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Summary of **'Histiocytic Sarcoma and Hemangiosarcoma Update**

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HISTIOCYTIC SARCOMA

Histiocytic sarcoma (HS) is an infrequently encountered malignant neoplasm that originates from dendritic cells. This disease can manifest in several patterns, including a solitary localized mass that may arise internally or externally, regional extension involving adjacent tissues or organs, or a disseminated form characterised by widespread multiorgan involvement. Earlier terminology referring to this condition as "malignant histiocytosis" is now considered obsolete, as improved classification has distinguished discrete subtypes, namely localized HS, disseminated HS, and hemophagocytic HS.

Reported anatomical locations for HS are diverse and include the lungs, lymph nodes, liver, spleen, stomach, intestines, pancreas, mediastinum, skin and subcutaneous tissues, skeletal muscle, central nervous system, bone, joints and joint spaces, bone marrow, nasal cavity, and ocular structures. Among canine periarticular neoplasms, HS represents the most frequently diagnosed tumour type. In these cases, immunohistochemistry is generally required to reliably distinguish periarticular HS from synovial cell sarcoma. Within the canine population, HS accounts for approximately five percent of primary brain tumours and around four and a half percent of secondary, or metastatic, intracranial tumours.

Hemophagocytic histiocytic sarcoma (HHS) represents a particularly aggressive variant of HS. This subtype occurs predominantly in dogs and is only rarely reported in cats. HHS arises from macrophages located within the splenic red pulp or bone marrow. Definitive differentiation of HHS from other HS subtypes requires identification of a characteristic immunohistochemical staining profile. Nevertheless, certain clinical features, in conjunction with haematological and biochemical abnormalities, may heighten clinical suspicion prior to tissue confirmation.

Incidence

Histiocytic sarcoma constitutes less than one percent of lymphoreticular system malignancies in dogs and is diagnosed more frequently in this species than in any other. The true incidence of HS in cats remains uncertain, although available evidence suggests that the disease is uncommon in feline patients.

Cause

The precise aetiology of HS has not been definitively established. However, multiple risk factors have been described in dogs, most notably genetic predisposition and the presence of chronic inflammatory processes.

Genetics

Although HS was initially described in the Bernese Mountain Dog, subsequent investigations have identified breed-associated predispositions in several additional breeds, including the Flat-Coated Retriever, Rottweiler, Miniature Schnauzer, and Pembroke Welsh Corgi. Inheritance studies have demonstrated that genetic susceptibility within the Bernese Mountain Dog population is widespread rather than restricted to specific lineages.

Specific molecular alterations have been identified in canine HS, including deletions involving tumour suppressor genes such as CDKN2A/B, RB1, and PTEN. These abnormalities have been documented in tumour samples from Bernese Mountain Dogs and Flat-Coated Retrievers. Breed-related differences in DNA copy number aberrations have also been observed and are thought to contribute to variation in tumour localisation, with Flat-Coated Retrievers demonstrating a particular predisposition for periarticular disease. Importantly, many of the chromosomal alterations identified in dogs show a high degree of conservation with those reported in human histiocytic disorders.

Inflammation

An association between pre-existing joint disease and the development of periarticular HS has been reported in Bernese Mountain Dogs as well as other breeds. Dogs diagnosed with periarticular HS were found to be approximately two and a half times more likely to have a history of orthopaedic disease affecting the involved joint when compared with control populations. Additionally, dogs receiving anti-inflammatory medications demonstrated a reduced risk of developing periarticular HS, suggesting a potential protective effect of inflammation modulation.

Signalment

Dogs affected by HS are most commonly middle-aged to older, although cases have been documented in animals as young as three years of age. While HS can occur in any breed, Bernese Mountain Dogs, Flat-Coated Retrievers, Miniature Schnauzers, Pembroke Welsh Corgis, and Golden Retrievers are disproportionately represented among reported cases.

