Hematopoietic Neoplasias in Horses: Myeloproliferative and Lymphoproliferative Disorders

Ana MUÑOZ[1, 2]*, Cristina RIBER[1, 2], Pablo TRIGO[2] and Francisco CASTEJÓN[2]

[1]Department of Animal Medicine and Surgery, Veterinary Teaching Hospital, School of Veterinary Medicine, University of Córdoba, Campus Universitario de Rabanales, 14071 Córdoba, Spain, [2]Equine Sport Medicine Centre, CEMEDE, University of Córdoba, Córdoba, Spain

Leukemia, i.e., the neoplasia of one or more cell lines of the bone marrow, although less common than in other species, it is also reported in horses. Leukemia can be classified according to the affected cells (myeloproliferative or lymphoproliferative disorders), evolution of clinical signs (acute or chronic) and the presence or lack of abnormal cells in peripheral blood (leukemic, subleukemic and aleukemic leukemia). The main myeloproliferative disorders in horses are malignant histiocytosis and myeloid leukemia, the latter being classified as monocytic and myelomonocytic, granulocytic, primary erythrocytosis or polycythemia vera and megakaryocytic leukemia. The most common lymphoproliferative disorders in horses are lymphoid leukemia, plasma cell or multiple myeloma and lymphoma. Lymphoma is the most common hematopoietic neoplasia in horses and usually involves lymphoid organs, without leukemia, although bone marrow may be affected after metastasis. Lymphoma could be classified according to the organs involved and four main clinical categories have been established: generalized-multicentric, alimentary-gastrointestinal, mediastinal-thymic-thoracic and cutaneous. The clinical signs, hematological and clinical pathological findings, results of bone marrow aspirates, involvement of other organs, prognosis and treatment, if applicable, are presented for each type of neoplasia. This paper aims to provide a guide for equine practitioners when approaching to clinical cases with suspicion of hematopoietic neoplasia.
Key words: *anemia, blood, clinical pathology, horses, leukemia*

Leukemia is the neoplasia of one or more cell lines of the bone marrow, with distorted proliferation and development of leukocytes and their precursors. It differs from lymphoma in that leukemias arise from the bone marrow and lymphoma from the lympoid organs. Leukemia includes myeloproliferative and lymphoproliferative disorders and can be characterized according to the cell of origin (lymphoid or myeloid), the evolution of the clinical signs (acute or chronic) and the presence or absence of abnormal cells in peripheral blood circulation (leukemic, subleukemic and aleukemic leukemia). Myeloproliferative disorders are defined as a primary bone marrow dysplasia or neoplasia in which one or more blood cells of non-lymphoid lines increase in number. Lymphoproliferative disorders indicate all the neoplastic and dysplastic conditions arising from lymphoid cells. Myelodysplasic disorders refer to cells that are not truly neoplastic, but there is a suspicion of neoplasia. Myelophthisic disorders refer to the replacement of normal bone marrow by neoplastic or inflammatory tissue, with a loss of the normal architecture of bone marrow, although this condition has been uncommonly reported in horses [1, 32]. A classification of the hematopoietic neoplasias in horses is presented in Fig. 1.

The neoplastic transformation may occur at several stages of the proliferation—maturation process. Thus, neoplastic transformation of pluripotent cells might result in a massive proliferation of undifferentiated cells that are not capable of maturation (acute
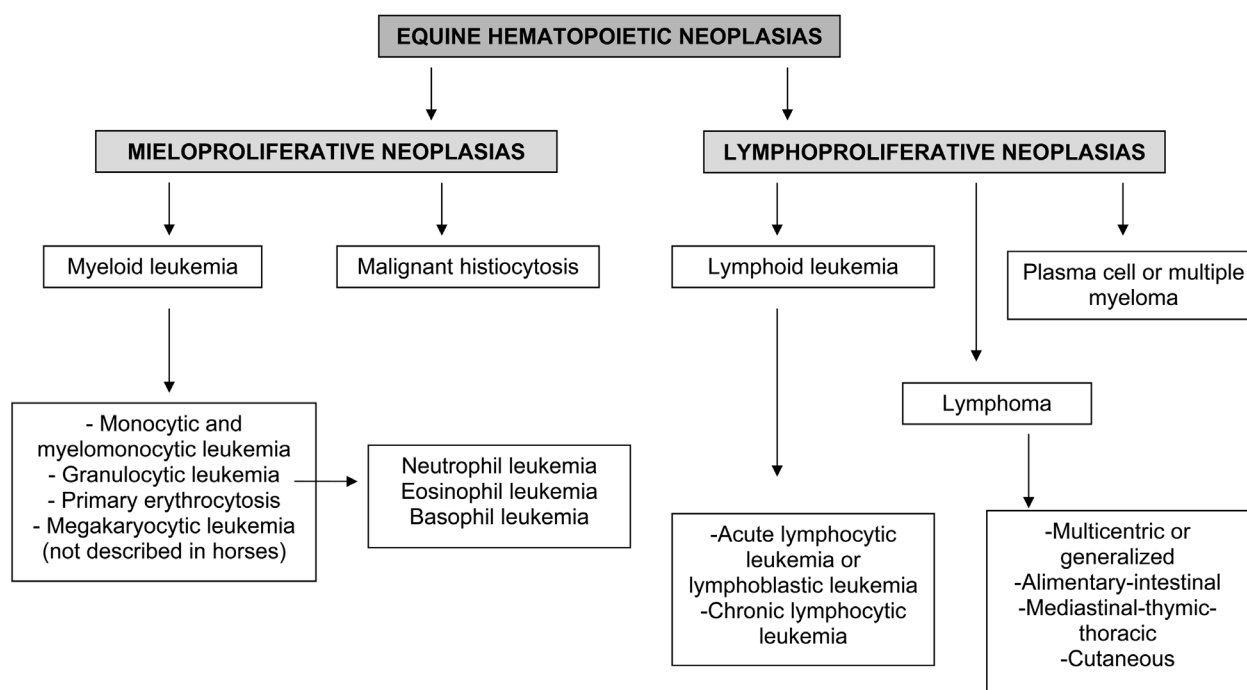
Fig. 1.   Classification of the hematopoietic neoplasias.

leukemia). An acute leukemia is an aggressive rapidly progressive condition with excessive numbers of abnormal undifferentiated or 'blast' cells which exceed 20% of bone marrow or blood cells. On the other hand, the transformation of later precursor cells might lead to an overproduction of mature, differentiated cells (chronic leukemia). A chronic leukemia is less aggressive, with slow progression. Nevertheless, the division between acute and chronic leukemia is not absolute, with cases that share features of both and some chronic type-leukemia might progress to an acute disease or 'blast cell crisis' [28]. Futhermore, in the leukemic leukemia, blood cell numbers are increased, in the subleukemic leukemia, there are an increased number of blast cells in blood, but the total number of white blood cells is within the reference range and in the aleukemic leukemia, there are no abnormal cells in the peripheral circulation, although abnormal bone marrow findings can be observed [63].

Equine Myeloproliferative Disorders

The two forms of myeloproliferative disorders described in horses are myeloid leukemia and malignant histiocytosis.

Myeloid leukemia

Myeloid leukemia in veterinary medicine has been traditionally classified into four categories: monocytic and myelomonocytic, granulocytic, primary erythrocytosis or absolute polycythemia and megakaryocytic leukemia. However, to the author's knowledge, cases of megakaryocytic leukemia have not been described in horses, although a familial megakaryocytic hypoplasia exists in Standardbred trotters [36].

