






Case Report

Equine multisystemic eosinophilic epitheliotropic disease in two horses in Italy**L. Stucchi[†] , C. M. Lo Feudo[†] , C. Valli[‡], A. Serra[†], P. Riccaboni[†] , E. Zucca[†]  and F. Ferrucci^{†,*} **[†]Department of Veterinary Medicine, Università degli Studi di Milano, Lodi, Italy; and [‡]Sharjah Equine Hospital, Sharjah, UAE

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Keywords: horse; EMEED; hypereosinophilia; eosinophilic infiltrate; weight loss**Summary**

Equine multisystemic eosinophilic epitheliotropic disease (EMEED) is a rare condition characterised by eosinophilic infiltration of multiple organs. The aim of the present work was to describe two clinical cases that occurred in Italy, where no previous EMEED cases have been reported. A 2-year-old Standardbred colt was referred for poor body condition, multiple oral ulcerations, ventral and limb oedema, nasal discharge and coughing. Relative eosinophilia, increased ALP, GGT, LDH and hypoalbuminaemia were detected. Abdominal ultrasonography showed hepatomegaly and hepatic biopsy revealed eosinophilic hepatitis. After euthanasia, post-mortem examination revealed eosinophilic infiltration and fibrosis of intestinal wall, liver, pancreas and mesenteric lymph nodes. The second case was a 13-year-old pony hospitalised for acute respiratory distress, poor body condition, nasal discharge, cough and dyspnoea. Leucocytosis with relative eosinophilia was detected. Thoracic ultrasonography showed disseminated comet tail artefacts. Endoscopy of the airways revealed disseminated white nodules in the nasal cavities and nasopharynx; biopsy showed eosinophilic infiltrates. After euthanasia, post-mortem examination revealed eosinophilic infiltration of intestinal wall, liver, mediastinal lymph nodes, lungs and kidneys. Both patients presented with poor body condition, which is the most common sign of EMEED. They also showed nasal discharge, and the second case showed respiratory distress and disseminated white nodules, which have not been reported previously. In both cases, liver involvement was observed. Post-mortem examination provided the most specific findings, such as lymphadenomegaly and eosinophilic infiltration of multiple organs. Although weight loss remains the main sign of EMEED, liver and airway evaluation was extremely useful for the diagnosis in these cases.

Introduction

Equine multisystemic eosinophilic epitheliotropic disease (EMEED) is a rare, chronic condition usually affecting young horses (2–4 years of age), but potentially occurring at any age (La Perle et al., 1998). Although Standardbreds and Thoroughbreds are thought to be predisposed (Black & Mace, 2004; Sanchez, 2018; Sanford, 1989; Schumacher et al., 2000), this disease can also affect horses of other breeds (Carmalt, 2004; Henson et al., 2002; La Perle et al., 1998; Laisse et al., 2017; Latimer et al., 1996; McCue et al., 2003; Platt, 1986; Singh et al., 2006). EMEED is characterised

by eosinophilic infiltration of multiple organs. Skin, gastrointestinal tract, liver, pancreas, lungs and lymph nodes are commonly involved (Black & Mace, 2004; Bosseler et al., 2013; Carmalt, 2004; Gehlen et al., 2003; Gibson & Alders, 1987; Henson et al., 2002; Horan et al., 2013; La Perle et al., 1998; Laisse et al., 2017; Latimer et al., 1996; McCue et al., 2003; Nimmo Wilkie et al., 1985; Pass & Bolton, 1982; Platt, 1986; Sanford, 1989). The clinical presentation may vary according to the organs affected (Singh et al., 2006). Weight loss is considered the most frequent clinical sign (Bosseler et al., 2013); diarrhoea, exudative dermatitis, ulcerative coronitis and oral ulceration are also commonly detected (Sanchez, 2018; Schumacher et al., 2000). Infrequently, horses may present with respiratory distress (Singh et al., 2006). The aetiology of EMEED is still unknown, although parasitic, allergic and bacterial causes have been suggested (Sanchez, 2018). In the literature, reports of EMEED are meagre. The present work aims to describe two clinical cases that occurred in Italy where, to the authors' knowledge, no other EMEED cases have been previously reported.

Case 1**History**

A 2-year-old Standardbred colt was referred with a 2-week history of recurrent fever, multiple oral ulcerations, ventral and limb oedema and weight loss.