HISTORY AND CLINICAL PRESENTATION

Clinical history and presenting signs associated with HS vary considerably depending on both the anatomical location and the extent of tumour involvement. Dogs with disseminated HS or HHS commonly exhibit non-specific systemic signs, including lethargy, generalised weakness, reduced appetite, progressive weight loss, abdominal enlargement, respiratory distress, and coughing. In contrast, lameness represents the most frequently reported clinical sign in dogs with periarticular HS.

PHYSICAL EXAMINATION FINDINGS

Physical examination findings reflect the distribution and severity of disease. In dogs with disseminated HS or HHS, commonly identified abnormalities include pyrexia, pallor of mucous membranes, spontaneous bruising, palpable masses involving the skin or subcutaneous tissues, enlargement of peripheral lymph nodes, increased respiratory rate, dyspnoea, and muffled cardiac or pulmonary auscultation. Abdominal distension may be present and can be accompanied by cranial organomegaly or a detectable fluid wave.

Dogs affected by periarticular HS typically present with lameness and may exhibit a palpable periarticular mass or evidence of joint-associated swelling. Enlargement of regional lymph nodes may also be detected on physical examination.

DIAGNOSIS

A definitive diagnosis of histiocytic sarcoma can be established through cytological or histological assessment of neoplastic tissue. In certain cases, tumour cells exhibit such marked pleomorphism or lack of differentiation that ancillary staining techniques are required to distinguish HS from other round cell tumours, carcinomas, or alternative sarcoma types. For the purpose of clinical staging, a standard diagnostic evaluation is recommended, consisting of a complete blood count, serum biochemistry profile, urinalysis, three-view thoracic radiography, and abdominal ultrasonography. Bone marrow evaluation may be indicated in selected cases, and where available and clinically appropriate, computed tomography or magnetic resonance imaging may be incorporated. Findings obtained during staging enable accurate classification of the disease as localized or disseminated, thereby informing prognosis and guiding therapeutic decision-making.

Pathologic Evaluation

Cytology

Cytological evaluation is commonly performed using fine-needle aspiration of a suspected mass. In some patients, diagnostic material may also be obtained from analysis of malignant

effusions when present. Cytological samples from HS typically contain large, discrete mononuclear cells demonstrating pronounced variation in cell and nuclear size. Nuclei are commonly round, oval, or kidney-shaped and frequently contain prominent nucleoli. The cytoplasm is usually moderate to abundant in volume, lightly basophilic, and often contains vacuoles. Mitotic activity is generally high, and atypical or bizarre mitotic figures as well as multinucleated giant cells may be observed. Evidence of erythrophagocytosis by neoplastic cells may also be present.

In many cases, the degree of pleomorphism and poor differentiation precludes definitive diagnosis based on cytology alone. When this occurs, immunocytochemistry using antibodies directed against the class A macrophage scavenger receptor CD204 may assist in supporting a diagnosis of HS. If cytology and immunocytochemistry fail to provide a conclusive diagnosis, histopathological examination is required.

Histopathology

Histopathological confirmation of HS may be achieved using a variety of biopsy approaches, including submission of an entire affected organ following surgical removal, excisional biopsy of a mass, or diagnostic sampling via incisional, wedge, or tru-cut biopsy techniques for both internal and external lesions. Microscopically, HS is characterised by sheets of large, pleomorphic mononuclear cells and multinucleated giant cells, often accompanied by frequent atypical mitotic figures. In some cases, tumour cells may exhibit a spindle-shaped morphology resembling other sarcoma types, either exclusively or in combination with the more typical mononuclear and multinucleated cell populations.

Immunohistochemistry performed on formalin-fixed tissue is routinely employed to differentiate HS from other round cell tumours, sarcomas, and carcinomas. Antibodies targeting CD18 or CD204 are commonly utilised for this purpose. In cases of hemophagocytic histiocytic sarcoma, active phagocytosis of erythrocytes and leukocytes by neoplastic cells is frequently observed and is relatively distinctive compared with other HS subtypes. Immunolabelling for CD11d may aid in confirming the diagnosis of HHS, particularly when clinicopathological findings are suggestive of this aggressive variant.