Primary erythrocytosis

Primary erythrocytosis, absolute polycythemia or polycythemia vera is a myeloproliferative disorder with increased red blood cells (RBC) without concomitant increases in erythropoietin concentration. Few reports of absolute erythrocytosis without hypoxemia, and therefore, with normal erythropoietin concentrations, have been described in horses. Beech *et al.* [3] presented a case of erythrocytosis in a horse, but evidence of a myeloproliferative disorder was not found. More recently, McFarlane *et al.* [46] reported a primary erythrocytosis in a 2-year-old Arabian gelding.

Erythrocytosis causes an increase in blood viscosity and expanded blood volume. There is a generalized venous engorgement, and even superficial vessels are

Table 1. Clinical and laboratory features of equine monocytic and myelomonocytic leukemia [5–7, 9, 10, 66]

	Features
Age	Diagnosed in horses between 2 and 11 years
Breeds	Standardbreds, Thoroughbreds, Quarter Horses, Hassians
Clinical signs	Fever, decreased exercise tolerance, depression, edema, petechiation, weight loss, epistaxis, coagulopathy, pneumonia, colic
Hematology	Anemia, thrombocytopenia
	Leukocytosis, normal leukocyte number or leukopenia
Bone marrow aspirates or biopsies	Immature cells of myeloid series
	Increased myeloid: erythroid ratio

prominent at rest. The mucous membranes have a dense muddy hyperemic color, associated with a marked decrease in cardiac output and poor tissue perfusion. The consequences are lethargy and weight loss. Epistaxis, gastrointestinal hemorrhage or thrombotic complications including laminitis, focal cutaneous necrosis and renal failure might occur [35].

Monocytic and myelomonocytic leukemia

This type of leukemia has been diagnosed in horses aged between 2 and 11 years, and of different breeds, such as Standardbred trotters, Thoroughbreds, Quarter Horses, and Hassians [6, 10, 60, 66] (Table 1). A great variety of clinical signs have been described in these horses, including fever, decreased exercise tolerance, unresponsive infection to antimicrobial therapy, anemia, depression, edema, petechiation, weight loss, epistaxis, coagulopathy, pneumonia and colic [5–7, 10, 66]. Edema, mucosal petechial hemorrhage and coagulopathy might be related to the large cell volume and limited deformability of the neoplastic population, leading to microvascular aggregation and extravasation [7].

The most common hematologic findings in monocytic and myelomonocytic leukemias are anemia, thrombocytopenia, and leukocytosis or normal WBC numbers, with blast cells or monocytoid cells in cases of leukemic leukemia [10]. In subleukemic leukemias, leukopenia is more common [5]. Bone marrow aspirates reveal abundant immature cells of the myeloid series and an elevated myeloid-to-erythroid ratio [5, 7, 9]. Brumbaugh *et al.* [9] presented the case of a 5-year-old Quarter Horse with a bone marrow myeloid-to-erythroid ratio of 30.5:1, absence of megakaryocytes and severe clotting disorders. Bienzle *et al.* [5] described absolute megakaryocytic hypoplasia, erythroid hypoplasia, depletion of granulocytic reserve, predominance of immature blast-like leukocytes and a myeloid-to-erythroid ratio of 50:1.

Cytochemistry is essential to classify monocytic leukemias [7, 9]. If the abnormal cells stain positive with Sudan Black B, cells are likely of myeloid lineage, whereas if they stain positive with α-naphthyl-acetate esterase, they are consistent with a monocytic line. Additionally, electron microscopy might reveal that monocytoid cells resemble peripheral blood monocytes [5].

Myelomonocytic leukemia in horses has been treated with a 21-day regime of cytosine arabinoside (10 mg/m^2, twice daily), but the treatment did not prevent the rapid progression of the neoplastic disease [66]. Cytarabine has been also used, together with corticoids in order to attenuate depression and loss of appetite derived from cytarabine therapy. However, this treatment was also unsuccessful [10].

Granulocytic leukemia

Granulocytic leukemia can be subdivided into neutrophil, eosinophil, or basophil leukemia. In the literature, both acute and chronic cases of granulocytic leukemia, mainly neutrophilic leukemia have been described in horses [29, 41, 49, 64]. To the authors' knowledge, there is only a report of an eosinophilic myeloproliferative disorder in horses [49]. These authors reported the case of a 10-month-old Standardbred colt, with edema and hemorrhagic diathesis. The colt had severe thrombocytopenia, anemia, mild hypoproteinemia and marked eosinophilia, with immature or atypical circulating eosinophils. Bone marrow aspirate showed atypical eosinophil precursors, with few erythroid precursors, and no megakaryocytes [49].

Neutrophilic leukemia has been described in young and mature horses, with non-specific clinical signs, including poor performance, progressive loss of physical condition, anorexia, limb edema, fever,

Table 2.   Clinical and laboratory features of equine granulocytic (neutrophilic) leukemia [29, 41, 49, 64]

	Features
Age	Both young and mature horses
Clinical signs	Poor performance, progressive loss of body condition, anorexia, edema, fever, petechiation, epistaxis, recurring infections
Hematology	Progressive normocytic normochromic anemia, anisocytosis, metarubricytes and rubricytes in blood
	Prolonged neutropenia or neutrophilia with bizarre immature granulocytic cells and blast cells
	Thrombocytopenia
Clinical pathology	Hypoproteinemia with hypoalbuminemia
Bone marrow aspirates or biopsies	Increase in myeloid:erythroid ratio
	Dysplastic myeloid cells

coagulation disorders (petechiation, episcleral hemorrhage, and epistaxis), ictericia due to hemolytic anemia and recurring, poorly responding infections [29, 41, 63, 64]. Clinical and laboratorial characteristics of neutrophilic leukemia in horses are summarized in Table 2.

A progressive normocytic normochromic anemia appears to be a consistent finding in horses with neutrophil leukemia [29, 41, 63, 64]. Searcy and Orr [64] in a Quarter Horse found a marked anisocytosis with occasional giant RBC, and presence of metarubricytes and rubricytes in the bloodstream, reflecting an asynchronous maturation of nucleus and cytoplasm in these cells. More recently, Johansson *et al.* [29] reported a chronic granulocytic anemia in a 4-year-old Swedish Warmblood, with abnormal circulating RBC, mild poikilocytosis, marked anisocytosis and presence of nucleated RBC in blood. Immature RBCs in peripheral blood are rare in horses and in this case, it was attributed to the neoplastic alterations in bone marrow [29]. Other putative cause of the anemia in these horses could be the hemorrhage secondary to coagulopathy because of thrombocytopenia and bleeding disorders and/or secondary to immune-mediated mechanisms [29, 63].

The combination of a prolonged neutropenia or neutrophilia with release of bizarre immature cells of the granulocytic series and blast cells (myelocytes and metamyelocytes) plus concurrent dyserythropoiesis and thrombocytopenia is highly suggestive of granulocytic leukemia. Searcy and Orr [64] found that many of the neutrophils appear to have mature cytoplasm but round nuclei and this apparent failure of nuclear segmentation resembled that of Pelger-Huet cells. However, more recently, Johansson *et al.* [29] did

not identify this type of cells in a horse with chronic neutrophil leukemia, in which there rather was a tendency toward hypersegmentation of the mature granulocyte nuclei and an absence of band neutrophils.

Marked thrombocytopenia is also a feature of reported cases of granulocytic leukemia [29, 63, 64]. This finding is consistent with an impeded production in the bone marrow because of the marked myelogenous proliferation. Occasionally, giant platelets can be found in peripheral blood [64].

The only clinical pathology data altered in granulocytic leukemia in horses is hypoproteinemia associated with hypoalbuminemia [29]. Bone marrow aspiration demonstrated a mild increase in myeloid: erythroid ratio, with a few immature and dysplastic myeloid cells [29].

