granulomatous disease in these cases is unknown. The patient in case one may have had a sequestered abscess that resulted in sepsis after immunosuppression. The abscess could have been an antigenic trigger, as could the meningioma or chronic liver disease. In the patient in case two, lesions developed after vaccination, leading to speculation regarding the role of vaccines in the pathogenesis of this disease. The horse was also diagnosed with herpesvirus infection and may have been a long-term carrier of the virus.

In the cases reported here, one horse did well after 4 weeks of oral administration of prednisolone with no recurrence of skin lesions at follow-up 8 months after initial presentation. In the other case, apparent resolution of granulomatous disease occurred with oral administration of dexamethasone at 0.1 mg/kg/day, but adverse effects of the treatment may have resulted in the horse’s death.
Experimental data support the concept that human sarcoidosis is an antigen-driven disorder in which Th1 lymphocytes react excessively against an undetermined self- or exogenous antigen. It has not been determined whether the cause is multifactorial or driven by a single antigen. Tuberculosis and other mycobacterial diseases have been considered as the major cause of human sarcoidosis because of the similar histopathology of the two entities and the increased incidence of tuberculosis in some patients with sarcoidosis. A recent report demonstrated through polymerase chain reaction (PCR) assays that mycobacterial DNA is present in 80% of cutaneous lesions of human sarcoidosis, although other studies have found no detectable mycobacterial DNA in multiple cases of lung and lymph node sarcoidosis. A viral origin has also been suggested, with herpesvirus or human immunodeficiency virus being suggested as possible causative agents.

Too few cases of equine idiopathic systemic granulomatous disease have been reported to allow valid genetic, infectious, or environmental associations to be made. The disease may be more common in the western United States, as are mycobacterial diseases in general. This has led to speculation that mycobacteria may play a role in the equine disease as well as in the human equivalent. In a series of four cases, three horses had positive *Borrelia* spp titers, with *Borrelia* spp DNA identified in one horse. The significance of this is unclear because the prevalence of positive *Borrelia* spp titers exceeds 20% of horses in endemic areas, and clinical illness associated with *Borrelia burgdorferi* infection is uncommon in horses. In a recent retrospective study of cutaneous equine sarcoidosis, PCR assays on paraffin-embedded specimens from eight horses were negative for *Mycobacteria* spp, *B. burgdorferi*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Corynebacterium pseudotuberculosis*.

Similar lesions have also been found in cattle with naturally occurring and experimentally induced hairy vetch (*Vicia sp*) toxicosis. The disease in cattle may be caused by vetch resulting from hypersensitivity to one or more plant constituents that induces the immunologic reaction. Similar generalized granulomatous disease has been found in horses that have ingested hairy vetch, but there has been no documented exposure to the plant in most reports.

Because neither culturing nor electron microscopy has revealed viral, bacterial, or fungal organisms, it is likely that idiopathic systemic granulomatous disease occurs because of an abnormal host immune response to either an ingested or inhaled environmental antigen or an underlying infectious or neoplastic process resulting in chronic antigenic stimulation.

**TREATMENT**

Response to therapy is not well documented because of the small number of case reports in the literature and the variable clinical course. The prognosis varies with chronicity and severity of the disease. Administration of corticosteroids is the preferred treatment. Immunosuppressive doses of glucocorticoids may be effective if administered early in the course of the disease before the onset of wasting. Recommended drugs and doses include prednisolone at 2 to 4 mg/kg PO q24h or dexamethasone at 0.2 to 0.4 mg/kg PO q24h. Prednisolone is preferred over prednisone in horses as shown in a recent study reporting reduced efficacy of prednisone due to poor absorption and lack of production of the active metabolite prednisolone. Corticosteroid therapy should be continued for several weeks to months with a slow taper when remission of clinical signs is achieved. There are a few reports of spontaneous remission or successful treatment with prednisolone. In a recent retrospective study, three of nine horses were euthanized soon after diagnosis, with the others surviving as long as 12 years. Of the six that survived, four had only cutaneous lesions, and the disease resolved without specific treatment in the other two horses.

It appears that horses with only cutaneous involvement have a better long-term prognosis. In less severe cases or cases that appear to regress, a single antigen trigger may no longer be present and/or the host immune response may be less reactive. Aggressive immunosuppression is probably warranted in most cases. However, the relative benefits and risks of long-term corticosteroid therapy should be weighed in cases with only cutaneous involvement because they may resolve with more conservative management.

**ACKNOWLEDGMENT**

The authors thank Dr. Shelley Newman and Phil Snow for their assistance with the photographs.

**REFERENCES**


2. Diagnostic differential(s) for idiopathic systemic granulomatous disease include(s)
   a. dermatophilosis.
   b. dermatophytosis.
   c. pemphigus foliaceus.
   d. all of the above

3. Biopsy specimens from the ________ can be easily obtained and are the most valuable in the diagnosis of idiopathic systemic granulomatous disease.
   a. lungs
   b. skin
   c. lymph nodes
   d. b and c

4. Skin biopsy specimens of horses with idiopathic systemic granulomatous disease show
   a. lymphocytic–plasmacytic infiltrate.
   b. granulomatous inflammation with multinucleated giant cells.
   c. nodular accumulations of neoplastic cells.
   d. intracellular bacteria.

5. The organ(s) most commonly involved in idiopathic systemic granulomatous disease is(are) the
   a. skin.
   b. lungs.
   c. eyes.
   d. a and b

6. A diagnostic workup for idiopathic systemic granulomatous disease might include
   a. a CBC and chemistry screen.
   b. thoracic radiography.
   c. abdominal ultrasonography.
   d. all of the above

7. Proposed causes of human sarcoidosis include
   a. infectious diseases such as tuberculosis.
   b. neoplasia.
   c. environmental pathogenesis with inorganic antigens as the trigger.
   d. a and c

8. Theories regarding the pathogenesis of equine idiopathic systemic granulomatous disease include
   a. mycobacterial infection.
   b. hairy vetch toxicosis.
9. The preferred treatment of idiopathic systemic granulomatous disease is administration of
   a. antibiotics.
   b. antifungals.
   c. corticosteroids.
   d. topical iodine.

10. The preferred oral corticosteroids in treating idiopathic systemic granulomatous disease in horses include
    a. prednisone.
    b. prednisolone.
    c. dexamethasone.
    d. b and c