Laboratory Evaluation

Complete blood count

Anaemia is a frequent haematological abnormality in dogs with HS and is most often regenerative, particularly when erythrophagocytosis by tumour cells is present. Thrombocytopenia and, in some cases, pancytopenia may also be identified and are typically attributable to bone marrow infiltration by neoplastic cells. In one study, HS represented the second most common underlying cause of pancytopenia in dogs.

Serum biochemistry and urinalysis

Biochemical abnormalities commonly associated with HS include elevations in liver enzyme activities, reduced serum cholesterol concentrations, and hypoalbuminaemia. These findings are particularly prevalent in dogs with hemophagocytic HS. Hypercalcaemia has been reported infrequently in canine HS and is considered an uncommon laboratory abnormality.

Diagnostic Imaging

Thoracic radiographs

When pulmonary involvement is present, thoracic radiographs may reveal a diffuse interstitial pattern, patchy areas of consolidation, or multifocal pulmonary masses. The right middle lung lobe has been identified as the most common site of origin for primary pulmonary HS. Enlargement of sternal or tracheobronchial lymph nodes may also be detected.

Abdominal ultrasound

Abdominal ultrasonography is useful for identifying lesions within visceral organs. Common ultrasonographic findings include hepatosplenomegaly, heterogeneous echotexture of the liver and spleen, discrete nodules or masses affecting multiple organs such as the liver, spleen, kidneys, or adrenal glands, lymphadenopathy, and the presence of abdominal effusion.

Advanced imaging

Computed tomography and magnetic resonance imaging may be employed in patients with either localized or disseminated HS. These imaging modalities can assist in defining the precise anatomical origin of a tumour and assessing the degree of local invasion, thereby facilitating surgical planning and radiation therapy design. Thoracic computed tomography has demonstrated superior sensitivity compared with radiography for detecting early pulmonary metastases across multiple tumour types. Both computed tomography and magnetic resonance imaging may also be valuable for identifying metastatic lesions involving the liver and spleen.

Novel Diagnostics and Biomarkers

CADET histiocytic malignancy assay

The CADET histiocytic malignancy assay is a commercially available diagnostic test that evaluates cytological or biopsy specimens for DNA copy number aberrations characteristic of

HS. Reported sensitivity and specificity for this assay are approximately seventy-eight percent and ninety-five percent, respectively.

Serum ferritin

Elevated serum ferritin concentrations have been documented in dogs with HS. This increase is believed to result from ferritin production by neoplastic cells, destruction of erythrocytes, hepatocellular injury, and release of ferritin secondary to tissue damage. Serum ferritin levels have been shown to be significantly higher in dogs with HS and immune-mediated haemolytic anaemia compared with dogs affected by inflammatory diseases or lymphoma. However, because ferritin is elevated in a variety of disease processes, its specificity as a biomarker for HS is limited.

TREATMENT

Given the highly aggressive biological behaviour of histiocytic sarcoma, effective management typically requires a combination of local and systemic therapeutic approaches, even in cases where disease appears localized at the time of diagnosis. Disseminated forms of HS are generally managed with systemic therapy alone.

Local Therapy

Surgery

For dogs with localized HS, surgical excision with wide margins is considered the preferred local treatment modality. Depending on tumour location, this may involve procedures such as limb amputation, splenectomy, or lung lobectomy. Data describing outcomes in dogs treated with surgery alone are limited. In a study involving dogs with periarticular HS, the median survival time for animals treated solely with amputation was six months, and metastatic disease developed in ninety-one percent of cases. More recent investigations focusing on primary pulmonary HS demonstrated that dogs undergoing surgical resection followed by chemotherapy experienced significantly longer progression-free survival, approximately nine months, and overall survival approaching one year, compared with dogs that did not receive surgical intervention.