Physical examination

Upon admission, the patient had a poor body condition score (BCS 2) (Carroll & Huntington, 1988), several oral ulcerations (**Fig 1**) and enlarged submandibular lymph nodes. The rectal temperature was 37.7°C, the respiratory rate was 8 breaths/min, and the heart rate was 30 beats/min. The horse also presented with ventral and limb oedema, mucous nasal discharge and coughing. At the physical inspection, the abdomen was distended; the mesenteric lymph nodes were enlarged on rectal palpation.

Laboratory findings

A complete blood count was within normal limits with the exception of a relative eosinophilia (5.1%, reference 0–2%). The serum biochemistry profile showed increased activities of alkaline phosphatase (510 U/L, reference 50–150 U/L), gamma glutamyl transferase (60.6 U/L, reference 6–24 U/L) and lactate dehydrogenase (418 U/L, reference 52–240 U/L); there was hypoalbuminaemia (15 g/L, reference 24–50 g/L),



Fig 1: Oral ulceration in Case 1.

relative hypergammaglobulinaemia (35.1%, reference 8.4–29%) and hyperfibrinogenaemia (5.21 g/L, reference 2–4 g/L). A glucose absorption test was performed, and the results showed severe malabsorption (basal glucose 5.33 mmol/L, peak 6.11 mmol/L at 120 min) (Mair et al., 1991).

Diagnostic imaging

Transabdominal ultrasonography, performed with a 3.3–5 MHz transducer (Esaote) (Ceriotti et al., 2016), revealed enlargement of the liver that was evident from the 6th to the 15th intercostal spaces on the right side of the thorax. The liver margins had a rounded appearance, and the parenchyma was diffusely hyperechoic. Furthermore, bile ducts were dilated with thickened walls. Irregularity of the peritoneal surface, suggestive of fibrin deposition, and a mild increase in peritoneal fluid were also detected. Splenic and renal parenchymas were normal.

Cytological and histopathological findings

The abdominocentesis revealed a modified transudate. Macroscopically, the fluid was serosanguinous, although cytological examination did not show any significant abnormalities. An ultrasound-guided liver biopsy was performed, and the histological results showed eosinophilic chronic-active hepatitis with portal and intralobular dissecting fibrosis, lobular atrophy and cholestasis. Cytology of a bone marrow aspirate was also performed; there was a myeloid erythroid ratio of 8:1 with hyperplasia of the eosinophil line in different maturative stages with numerous free eosinophilic granules.

Diagnosis

According to clinical, diagnostic imaging and laboratory findings, a presumptive diagnosis of EMEED was made. Due to the worsening of the clinical condition and considering the poor prognosis of the disease, with the agreement of the owner, the horse was subjected to euthanasia.

Post-mortem examination

Macroscopically, post-mortem examination revealed poor body condition. A moderate amount of abdominal serofibrinous exudation was also present. Mesenteric lymph

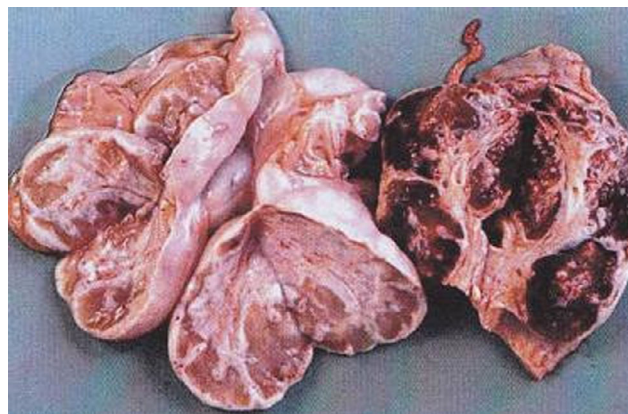


Fig 2: Section of mesenteric lymph nodes markedly enlarged with a fibrotic aspect and presence, in the central portion, of scattered mineralised nodules in Case 1.

nodes were diffusely enlarged and firm; the cut surface revealed an abundant white stroma (Fig 2). The liver was enlarged, firm and showed an irregular surface. A large adhesion between the large colon and the parietal peritoneum was also detectable. The intestinal and colon walls were moderately and diffusely thickened, while the mucosal layer did not show any alteration. The intestine contained normal ingesta. Moderate lung oedema was also detectable.