In knowledge of the authors, no feasible treatments are currently available.

Malignant histiocytosis
Malignant histiocytosis is a rapidly progressive myeloproliferative disease with proliferation of mononuclear phagocytes that are intermediate in differentiation between monoblasts and tissue histiocytes. Histiocytes are a subset of WBC that occur in tissues and serve as integral role in functioning of the immune system. This type of neoplasia has been described in dogs [8, 20], cats [13, 14] and there is one report in an Arabian filly [39]. This filly presented loss of body weight, anorexia and fever. Other abnormal findings were thrombocytopenia, anemia, and leukopenia with marked neutropenia but with normal lymphocytic and monocytic series. Large histiocytic cells were seen in lymph nodes and in bone marrow.

Table 3. Clinical and laboratory features of equine lymphocytic leukemia [4, 15, 40, 58]

	Features
Age	3–20 years
Clinical signs	Anorexia, weight loss, intermittent fever, depression, petechial hemorrhage, mild colic, non-painful pitting edema, enlargement of lymph nodes, tachycardia, tachypnea, soft fecal consistency
Hematology	Non-regenerative anemia
	Leukocytosis in case of leukemic leukemia
	Lymphoblasts in blood
	Thrombocytopenia
Clinical pathology	Hyponatremia, hypokalemia, hypochloremia, hyperphosphatemia.
	Increased alkaline phosphatise, γ-glutamyl transferase and aspartate aminotransferase
	Hypertrigliceridemia
	Azotemia, hypoalbuminemia, hyperglobulinemia and increased creatinine concentrations.
Bone marrow aspirates or biopsies	Blast cells of lymphoid origin
Involvement of other organs	Lymph nodes, spleen, lungs, heart, liver, kidneys, gastrointestinal system, myocardium
Diagnostic challenge	To differentiate from lymphoma with bone marrow infiltration

Cytochemical stains have been used in order to define the cell populations involved. The cells were positive to α-naphthyl-butyrate esterase, which suggested that they were of a monocytic (i.e. histiocytic) or megakaryocytic origin and to lyzozyme, which is the preferred stain in human malignant histiocytosis [39].

Additionally, an involvement of the medullar portion of the lymph nodes, the red pulp of the spleen, and the sinusoids of the liver as well as the bone marrow has been reported, and this pattern of distribution of the neoplastic cells is considered characteristic of malignant histiocytosis. These cells are variable in size with large multinucleated giant cells and anaplastic histiocytes have pleomorphic nuclei and abundant pale-staining cytoplasm, with hematopoietic cells phagocytosis [39].

Lymphoproliferative Disorders

The three lymphoproliferative disorders described in horses are lymphoid leukemia, plasma cell myeloma and lymphoma.

Lymphoid leukemia

Lymphoid leukemia is the neoplastic proliferation of lymphocytes, which can be classified into two categories: lymphocytic leukemia or chronic lymphocytic leukemia, when the predominant cell type is the mature lymphocyte and lymphoblastic leukemia or acute lymphocytic leukemia, when the predominant cell type is the immature lymphocyte. Leukemic, subleukemic and aleukemic lymphoid leukemias have been diagnosed in horses. However, primary lymphoid leukemias are rare and they should be differentiated from advanced lymphoma with a leukemic phase [15, 63].

Clinical characteristics of lymphoid leukemia are presented in Table 3. The range of age reported in the literature is very wide, from 3 [40] to 20 years [15]. Similarly to other neoplastic conditions, clinical signs are non-specific and include anorexia, weight loss, intermittent fever, depression, petechial hemorrhages, mild colic, non-painful pitting edema, enlargement of lymph nodes, tachycardia, tachypnea, and soft fecal consistency [4, 15, 40, 58, 63].

The results of the hematological analysis are variable. Dascanio *et al.* [15] observed marked leukocytosis in two horses with lymphocytic leukemia, lymphocytosis, thrombocytopenia and increased band cells in one horse. The peripheral lymphocytes of one of these horses were similar in appearance to normal small equine lymphocytes, whereas the other horse showed slight larger lymphocytes. On the contrary, Lester *et al.* [40] found a non-regenerative anemia, with neutropenia, thrombocytopenia and normal lymphocyte count. One of horses of this report had lymphoblast in blood smears [40]. Therefore, the

presence or absence of lymphocytosis would depend on whether the neoplasia is leukemic, subleukemic or aleukemic.

Different stains could be used for cytochemical reaction profiling in order to distinguish between the different types of hematopoietic neoplasia (granulocytic, monocytic or lymphocytic). The most commonly used are hematoxylin and eosin, toluidine blue, periodic acid-Schiff stains, phosphotungstic acid-hematoxylin, Wright-Giemsa stains, peroxidase, Sudan Black B, acid phosphatase, alkaline phosphatase, chloroacetate esterase and α-naphthyl-butyrate esterase. Cells from peripheral blood, bone marrow and different organs in the reported cases of lymphocytic leukemia were uniformly negative to most of these stains (peroxidase, Sudan Black B, α-naphthyl-butyrate esterase, acid phosphatase, periodic acid-Schiff stain, chloroacetate esterase and leukocyte alkaline phosphatase), indicating their lymphoid origin [63].

Dascanio *et al.* [15] isolated blood lymphocytes from horses with lymphocytic leukemia and characterized these cells using a panel of monoclonal antibodies to identify equine lymphocyte subpopulations and major histocompatibility complex antigens. Further, blood lymphocytes were subjected to mitogen-induced lymphocyte blastogenesis using B-cell mitogen lipopolysaccharide and T-cell mitogen concanavalin A and phytohemagglutinin. According to their results, one horse presented characteristics of leukemia of T lymphocytes and the other, characteristics of B lymphocytes. In human beings, only 2–5% of the patients with chronic lymphocytic leukemia have characteristics of T lymphocytes [57].

The alterations in clinical pathology data reported in horses with lymphocytic leukemia are hyponatremia and hypokalemia, increased alkaline phosphatase, gamma glutamyl transferase and aspartate aminotransferase and hypertrigliceridemia [40], hyperphosphatemia, azotemia, hypoalbuminemia, hyperglobulinemia and increased creatinine concentrations [15]. These last authors described a tall, narrow-based peak in the gamma region identified by serum protein electrophoresis. An increase in IgG concentrations, together with a decrease in IgA and IgM concentrations was confirmed. In addition, in this report, one horse developed proteinuria and the electrophoretic study showed a tall, narrow-based gamma globulin spike, which accounted for 80% of the urine protein, with small peaks of albumin, alpha, and beta proteins [15].

Lester *et al.* [40] described the cytology of bone marrow aspirates from three horses with primary lymphoid leukemia and pancytopenia. One horse had 75% blast cells of lymphoid origin, another showed increased myelofibrosis and a relative increase in lymphocytes and the third horse had decreased numbers of myeloid and erythroid precursors, no megakaryocytes, and a large number of poorly differentiated blast cells consistent with a lymphoid origin [40].

Neoplastic infiltrations have been found in different organs in lymphocytic leukemias, such as lymph nodes, spleen, lungs, heart, liver, kidneys, gastrointestinal system and myocardium [15, 40]. If the lymph nodes show neoplastic hematopoietic cells, it is a challenge to determine whether the problem is a primary lymphocytic leukemia or a lymphoma with a leukemic phase (secondary lymphocytic leukemia). Both processes can be differentiated by the degree of involvement of the peripheral tissues as compared with the involvement of the bone marrow, and by the distribution of the neoplastic cells within the marrow. Primary leukemias have lesser involvement of tissues than lymphomas. In addition, primary leukemias tend to have a more diffuse involvement of the bone marrow, whereas secondary leukemias often have focal aggregates of neoplastic cells lying adjacent to the paratrabecular blood sinuses [56].