Radiation therapy

The effectiveness of radiation therapy for HS has not been extensively characterised. In a study of Flat-Coated Retrievers, most of which had joint-associated HS, dogs receiving radiation therapy survived longer than those that did not, with a median survival time of approximately six months. Another treatment approach combining palliative radiation therapy with lomustine resulted in a median survival time of roughly seven months. Further

studies are required to establish optimal radiation protocols and to better define their role in HS management.

Systemic Therapy

Chemotherapy

Lomustine (CCNU) is currently regarded as the most effective chemotherapeutic agent for HS. In dogs, lomustine is administered orally at doses ranging from sixty to ninety milligrams per square metre every three weeks, while cats typically receive forty to fifty milligrams per square metre every three to six weeks. In dogs with measurable disease, reported response rates range from twenty-nine to forty-six percent, with a median duration of response of approximately three months. In one study, dogs that responded to lomustine survived a median of nearly six months, whereas non-responders had a median survival of only two months. The use of lomustine as adjuvant therapy following local treatment has been shown to significantly prolong survival in dogs with localized HS, with reported median survival times of up to nineteen months.

Doxorubicin has also been utilised in the treatment of HS, typically administered intravenously at a dose of thirty milligrams per square metre in dogs weighing more than fifteen kilograms, or one milligram per kilogram in cats and smaller dogs, every two to three weeks. When used in combination with lomustine in an alternating schedule every two weeks, this regimen achieved a response rate of fifty-eight percent and a median time to disease progression of approximately six months.

Dacarbazine has been evaluated as a rescue agent in dogs with HS, administered intravenously at doses of nine hundred to one thousand milligrams per square metre every three weeks. In this setting, a response rate of approximately eighteen percent was reported, with responders experiencing an event-free survival time of seventy days.

Epirubicin, administered intravenously at thirty milligrams per square metre every three weeks, has been assessed both as a single-agent rescue therapy and in combination with lomustine as first-line treatment. This agent demonstrated an overall response rate of twenty-nine percent and a median time to progression slightly exceeding two months.

Vinorelbine has been evaluated in a limited number of dogs with HS at doses of fifteen milligrams per square metre administered intravenously every one to two weeks. In this small cohort, partial responses were observed in two of nine dogs, with response durations of over five months and more than two years, respectively. An additional four dogs achieved stable disease for a median duration of two months.

Metronomic chemotherapy protocols using low-dose lomustine or chlorambucil have also been employed in dogs with HS. Lomustine has been administered orally at a dose of approximately 2.84 milligrams per square metre daily, while chlorambucil has been given at four milligrams per square metre daily. Due to small case numbers, treatment efficacy could not be definitively determined.

Novel Therapy

Bisphosphonates have been investigated as potential therapeutic agents for HS based on their capacity to deplete macrophages and enhance the cytotoxic effects of conventional chemotherapy. Liposomal clodronate has demonstrated the ability to induce apoptosis in HS cell lines and produced significant tumour responses in two of five dogs treated in vivo. Larger-scale clinical evaluations are currently lacking.

In vitro studies have shown that the combination of clodronate and vincristine results in synergistic cytotoxicity associated with increased cell cycle arrest. Additionally, zoledronate has been shown to enhance doxorubicin uptake by malignant histiocytic cells and significantly increase tumour cell death in vitro.

Other Medical Management

Corticosteroids are frequently prescribed to alleviate clinical signs in dogs with advanced HS. However, their use has been identified as a significant negative prognostic factor for survival in multiple studies. This association may, in part, reflect selection bias, as corticosteroids are often administered to patients with more severe disease.

FOLLOW-UP

Dogs diagnosed with HS are typically monitored through regular re-evaluation, including physical examinations, laboratory testing, and periodic restaging using thoracic and abdominal imaging modalities such as radiography, ultrasonography, or advanced imaging when indicated. The frequency and extent of follow-up assessments are guided by the form and anatomical distribution of the disease.