Microscopically, there was severe infiltration of eosinophils into the intestinal wall, particularly abundant in the mucosa and, to a lesser degree, the submucosa. The stroma was dilated and filled by inflammatory cells; the lymphatic vessels were also enlarged. The submucosal layer was oedematous and infiltrated by eosinophils, and to a lesser degree by lymphocytes and plasma cells; rare neutrophils were detected. The liver and pancreas showed fibrosis due to enlargement of stromal connective tissue, severely infiltrated by a large number of eosinophils and irregular proliferation of hepatic bile ducts. The mesenteric lymph nodes showed severe fibrosis and eosinophilic infiltration.

Case 2

History

A 13-year-old pony gelding known to be suffering from severe equine asthma was referred for acute respiratory distress.

Physical examination

The animal presented with bilateral serous nasal discharge, spontaneous coughing, dyspnoea, tachypnoea (40 breaths/min) and tachycardia (51 beats/min). Diffuse crackles and wheezes were detectable on auscultation of both sides of the chest. The rectal temperature was within normal limits (37.2°C), and the body condition was poor (BCS 2) (Carroll & Huntington, 1988).

Laboratory findings

The blood count showed leucocytosis (WBC: $18.4 \times 10^9/L$) with marked relative eosinophilia (10%, reference 0–2%) and increased platelets (PLT: $470 \times 10^3/L$, reference $100\text{--}350 \times 10^3/L$), prothrombin time (PT: 15.2 s, reference 8–13 s)

and activated partial thromboplastin time (APTT: 67.7 s, reference 30–60 s). Arterial blood gas analysis revealed hypoxaemia (66 mmHg, reference 90–112 mmHg) and hypercapnia (56 mmHg, reference 35–45 mmHg).

Diagnostic imaging

Thoracic ultrasonography showed disseminated comet tail artefacts on both sides of the lung. Abdominal ultrasonography showed the presence of diffuse renal and hepatic hyperechoic small (1–4 mm) rounded lesions. Radiographic examination of the caudo-dorsal aspects of the lung revealed a markedly increased interstitial pattern (Fig 3). Endoscopy of the airways demonstrated the presence of disseminated small white nodules on the mucosal surface of nasal passages and nasopharynx (Fig 4).

Cytological and histopathological findings

Cytological examination (Ferrucci et al., 2013) of bronchoalveolar lavage showed eosinophilic inflammation (24% of eosinophils).

Biopsies of the airway nodules and the liver were obtained. The airway nodules were characterised by the presence of a fibrous coat surrounding eosinophilic infiltrates. The histological evaluation of the liver biopsy demonstrated the presence of occasional eosinophilic infiltrates in the periportal and intralobular spaces.

Diagnosis

Based on clinical signs and the results of ancillary diagnostic tests, a presumptive diagnosis of EMEED was achieved. Corticosteroid treatment was proposed but, considering the poor clinical condition and the poor prognosis, with the agreement of the owner, the patient was subjected to euthanasia.

Post-mortem examination

As in the previous case, the second patient also presented in poor bodily condition. A large amount of calcified nodules were scattered in the liver, mediastinal lymph nodes, lungs and kidneys (Fig 5). Microscopically, all these organs were largely infiltrated by eosinophils. The intestine showed the presence of a subacute form of mucous enteritis with a severe eosinophilic infiltration.

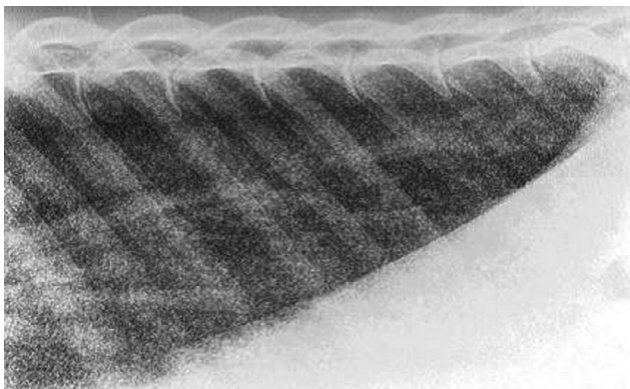


Fig 3: Radiographic image of the dorso-caudal region of the lung in Case 2, showing an increased interstitial pattern.