Plasma cell myeloma

Multiple or plasma cell myeloma is a neoplastic proliferation of plasma cells or plasmacytoid lymphocytes (i.e. large B lymphocytes with some characteristics of plasma cells) that primarily involves the bone marrow but might originate from extramedullary locations. This neoplasia results in an uncontrolled production of Ig or Ig fragment (named paraprotein or M-component) from a single plasma cell clone, detectable by serum and/or urine electrophoresis [2, 18]. The paraprotein may be complete Ig, free light chain, light chain fragments or polymers, or partial Ig missing one or both chains [38]. It is an uncommon neoplasia, and it has been reported in several species, including human beings, cats, dogs, and horses [2, 18, 21, 25, 34, 44, 45, 55].

The minimum criteria for the diagnosis of multiple myeloma in human beings include a combination of one major and one minor criteria or a combination of three minor criteria [23]. Major criteria include the

Table 4. Clinical and laboratory features of equine plasma cell myeloma [2, 18, 25, 34, 44, 55]

	Features
Age	3 months–25 years (mean: 11 years)
Breeds	Arabians, Quarter Horses, Morgans, Tennessee Walking Horses, American Paints
Gender	Both females and males
Clinical signs	Weight loss, anorexia
	Limb edema, increased susceptibility to bacterial infections, bleeding (epistaxis), enlarged lymph nodes.
	Radiculopathies, back pain, weakness, paralysis and/or ataxia of hind limbs, bone pain.
Hematology	Normocytic, normochromic anemia
	Leukopenia
	Thrombocytopenia
Clinical pathology	Hyperproteinemia, hypoalbuminemia, monoclonal gammopathies (mainly IgG), decrease of other immunoglobulin classes.
	Proteinuria, azotemia, hyponatremia, hypocholesterolemia, hypercalcemia
Radiography	Focal bone lysis, periosteal reaction, sclerosis and diffuse osteoporosis. Pathological fractures.
Bone marrow aspirates or biopsies	Bone marrow plasmocytosis
Involvement of other organs	
Criteria for the diagnosis	Major criteria: 1) Bone marrow plasmocytosis; 2) plasmocytoma in biopsy; 3) Identification of M-component or paraprotein in serum and/or urine.
	Minor criteria: 1) serum or urine M-component; 2) osteolytic bone lesions; 3) 50% or greater decrease in normal immunoglobulin classes.

detection of bone marrow plasmocytosis (more than 30%), a diagnosis of plasmocytoma on biopsy and the identification of M-component or paraprotein in the serum and/or urine [23]. Minor criteria include marrow plasmocytosis (less than 30%), serum or urine M-component in lower concentrations, osteolytic bone lesions and a 50% or greater decrease in the concentrations of normal Ig classes [23].

The clinical characteristics are described in Table 4. Horses diagnosed with this condition range in age from 3 months to 25 years, with a mean age of 11 years. It has been described in different horse breeds, such as Arabians, Quarter Horses, Morgans, Tennessee Walking Horses, and American Paints [2, 18, 25, 34, 44, 55]. It seems that both male and female are represented equally, although the reduced numbers of described cases makes difficult to get conclusions concerning the differences between genders in prevalence of this neoplasia.

The clinical signs of multiple myeloma might vary with the level of plasma cell proliferation, the location and the spread of the neoplasia, and the nature and the extent of the paraproteinemia [55]. The most common complaint in the initial examination of horses with multiple myeloma is weight loss [2, 18, 25, 34, 44]. Limb edema is also common in these horses [18, 34, 55], although their pathophysiologic mechanisms are unknown. It has been suggested that paraprotein-induced hypervolemia or blood hyperviscosity or both facts could be contributory. Increased vascular permeability has been proposed as the cause of edema with osteosclerotic myeloma in human beings [65].

It has been demonstrated that human patients with myeloma are more susceptible to bacterial infections [27] and the same appears to be true in horses. These animals show bacterial respiratory tract infection [18, 25, 55] and one case of arythenoid chondritis has also been described [18]. The suspected reasons for this increased susceptibility to infections are deficiency of normal Ig, diminished bone marrow reserves, impaired neutrophil phagocytosis and a defective complement system [18, 51, 55].

Radiculopathies derived from vertebral lesions are common neurological complications of myeloma in human patients, and also compressive extradural masses can produce back pain, weakness, and paralysis of the lower extremities and fecal or urinary incontinence in 10% of human patients. Edwards *et al.* [18] described rear leg paresis and/or ataxia in three horses with multiple myeloma. In one horse, spinal canal was examined post-mortem and spinal cord compression caused by an extradural tumor mass was

found [18].

Bleeding is a common clinical sign of myeloma in humans [31, 37] and epistaxis has been also found in horses [18, 25]. The primary cause of bleeding seems to be thrombocytopenia, although a paraprotein-mediated functional inhibition of platelets and coagulation factors has been reported [53]. Hyperviscosity is a well-known complication of myeloma in humans, and it results in sluggish capillary blood flow and expanded plasma volume [38]. The clinical signs derived from hyperviscosity include bleeding, retinopathy with decreased vision, prominent choroidal vasculature, neurological dysfunction, congestive heart failure and, swelling of all fetlock joints [18]. Palpable lymphadenopathy has been reported in two horses [18] and it is uncommon in human patients [31, 37].

Bone pain is the most common presenting complaint in human patients [31, 37], but it is infrequently recognized in horses with myelomas [18, 55].

A normocytic, normochromic anemia eventually develops in almost all people and horses with multiple myeloma [18, 25, 34, 55]. The main causes involved in anemia are blood loss, diminished erythropoiesis secondary to myelophtisis and infection, and plasma volume expansion secondary to the osmotic effect of the paraprotein [18, 37, 55]. However, there are some reports of macrocytic anemia, which could have been associated with regeneration and/or dyserythrocytosis because of myelophthisis [18, 34]. Folate deficiency secondary to enhanced use by the tumor is the probable mechanism of macrocytosis in human patients [37]. Pronounced rouleaux formation of RBC has been described in over half of human patients [31, 37], but it is difficult to observe in horses with myeloma because of the normal appearance of rouleaux in equine blood smears [18].

Leukopenia and thrombocytopenia although have been reported in horses with myeloma [18, 25, 34, 55], becomes more evident as the disease progresses, owing to progressive myelophthisis [31, 37, 55]. Circulating plasma cells have been found in human patients and some of these cases meet the inclusion of plasma cell leukemia (blood plasmocytosis$> 2,000/\mu l$ and at least 20% of the differential count) [31, 37].

Hyperproteinemia, with hypoalbuminemia and hyperglobulinemia, are characteristics of human and horse myelomas, but they are not invariable features [2, 18, 51, 55]. The mechanisms of the hypoalbuminemia are unknown, but their severity in human patients

correlated with the extent of tumor proliferation and, therefore, is of diagnostic and prognostic value [12]. There is a report of one horse with a solitary osseous lesion that was normoproteinemic. This fact could have resulted from the tumor cells being nonsecretory [18].