PROGNOSIS

Survival outcomes for dogs with HS vary considerably depending on disease distribution and treatment approach. Dogs with localized disease that receive adjuvant therapy generally experience longer survival times than those with disseminated disease. Periarticular HS is associated with a more favourable prognosis compared with other localized forms, with a reported median survival time of thirteen months versus approximately four months for

non-periarticular HS. This improved outcome has been observed even in cases where metastatic disease was suspected at the time of diagnosis.

In dogs with primary pulmonary HS, those treated with chemotherapy alone had a median survival time of approximately four months, whereas dogs receiving both surgical intervention and chemotherapy survived for just over one year. Hemophagocytic HS represents the most aggressive variant of the disease and is commonly characterised by extensive organ infiltration and severe haematological and bone marrow abnormalities. To date, no effective treatment strategy has been identified for HHS, and reported survival times range from only a few days to one or two months regardless of therapy.

Negative prognostic indicators for HS include prior administration of corticosteroids, anaemia, thrombocytopenia, and hypoalbuminaemia. These factors may, at least in part, reflect their association with the hemophagocytic form of the disease.

HEMANGIOSARCOMA

Hemangiosarcoma (HSA) is a highly malignant neoplasm that arises from endothelial cell precursors originating in the bone marrow. The most frequently affected primary anatomical sites include the spleen, heart, skin and subcutaneous tissues, and liver. Less commonly reported primary locations encompass the kidneys, retroperitoneal space, skeletal muscle, bone, ocular tissues, oral cavity, nasal cavity, urinary bladder, and lungs. The biological behaviour of HSA varies according to the site of origin, with tumours confined to the skin, particularly those limited to the dermis, generally associated with a more favourable prognosis than those arising in visceral locations.

Hemangiosarcoma is characterised by rapid growth, marked local invasiveness, and a high propensity for metastasis. Microscopic metastatic spread typically occurs early in the disease course, most often via haematogenous dissemination or through direct seeding of tumour cells within body cavities following tumour rupture. Metastatic lesions may develop at virtually any site; however, the liver, omentum, and lungs are the most commonly affected organs. HSA represents the most frequent secondary intracranial neoplasm in dogs, and necropsy studies have demonstrated cerebral metastases in approximately fourteen percent of canine cases.

Incidence

Hemangiosarcoma is diagnosed more commonly in dogs than in any other domestic species, although it accounts for only around two percent of all canine tumours. Within the canine population, the spleen is the organ most frequently involved.

Analysis of multiple studies has shown that roughly two-thirds of ruptured splenic masses in dogs are malignant, and of those malignant lesions, approximately two-thirds are diagnosed as HSA. This observation has led to the informal adoption of the so-called “rule of two-thirds” or “double two-thirds rule” in clinical practice. While the presence of a nontraumatic hemoabdomen increases the likelihood that HSA is the underlying cause, benign splenic tumours cannot be excluded based solely on this finding.

The true incidence of HSA in cats remains poorly defined but appears to be substantially lower than that observed in dogs. In a study assessing cats presenting with spontaneous hemoabdomen, nearly half were diagnosed with neoplastic disease, while the remainder had benign conditions. Among cats with neoplasia, splenic HSA was the most frequently identified histological diagnosis, accounting for approximately thirty-seven percent of cases.

Cause

The definitive aetiology of canine HSA has not been established. Nevertheless, several risk factors have been identified, including exposure to ultraviolet radiation, hormonal influences associated with neutering status, and underlying genetic abnormalities.

Ultraviolet light exposure

Chronic exposure to ultraviolet radiation has been associated with the development of superficial cutaneous HSA affecting the ventral abdomen and conjunctiva in lightly pigmented, short-haired dog breeds. Breeds such as Whippets and Italian Greyhounds appear particularly predisposed to this form of the disease.

Hormonal status

Several studies have suggested a relationship between gonadectomy and the risk of developing HSA. Cardiac HSA has been reported to occur four times more frequently in spayed females compared with intact females, and spayed females have been shown to have more than twice the risk of developing splenic HSA relative to intact counterparts. In Golden Retrievers, females spayed after one year of age demonstrated a fourfold increase in HSA risk compared with intact dogs or those neutered before one year of age. Similarly, spayed female Vizslas were found to be nine times more likely to develop HSA than intact females, while male Vizslas castrated after one year of age exhibited a fivefold increased risk compared with intact males.