Fig 4: Endoscopic image of the ethmoidal region of the left nasal cavity showing the presence of the small nodules on the mucosa in Case 2.



Fig 5: Lung and mediastinal lymph node section in case 2. Both organs are infiltrated with multiple small white calcific nodules.

Discussion

Equine multisystemic eosinophilic epitheliotropic disease is a rare condition affecting several organ systems (La Perle et al., 1998; Singh et al., 2006). Less than fifty cases have been reported in the literature prior to 2013 (Pucheu-Haston & Del Piero, 2013), and only another report was described during the following four years (Laisse et al., 2017). To date, no EMEED cases have been reported in Italy.

The clinical features of the two horses in the present report were similar to those described in previously EMEED cases. Both patients presented in poor bodily condition, which is the most commonly reported clinical sign (95% of cases) (Bosseler et al., 2013). Despite the fact that skin lesions are reported as the second most common clinical sign (77%) (Carmalt, 2004; McCue et al., 2003), they were not evident in either of our patients; absence of skin lesions has been reported in only two previous cases (Latimer et al., 1996; Platt, 1986). Case 1 showed several oral ulcers, which commonly affect the lingual and buccal mucosae in EMEED cases (Schumacher et al., 2000). In a previous report, similar lesions have been described, associated with the presence of severe duodenal erosions and skin lesions (Henson et al., 2002). Both patients in this study were not febrile at the time of admission, which is consistent with previously reported

cases (Henson et al., 2002; La Perle et al., 1998; Latimer et al., 1996; Nimmo Wilkie et al., 1985; Sanford, 1989). Conversely, neither of them presented with diarrhoea, which is commonly reported in several EMEED cases (Black & Mace, 2004; Gehlen et al., 2003; Gibson & Alders, 1987; Henson et al., 2002; Laisse et al., 2017; Pass & Bolton, 1982; Platt, 1986), presumably due to malabsorption caused by eosinophilic infiltration. The ventral abdominal and limb oedema, as seen in Case 1, is an inconsistent clinical sign, but has been previously reported in some cases (Gibson & Alders, 1987; Laisse et al., 2017; Latimer et al., 1996), believed to be a consequence of the protein loss from the infiltrated small intestine.

Case 1 showed a severe malabsorption after the oral glucose absorption test in agreement with other cases (Gibson & Alders, 1987; Pass & Bolton, 1982; Platt, 1986). On the other hand, some studies showed a normal glucose absorption test (Gibson & Alders, 1987; Henson et al., 2002; La Perle et al., 1998; McCue et al., 2003). Respiratory distress and nasal discharge have been reported in a few cases (Horan et al., 2013; McCue et al., 2003; Singh et al., 2006). In both of our patients, nasal discharge was present, and, in Case 2, the most significant clinical finding was respiratory distress, which was suspected to be caused by the diffuse infiltration of the calcified nodules in the lungs, this finding has not previously been described in EMEED.

Both of our patients presented with relative eosinophilia; these data are consistent with some previous reports (Black & Mace, 2004; Bosseler et al., 2013; Carmalt, 2004; Gibson & Alders, 1987; Henson et al., 2002; Laisse et al., 2017; Latimer et al., 1996; McCue et al., 2003). However, eosinophilia is an inconsistent feature in EMEED cases. Eosinophilia is frequently associated with parasitism, hypersensitivity disorders and lymphosarcoma. Hypereosinophilic syndrome has been reported in association with T-cell neoplasia in several species, including people, dogs and cats (Barrs et al., 2002; Marchetti et al., 2005; Romero Fernández et al., 2011; Sykes et al., 2001). Some horses affected by EMEED also showed eosinophil precursors in bone marrow samples, suggesting the development of a myeloproliferative disorder (Carmalt, 2004; Singh et al., 2006). The same condition was observed also in one of our patients: Case 1, indeed, showed an increase in the maturative stages of the eosinophil series.

The most common alterations of the biochemical values in case of EMEED are hypoalbuminaemia and elevation in serum GGT and ALP activities (Sanchez, 2018), which were also observed in Case 1.

Other reported observations include liver dysfunction (40%) (Henson et al., 2002; Horan et al., 2013). In our cases, both subjects presented signs of both functional and morphologic hepatic involvements.