Hyperglobulinemia is common in horses with myeloma, with monoclonal gammopathies [18, 44, 55]. In horses, the main differential diagnosis for monoclonal gammopathies includes multiple myelomas, malignant lymphomas and so-called benign monoclonal gammopathies [18, 33, 69]. In horses and human beings, subclasses of IgG are the predominant paraproteins associated with myeloma, whereas in dogs IgG- and IgA- type multiple myelomas are of equal prevalence [2, 18, 21, 37, 45]. Barton *et al.* [2] and Pusterla *et al.* [55] described several cases of multiple myeloma with IgA gammopathy in horses. Barton *et al.* [2] presented a case of multiple myeloma with polyclonal gammopathy. Polyclonal gammopathy is commonly associated with chronic inflammation or infection, chronic liver disease, neoplasia, and other conditions that cause nonspecific antigenic stimulation and activation of large numbers of B-cell clones, with synthesis of antibodies from all Ig types. In the report of Barton *et al.* [2], later in the course of the disease, presumably when the synthesis of a single Ig class from the neoplastic plasma cell clone exceeded the production of other Igs, a monoclonal gammopathy was observed. By means of radial immunodiffusion, a marked increase in IgA concentrations was identified [2].

Most of the reports in horses with multiple myeloma have described a decrease in other Ig types, with could have been associated with decreased synthesis and/or accelerated catabolism [18].

Proteinuria (proteinuria of Bence-Jones) is also commonly found in human beings, but less commonly in horses with myeloma [18, 21, 37, 55]. Renal insufficiency is common in human beings with myeloma and it is considered the second cause of death. The renal lesions may induce either a primary glomerular disease or a cast nephropathy, and the predominant form of the renal disease probably is dependent on the size and isoelectric point of the paraprotein. Direct infiltration by the neoplastic cells can also interfere with renal function. However, azotemia is not common in horses with myeloma and therefore, it is thought that renal failure is not a common cause of clinical disease or mortality in horses,

despite the proteinuria [18, 55]. The alkaline pH of horse urine may help to prevent the formation of tubular protein casts by reducing the coprecipitation of Tamm-Horsfall proteins and myeloma paraproteins [55].

Edwards *et al.* [18] described three horses with myeloma with hyponatremia. True hyponatremia has been reported in human beings with myeloma [48]. Suggested mechanisms are displacement of Na ions by cationic paraproteins and decreased plasma water secondary to unusual hydration characteristics of paraproteins [18]. There was one description of a horse with myeloma and hypocholesterolemia that could have been due to anorexia and weight loss [18], although other factors may be involved.

Approximately one-third of the human patients with myeloma are hypercalcemic, although hypercalcemia is not a consistent feature in horses [18]. Hypercalcemia of malignancy has been reported in association with several neoplastic diseases in equids, such as lymphoma, squamous cell carcinoma, adrenocortical carcinoma, and gastric carcinoma [19, 43]. Several mechanisms have been proposed to explain this hypercalcemia, including lytic bone metastases, true hyperparathyroidism occurring simultaneously with the malignant disease, tumor-produced prostaglandins, and tumor-produced osteoclast activating factor [51]. Other reason of hypercalcemia is the increased release of parathyroid hormone-related protein (PTHrP) which can be synthesized by normal cells activated by the presence of a malignancy or by neoplastic cells [2]. In many neoplastic diseases, there is a direct correlation between PTHrP and serum Ca concentrations [70]. As a consequence, the concurrent demonstration of high serum PTHrP concentration and hyperglobulinemia in a horse with hypercalcemia could be highly suspicious of myeloma [2].

The most common coagulation test abnormality in human myeloma patients is a prolongation of the thrombin time [62]. This finding is associated with paraprotein-fibrin binding that impairs fibrin monomer polymerization. Additionally, platelet dysfunction has been linked with paraprotein coating of thrombocytes. In fact, in one horse with myeloma, Edwards *et al.* [18] described a coagulopathy with prolonged bleeding time and decreased platelet adhesion and clot retraction.

Radiological changes have been described in myeloma in different species [18, 51]. The most common lesion observed in horses with myeloma is a punctate, focal bone lysis. Other lesions are periosteal reaction, sclerosis and diffuse osteoporosis. Pathological fractures are also common radiographic findings in myeloma in human beings [51].

Plasmocytosis in the bone marrow is one of the criteria for multiple myeloma in human beings [51] and it has been described also in horses [44, 45]. However, marrow plasmocytosis has been found in diseases other than myeloma [37]. The proportion of plasma cells in a bone marrow aspirate can range from less than 5% to almost 100%, because the involvement of the marrow in myelomas is usually focal rather than diffuse [18, 34].

Negative prognostic indicators for plasma cell myeloma in other species include the existence of Bence-Jones proteinuria, plasma cell leukemia, pancytopenia, renal azotemia and hypercalcemia. The lifespan of horses diagnosed with myeloma usually does not exceed two years, and most of them are euthanized owing to the advanced stage of the disease in the moment of the diagnosis [55].

The treatment is not practical but one case with melaphan (at 7 mg/m^2), SID for 5 days every three weeks resulted in remission/ stabilization of signs that lasted for up to a year. Supportive broad-spectrum antibiotics are also necessary [35].

Lymphoma

Lymphoma is a neoplasia of lymphoid organs, such as lymph nodes, spleen and gut-associated lymphoid tissue, and generally refers to solid tumors without leukemia, although bone marrow may be involved after metastasis and differential diagnosis of lymphocytic leukemia should be made [63]. Although lymphoma is not common in horses, it is the most frequent malignant neoplasm encountered [47, 54, 63]. The incidence of this neoplasia is of 0.7–3.2/100,000 horses [35, 61]. Summarized clinical information about equine lymphomas is shown in Table 5.

The ages of the affected horses range from fetus to old. No specific risk factors have been reported and there is no sex or breed predilection [47, 63]. More of the reported cases are horses with ages between 4 and 10 years, suggesting that lymphoma is relatively common in young horses [24, 35, 47]. Etiology is unknown, and although involvement of retroviral or corynebacterial infections in malignant transformation has been speculated, it remains unproven because transmission experiments failed to induce tumors [47].

Four categories of lymphoma have been established

Table 5. Clinical and laboratory features of equine lymphoma [17, 26, 35, 47, 54, 63, 67]

	Features
Age	From fetus to old age. More common in horses aged 4–10 years
Breeds	No breed predisposition
Gender	No gender predisposition
General clinical signs	Weight loss, cachexia, edema, regional lymphadenopathy, depression, lethargy, recurrent fever
Clinical forms	Multicentric or generalized: lymph nodes, liver, intestine, kidney, lung and bone marrow affected. Other locations: upper airways, spinal cord, central nervous system, heart, retrobulbar space
	Alimentary or gastrointestinal: malabsorption, diarrhea, colic, luminal bleeding, enlarged mesenteric lymph nodes
	Mediastinal, thymic or thoracic: distended jugular veins, tachycardia, tachypnea, pleural effusion, cough, edema in forelimbs
	Cutaneous: multifocal, firm, sometimes ulcerated nodules.
Hematology	Anemia, neutrophilia
	Pancytopenia if bone marrow is affected
	Lymphocyte count: normal or reduced. Atypical lymphocytes on peripheral blood
Clinical pathology	Hyperfibrinogenemia, hyperglobulinemia, hypoalbuminemia
	Total plasma proteins normal, low or elevated
	Decreased of immunoglobulins
	Hypercalcemia

according to the affected organs and extension: multicentric or generalized, alimentary or intestinal, mediastinal, thoracic or thymic and cutaneous, being the generalized and cutaneous forms the most common [47, 54]. Furthermore, solitary tumors at extranodal sites have been reported in tongue, bladder, leg, and ovary [22, 59, 68].

The major clinical manifestations of lymphoma depend on the degree of the organ involvement, the specific organs involved in an individual patient and the duration of the disease. In general, the most common signs are weight loss, sometimes with extreme cachexia, ventral and limb subcutaneous edema, regional lymphadenopathy, depression, lethargy and recurrent fever [17, 35, 63]. Dependent edema is common and occurred in horses with decreased, normal or increased serum protein concentrations. The most likely cause is impaired lymphatic drainage because of wide-spread tumor involvement of lymph nodes [47, 63]. Most clinical signs are progressive over weeks of months, although they may have a sudden onset.