It should be noted that the most important and specific findings were observed – as in most of the cases in the literature – during the post-mortem examination.

Both horses showed enlarged lymph nodes; in particular, the pony showed mediastinal lymph node involvement, while the Standardbred had submandibular and mesenteric lymph node enlargement. Lymph node enlargement is a common finding among the EMEED cases (Bosseler et al., 2013; Gehlen et al., 2003; Henson et al., 2002; La Perle et al., 1998; Laisse et al., 2017; Latimer et al., 1996; Nimmo Wilkie et al., 1985; Pass & Bolton, 1982; Platt, 1986; Sanford, 1989). In particular, a marked enlargement of the mesenteric and caecocolic

lymph nodes have been reported reported by different authors (McCue et al., 2003; Nimmo Wilkie et al., 1985; Sanford, 1989). Although some authors reported the involvement of additional lymph nodes, such as submandibular (Henson et al., 2002; McCue et al., 2003), prescapular (Henson et al., 2002) and renal (Singh et al., 2006), mediastinal involvement has not previously been observed. Eosinophilic infiltrate was detected in each enlarged lymph node.

The small intestine is another common and specific site of eosinophilic infiltrates in EMEED (Black & Mace, 2004; Bosseler et al., 2013; Gehlen et al., 2003; Gibson & Alders, 1987; Henson et al., 2002; La Perle et al., 1998; Laisse et al., 2017; Latimer et al., 1996; McCue et al., 2003; Nimmo Wilkie et al., 1985; Pass & Bolton, 1982; Platt, 1986; Sanford, 1989). The other organs with an eosinophilic infiltrative pattern found in our cases – liver, pancreas, kidney, lungs – agrees with previous reports. According to the literature, the pancreas seems to be a typical organ affected by eosinophilic infiltrates in cases of EMEED (Black & Mace, 2004; Bosseler et al., 2013; La Perle et al., 1998; Laisse et al., 2017; Latimer et al., 1996; Nimmo Wilkie et al., 1985; Pass & Bolton, 1982; Platt, 1986; Sanford, 1989). Conversely, only a few cases of kidney involvement have been reported (Bosseler et al., 2013; Gibson & Alders, 1987).

The nature of the eosinophilic infiltrates in the course of EMEED has not been extensively studied yet. Although eosinophilic infiltrates are commonly related to parasitic infections or allergic responses, recently different functions have been identified. Indeed, they seem to be implicated in the pathogenesis of chronic inflammation, in particular in the development of tissue hyperplasia and fibrosis (Higuchi et al., 2008); these findings are commonly encountered in infiltrated organs of EMEED affected horses, as in the case of the liver and the pancreas of Case 1. Therefore, it has been hypothesised that the clinical and physiological alterations regarding these organs could be a consequence of hyperplasia, fibrosis and release of granules content, rather than of the eosinophilic infiltration itself (Kovalszki et al., 2012).

Moreover, different subpopulations of eosinophils have been identified, which could be related to as many different functions; for example, in human medicine, it has been observed that the eosinophilic population residing in the lungs shows several differences compared with the eosinophilic population recruited from the airways (Brosnahan, 2018). Furthermore, some eosinophils at steady state demonstrated to have a function in homeostasis regulation (homeostatic eosinophils, hEOS); these eosinophils are different from the inflammatory eosinophils (iEOS) recruited in case of infection or allergic disease (Weller & Spencer, 2017). Therefore, the evaluation of the different subpopulations infiltrating the tissues in cases of EMEED could represent a valid tool to better understand the pathophysiology of this disease.

Conclusion

These are the only cases of EMEED reported in Italy. Due to the non-specific signs of this disorder, it could be possible that this condition is still underdiagnosed. Although weight loss is considered to be the main sign, in both cases the evaluation of the liver and of the respiratory tract, in absence of skin lesions, were extremely helpful for the diagnosis.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

The manuscript reports two clinical cases, and no ethical approval has been required. All procedures have been performed following high standard of veterinary care and had the informed consent of the owner.

Authorship

L. Stucchi, F. Ferrucci and E. Zucca contributed to the clinical activities on the horses. P. Riccaboni contributed to pathological examinations. C. Lo Feudo, C. Valli and A. Serra contributed to preparation of the manuscript. All authors critically reviewed the manuscript and approved the final version.

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