The tissues most often involved in the multicentric or generalized lymphoma are, in decreasing order of frequency: lymph nodes (including the palpable peripheral lymph nodes, although in most of the cases, the only enlargement is in internal lymph nodes), liver (causing metabolic derangements and obstructive icterus) [11, 61], spleen [11], intestine (inducing colic or malabsorption syndrome with diarrhea or both) [26, 47], kidney (with hematuria or chronic renal failure), lung (leading to a chronic cough and mediastinal fluid accumulation with pleural effusion) and bone marrow [32]. More rarely, tumors can invade the upper airways, causing respiratory obstructions and coughing, spinal cord [30], with spinal compression and neurological signs, including paraplegia and hemiplegia, central nervous system [50], heart [50, 54] causing arrhythmias and altered valvular function, and retrobulbar space, with exophthalmos. Given the degree of organ involvement in the multicentric form, this syndrome could be very similar to intestinal lymphoma with metastasis. The reasons for multicentric form instead solitary lesions have not been elucidated.

Alimentary lymphoma may be a primary neoplastic disease or may represent part of a multicentric disease or a metastasic spread from a primary focus somewhere else in the body [42]. Diffuse involvement of the small intestine is more common than other forms, although the stomach and the large colon may be affected. Mesenteric lymph nodes are commonly infiltrated with malignant cells [35, 42]. When the small intestine is affected, there is a failure of digestion and more significantly absorption although in the early stages the normal large colon could counteract the malfunction

and the condition may pass unnoticed [35]. The disease may take the form of discrete focal tumor masses in the intestinal wall or a diffuse intestinal infiltrate of neoplastic cells that may cause malabsorption [42]. It seems that the focal form is more often seen in older horses while the diffuse form is more common in younger animals. Diarrhea would appear if the condition affects the large colon. Colic can be another clinical signs when discrete masses cause a no-strangulating obstruction. Metastases tend to occur later in the disease [35]. Villous atrophy, mucosa ulcers and luminal bleeding are common [42].

Mediastinal, thoracic or thymic lymphoma is characterized by weight loss, inappetence, ventral edema, distended jugular veins, muffled heart sounds, tachycardia, tachypnea, pyrexia and pleural effusion. Other signs that may be detected are peripheral lymphadenopathy, cough, and forced respiratory sounds. Some of these signs are the consequence of compression in the intrathoracic structures, particularly the lymphatic vessels such as the cranial and caudal lymphatic ducts and the veins. The result is the accumulation within the forelimbs and pleural cavity [17, 35, 67]. In some cases, dysphagia could be found as a result of compression of thoracic part of the esophagus [67]. Although cytological examination of the pleural fluid could help to diagnose this neoplasia, often fails to find any evidence of a neoplastic process in the thorax. Uncommon, but neoplastic cells have been described, with lymphoblasts, and lymphocytes with irregular nuclei and mitotic figures [17].

In the cutaneous form of lymphoma, multifocal, firm, subcutaneous nodules in the skin are the most common findings. Some of them could ulcerate and exude a plasma-like substance. The nodules may present alopecia and become inflamed. The common locations of the lesions are shoulder, axillae, trunk, and perineum [16, 35].

The diagnostic work-up of a horse with suspected lymphoma should include a complete physical examination, rectal palpation to assess mesenteric lymph nodes and mass lesions, a complete hematology and biochemical profile, determination of IgM, IgG and IgA concentrations, lymph node aspiration if a palpable enlarged superficial lymph node is found, abdominocentesis or thoracocentesis if there is a suspicion of involvement of the abdomen or thorax, ultrasonography of the liver and spleen, bone marrow aspiration or biopsy if a leukemic phase is suspected and biopsy of any mass lesion [63].

Anemia is the most common laboratorial finding and could be the result of premature destruction of RBC coated with antibodies (Coomb's-positive immune-mediated hemolytic anemia), inadequate production because of myelophthisis, blood loss (i.e. bleeding ulcers), anemia of chronic inflammation or a combination of these mechanisms [47, 63]. Neutrophilia has been described in some horses and may have resulted from inflammation secondary to tumor necrosis. Pancytopenia is less common, but when appears indicate bone marrow infiltration. Similarly, lymphocytic leukemia is rare and associated with bone marrow involvement. Although the lymphocyte count in blood is usually normal or reduced, the presence of atypical or obviously neoplastic lymphocytes on a peripheral blood smear appears in 30–50% of the cases [47]. The leukemic phase of lymphoma, although rare, is more likely to occur in cases of multicentric lymphoma in comparison with other forms of the disease [63]. The morphology of neoplastic lymphocytes in horses is highly variable. On cytological preparations, they often appear as large lymphoid cells, with a variable nucleus: cytoplasm ratio, multiple nucleoli, nuclear chromatic clumping, cytoplasmic basophilia, and vacuolation. Mitotic figures and binucleate cells can be found. It has been demonstrated that most horse lymphomas are of B-cell origin, even though the presence of 40–80% small T-lymphocytes was common [47].

The most common alterations in the biochemical profile in horses with lymphoma are hyperfibrinogenemia, hyperglobulinemia, hypoalbuminemia and although total plasma proteins could be low, normal or elevated, the albumin: globulin ratio is often reduced, particularly when there is gastrointestinal involvement [42, 47, 63]. Hyperfibrinogenemia could derive from cytokine stimulation, in particular interleukin IL-6, an essential cytokine for induction of Ig synthesis by plasma cells [47]. It has been suggested that IgM and sometimes, IgG, and IgA may be reduced in some horses with lymphoma [63], because of one or some of these reasons: 1) Decreased number of B cells or plasma cells; 2) Functional defect in the B cells or plasma cells that prevent them from synthesizing IgM; 3) Lack of help or assistance from CD4+ cells; 4) Increased catabolism of Ig. However, more recently, Perkins *et al.* [52] found that the sensitivity and specificity of serum IgM concentrations in diagnosing equine lymphoma was poor. Additionally, a mild elevation in liver-derived

serum enzymes may occur subsequent to hepatic involvement, with hyperbilirrubinemia. Hypercalcemia of malignancy is common in lymphoma [63].

The prognosis for most forms of lymphoma is poor, there is limited experience in treating horses with this neoplasia and unfortunately they are markedly debilitated by the time the diagnosis is made. Anecdotal reports of chemotherapeutic protocols have been made without documental published outcomes. Protocols may include vincristine, cyclophosphamide, and prednisone. Nevertheless, these protocols can not stop the progression of the disease [35]. However, clinical observations have indicated that the cutaneous form could persist over years without apparent progression or might progress in response to steroid hormone changes. However, Meyer *et al.* [47] assessed equine lymphoma tissues for expression of estrogen or progesterone receptors and they found that these receptors are rarely identified in neoplastic tissues. According to their results, the existence of a link between hormonal state and neoplastic lymphocyte proliferation or regression has not been elucidated yet.

In summary, the present article summarizes the clinical signs, laboratorial analysis and other diagnostic methods of the hematopoietic neoplasias in horses. Although they are not as common as in small animals and human beings, equine practitioners should be aware of these conditions and be able to interpret clinical and laboratorial finding results in the light of this knowledge. Therefore, the aim of this report was to update practitioners on diagnostic approaches for horses with hematopoietic neoplasia.

References

1. Angel, K.L., Spano, J.S., Schumacher, J., and Kwapien, R.P. 1991. Myelophthisic pancytopenia in a pony mare. *J. Am. Vet. Med. Assoc.* **198**: 1039–1042.
2. Barton, M.H., Sharma, P., LeRoy, B.E., and Howerth, E.W. 2004. Hypercalcemia and high serum parathyroid hormone-related protein concentration in a horse with multiple myeloma. *J. Am. Vet. Med. Assoc.* **3**: 409–413.
3. Beech, J., Bloom, J.C., and Hodge, T.G. 1984. Erythrocytosis in a horse. *J. Am. Vet. Med. Assoc.* **184**: 986–989.
4. Bernard, W.W., Sweeney, C.R., and Morris, F. 1988. Primary lymphocyte leukemia in a horse. *Equine Pract.* **10**: 24–30.
5. Bienzle, D., Hudgson, S.L., and Vernau, W. 1993. Acute myelomonocytic leukemia in a horse. *Can. Vet. J.* **34**: 36–37.
6. Blue, J., Perdizet, J., and Brown E. 1987. Pulmonary aspergillosis in a horse with myelomonocytic leukemia. *J. Am. Vet. Med. Assoc.* **190**: 1562–1564.
7. Boudreaux, M.K., Blue, I.T., Durham, S.K., and Vivrette, S.L. 1984. Intravascular leukostasis in a horse with myelomonocytic leukemia. *Vet. Pathol.* **21**: 544–546.
8. Brown, D.E., Thrall, M.A., Getzy, D.M., Weiser, M.G., and Ogilvie, G.K. 1994. Cytology of canine malignant histiocytosis. *Vet. Clin. Pathol.* **23**: 118–123.
9. Brumbaugh, G.W., Stitzel, K.A., Zinkl, J.G., and Feldman, B.F. 1982. Myelomonocytic myeloproliferative disease in a horse. *J. Am. Vet. Med. Assoc.* **180**: 313–316.
10. Buechner-Maxwell, V., Zhang, C., Robertson, J., Jain, N.C., Antczak, D.F., Feldman, B.F., and Murray, M.J. 1994. Intravascular leukostasis and systemic aspergillosis in a horse with subleukemic acute myelomonocytic leukemia. *J. Vet. Intern. Med.* **8**: 258–263.
11. Chaffin, M.K., Schmitz, D.G., Brumbaugh, G.W., and Hall, D.G. 1992. Ultrasonographic characteristics of splenic and hepatic lymphosarcoma in three horses. *J. Am. Vet. Med. Assoc.* **201**: 743–747.
12. Chen, Y-H., and Magalhaes, M.C. 1990. Hypoalbuminemia in patients with multiple myeloma. *Arch. Intern. Med.* **150**: 605–610.
13. Cortese, L., Paciello, O., and Papparella, S. 2008. Morphological characterization of malignant histiocytosis in a cat. *Folia Morphol (Warsz)* **67**: 299–303.
14. Court, E.A., Earnest-Koons, K.A., Barr, S.C., and Gould, W.J. 2nd. 1993. Malignant histiocytosis in a cat. *J. Am. Vet. Med. Assoc.* **203**: 1300–1302.
15. Dascanio, J.J., Zhang, C.H., Antczak, D.F., Blue, J.T., and Simmons, T.R. 1992. Differentiation of chronic lymphocytic leukemia in the horse: a report of two cases. *J. Vet. Intern. Med.* **6**: 225–229.
16. De Bruin, C.M., Veenman, J.N., Rutten, V.P.M.G., Teske, E., Van Nieuwstadt, R.A., and Van den Ingh, T.S.G.A.M. 2007. Clinical, histopathological and immunophenotypical findings in five horses with cutaneous malignant lymphoma. *Res. Vet. Sci.* **83**: 63–72.
17. De Clercq, D., Van Loon, G., Lefére, L., and Deprez, P. 2004. Ultrasound-guided biopsy as a

diagnostic aid in three horses with a cranial mediastinal lymphosarcoma. *Vet. Rec.* **154**: 722–726.

18. Edwards, D.F., Parker, J.W., Wilkinson, J.E., and Helman, R.G. 1993. Plasma cell myeloma in the horse. A case report and literature review. *J. Am. Vet. Med. Assoc.* **7**: 169–176.

19. Fox, A., and Miller, L. 1987. Equine adrenocortical carcinoma with hypercalcemia. *Vet. Pathol.* **24**: 190–192.

20. Fulmer, A.K., and Mauldin, G.K. 2007. Canine histiocytic neoplasia: an overview. *Can. Vet. J.* **48**: 1041–1050.

21. Geelen, S.N., Bernadina, W.E., Grinwis, G.C., and Kalsbeek, H.C. 1997. Monoclonal gammopathy in a Dutch warmblood mare. *Vet. Quaterly* **19**: 29–32.

22. Gerard, M.P., Healy, L.N., Bowman, K.F., and Miller, R.T. 1998. Cutaneous lymphoma with extensive periarticular involvement in a horse. *J. Am. Vet. Med. Assoc.* **213**: 391–393.

23. Grogan, T.M., Van Camp, B., Kyle, R.A., Müller-Hermelink, H.K., and Harrs, N.L. 2001. Plasma cell neoplasms. pp.142–148. *In*: World Health Organization. Classifications of tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid tissues (Jafle, E.S., Harris, N.L., Stein, H., Vardman, J.W. eds.), IARC Press, Lyon.

24. Hayle, P.T., and Spraker, T. 1983. Lymphosarcoma in an aborted equine fetus. *Vet. Pathol.* **20**: 647–649.

25. Henry, M., Prasse, K., and White, S. 1989. Hemorrhagic diathesis caused by multiple myeloma in a three-month old foal. *J. Am. Vet. Med. Assoc.* **194**: 392–394.

26. Herraez, P., Berridge, B., Marsh, P., Weeks, B., and Ramiro-Ibañez, F. 2001. Small intestine large granular lymphoma in a horse. *Vet. Pathol.* **38**: 223–226.

27. Jacobson, D.R., and Zolla-Pazner, S. 1986. Immunosuppression and infection in multiple myeloma. *Semin. Oncol.* **13**: 282–290.

28. Jaffe, E.S., Harris, N.L., and Stein, H. 2001. World Health Organization Classification of Tumours: Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues. pp.20–28. IARC Press, Lyon.

29. Johansson, A.M., Skidell, J., Lilliehöök, I., and Tvedten, H.W. 2007. Chronic granulocytic leukemia in a horse. *J. Vet. Intern. Med.* **21**: 1126–1129.

30. Kannegieter, N.J., and Alley, M.R. 1987. Ataxia

due to lymphosarcoma in a young horse. *Aust. Vet. J.* **64**: 377–379.

31. Karadia, S.B. 1980. Multiple myeloma: a clinicopathologic study of 62 consecutively autopsied cases. *Medicine* **59**: 380–392.

32. Kelton, D.R., Holbrook, T.C., Gilliam, L.L., Rizzi, T.E., Brosnaham, M.M., and Confer, A.W. 2008. Bone marrow necrosis and myelophthisis: manifestations of T-cell lymphoma in a horse. *Vet. Clin. Pathol.* **37**: 403–408.

33. Kent, J.E., and Roberts, C.A. 1990. Serum protein changes in four horses with monoclonal gammopathy. *Equine Vet. J.* **22**: 373–376.

34. Kim, D.M., Taylor, H.W., Eades, S.C., and Cho, D.Y. 2005. Systemic AL amyloidosis associated with multiple myeloma in a horse. *Vet. Pathol.* **42**: 81–84.

35. Knottenbelt, D.C. 2003. Internal neoplasia: lymphosarcoma and myeloproliferative disease. *In*: 9° Congressso Nazionale Multisala SIVE, Italy.

36. Kohn, C.W., Swardson, C., Provost, P., Gilbert, R.O., and Couto, C.G. 1995. Myeloid and megakaryocytic hypoplasia in related Standardbreds. *J. Vet. Intern. Med.* **9**: 315–323.

37. Kyle, R.A. 1975. Multiple myeloma: review of 869 cases. *Mayo Clin. Proc.* **50**: 29–40.

38. Kyle, R.A., and Greipp, P.R. 1978. The laboratory investigation of monoclonal gammopathies. *Mayo Clin. Proc.* **53**: 719–739.

39. Lester, G.D., Alleman, A.R., Raskin, R.E., and Mays, M.B. 1993. Malignant histiocytosis in an Arabian filly. *Equine Vet. J.* **25**: 471–473.

40. Lester, G.D., Alleman, A.R., Raskin, R.E., and Meyer, J.C. 1993. Pancytopenia secondary to lymphoid leukemia in three horses. *J. Vet. Intern. Med.* **7**: 360–363.

41. Lewis, H.B., and Leitch, A. 1975. A case of granulocytic leukemia in the horse. pp. 141–143. *In*: Equine Hematology Proceedings of the American Association of Equine Practitioners, Boston.

42. Mair, T.S., Pearson, G.R., and Divers, T.J. 2007. Malabsorption syndromes in the horse. *Equine Vet. Educ.* **18**: 299–308.

43. Mair, T.S., Yeo, S.P., and Lucke, V.M. 1990. Hypercalcaemia and soft tissue mineralisation associated with lymphosarcoma in two horses. *Vet. Rec.* **126**: 99–101.

44. Markel, D.D., and Dorr, T.E. 1986. Multiple myeloma in a horse. *J. Am. Vet. Med. Assoc.* **188**: 621–624.

45. McConkey, S., Lopez, A., and Pringle, J. 2000.

Extramedullary plasmocytoma in a dog with ptyalism and dysphagia. *J. Vet. Diagn. Invest.* **12**: 282–284.

46. McFarlane, D., Sellon, D.C., and Parker, B. 1998. Primary erythrocytosis in a 2-year-old Arabian gelding. *J. Vet. Intern. Med.* **12**: 384–388.

47. Meyer, J., DeLay, J., and Bienzle, D. 2006. Clinical, laboratory, and histopathologic features of equine lymphoma. *Vet. Pathol.* **43**: 914–924.

48. Miseta, A., Kellermayer, M., Kollar, B., and Bogner, R. 1989. Paraproteins associated with low plasma sodium levels. *Physiol. Chem. Phys. Med. NMR* **21**: 171–175.

49. Morris, D.D., Bloom, J., Roby, K.A., Woods, K., and Tablin, F. 1984. Eosinophilic myeloproliferative disorder in a horse. *J. Am. Vet. Med. Assoc.* 185: 993–996.

50. Morrison, L.R., Freel, K., Henderson, I., Hahn, C., and Smith, S.H. 2008. Lymphoproliferative disease with features of lymphoma in the central nervous system of a horse. *J. Comp. Pathol.* **139**: 256–261.

51. Oken, M.M. 1984. Multiple myeloma. *Med. Clin. North Am.* **68**: 757–787.

52. Perkins, G.A., Nydam, D.V., Flaminio, M.J., and Ainsworth D.M. 2003. Serum IgM concentrations in normal, fit horses and horses with lymphoma or other medical conditions. *J. Vet. Intern. Med.* **17**: 337–342.

53. Perkins, H.A., MacKenzie, M.R., and Rudenberg, H.H. 1970. Hemostatic defects in dysproteinemias. *Blood* **35**: 695–707.

54. Polkes, A.C., Alleman, A.R., Lester, G.D., Beurgelt, C.D., and McSherry, L.J. 1999. B-cell lymphoma in a horse with associated Sézary-like cells in the peripheral blood. *J. Vet. Intern. Med.* **13**: 620–624.

55. Pusterla, N., Stacy, B.A., Vernau, W., De Cock, H.E.V., and Magdesian, K.G. 2004. Immunoglobulin A monoclonal gammopathy in two horses with multiple myeloma. *Vet. Rec.* **155**: 19–23.

56. Raskin, R.E., and Krehbiel, J.D. 1988. Histopathology of canine bone marrow in malignant lymphoproliferative disorders. *Vet. Pathol.* **25**: 83–88.

57. Rawstron, A.C., Bennett, F.L., O'Connor, S.J., Kwok, M., Fenton, J.A., Plummer, M., De Tute, R., Owen, R.G., Richards, S.J., Jack, A.S., and Hillmen, P. 2008. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. *N. Engl. J. Med.* **359**: 575–583.

58. Rendle, D.I., Durham, A.E., Thompson, J.C., Archer, J., Mitchell, M., Saunders, K., Milliere, J., Paillot, R., Smith, K.C., and Kydd, J.H. 2007. Clinical, immunophenotypic and functional characterization of T-cell leukaemia in six horses. *Equine Vet. J.* **39**: 522–528.

59. Rhind, S.M., and Dixon, P.M. 1999. T-cell rich B cell lymphosarcoma in the tongue of a horse. *Vet. Rec.* **145**: 554–555.

60. Ringger, N.C., Edens, L., Bain, P., Raskin, R.E., and Larock, R. 1997. Acute myelogenous leukaemia in a mare. *Aust. Vet. J.* **75**: 329–331.

61. Roccabianca, P., Paltrinieri, S., Gallo, E., and Giuliani, A. 2002. Hepatosplenic T-cell lymphoma in a mare. *Vet. Pathol.* **39**: 508–511.

62. Sanchez-Avalos, J., Soong, B.C.F., and Miller, S.P. 1969. Coagulation disorders in cancer. II. *Multiple Myeloma. Cancer* **23**: 1388–1398.

63. Savage, C.J. 1998. Lymphoproliferative and myeloproliferative disorders. *Vet. Clin. North Am. Equine Pract.* **14**: 563–577.

64. Searcy, G.P., and Orr, J.P. 1981. Chronic granulocytic leukemia in a horse. *Can. Vet. J.* **22**: 148–151.

65. Silberstein, L., Duggan, D., and Berkman, E. 1985. Therapeutic trial of plasma exchange in osteosclerotic myeloma associated with the POEMS syndrome. *J. Clin. Apher.* **2**: 253–257.

66. Spiers, S.J., Madewell, B.R., Zinkl, J.E., and Ryan, A.M. 1986. Acute myelomonocytic leukemia in a horse. *J. Am. Vet. Med. Assoc.* **188**: 861–863.

67. Sugiyama, A., Takeuchi, T., Morita, T., Matsuura, A., Kanda, T., Shimada, A., Amaya, T., and Hikasa, Y. 2008. Mediastinal lymphoma with complete atrioventricular block in a horse. *J. Vet. Med. Sci.* **70**: 1101–1105.

68. Sweeney, R.W., Hamir, A.N., and Fisher, R.R. 1991. Lymphosarcoma with urinary bladder infiltration in a horse. *J. Am. Vet. Med. Assoc.* **199**: 1177–1178.

69. Traub-Dargatz, J., Bertone, A., Bennett, D., Jones, R.L., Weingand, K., Hall, R., DeMartini, J.C., Lavach, J.D., and Roberts, S.M. 1985. Monoclonal aggregating immunoglobulin cryoglobulinemia in a horse with malignant lymphoma. *Equine Vet. J.* **17**: 470–473.

70. Vasilopulos, R.J., and Mackin, A. 2003. Humoral hypercalcemia of malignancy: diagnosis and treatment. *Compend. Contin. Educ. Pract. Vet.* **25**: 129–136.