Genetics

Genetic investigations have identified inactivation of the tumour suppressor gene PTEN in more than half of evaluated canine HSA samples. Additional studies have demonstrated

overexpression of key cell cycle and survival proteins, including retinoblastoma protein, cyclin D1, Bcl-2, and survivin. Elevated concentrations of multiple angiogenic factors, such as vascular endothelial growth factor, platelet-derived growth factor, and endothelin-1, have been detected in the blood and effusions of dogs with HSA, along with overexpression of their corresponding receptors within tumour tissues. Dysregulation of these angiogenic pathways is thought to contribute significantly to HSA pathogenesis. Recent genomic analyses have identified several molecularly distinct subtypes of HSA, although the clinical relevance of these findings has yet to be fully determined.

Signalment

Hemangiosarcoma most commonly affects older dogs, with a reported median age at diagnosis of approximately ten years. Several studies suggest a male predominance. German Shepherd Dogs, Golden Retrievers, and Labrador Retrievers appear to be at increased risk. In cats, HSA typically affects older individuals, and no consistent sex or breed predisposition has been identified.

HISTORY AND CLINICAL PRESENTATION

Most dogs with visceral HSA present on an emergency basis as a consequence of tumour rupture and internal haemorrhage. Clinical signs are frequently attributable to acute blood loss anaemia and, in cases involving cardiac HSA, cardiac tamponade and/or right-sided congestive heart failure. Common presenting complaints include sudden weakness, lethargy, and collapse. Additional historical findings may include decreased appetite, progressive weight loss, abdominal enlargement, vomiting, and respiratory distress.

Clinical presentation of cutaneous HSA varies depending on whether the tumour is confined to the dermis, extends into the subcutaneous tissues, or involves underlying muscle. In most cases, owners report the presence of a visible mass. A history of sun exposure or sunbathing behaviour may be noted in dogs diagnosed with dermal HSA.

PHYSICAL EXAMINATION FINDINGS

Physical examination findings are influenced by tumour location and disease extent. Dogs with visceral HSA frequently exhibit pale mucous membranes, tachycardia, cardiac murmurs, arrhythmias, weak or hyperdynamic peripheral pulses, increased respiratory rate, dyspnoea, muffled cardiac or pulmonary sounds, abdominal distension, cranial organomegaly, and a palpable abdominal fluid wave.

Dogs with dermal HSA typically present with small, discrete cutaneous lesions that often resemble blood-filled blisters. These lesions most commonly occur on the ventral abdomen, inguinal region, and conjunctiva. Subcutaneous and intramuscular forms of HSA generally

manifest as larger, deeper masses with dark discolouration or a bruised appearance. When tumours arise on or near a limb, distal swelling and lameness may be observed.

DIAGNOSIS

Histopathological examination remains the definitive diagnostic standard for hemangiosarcoma, although cytology may be diagnostic in a subset of cases. In clinical practice, a presumptive diagnosis is often established based on patient history, signalment, and physical examination findings. As a result, comprehensive clinical staging is frequently performed prior to obtaining a definitive histological diagnosis. Standard staging includes a complete blood count, serum biochemistry profile, urinalysis, three-view thoracic radiography, and abdominal ultrasonography. When indicated and available, additional modalities such as echocardiography, computed tomography, or magnetic resonance imaging may be utilised. Information obtained during staging permits accurate classification of disease stage and supports prognostication and therapeutic planning.

Pathologic Evaluation

Cytology

The diagnostic yield of cytology for hemangiosarcoma is generally low, largely due to extensive peripheral blood contamination within aspirates. In selected cases involving subcutaneous or intramuscular tumours, aspiration of more solid tumour regions may provide sufficient cellular material for diagnosis. Neoplastic cells associated with HSA are typically spindle-shaped to stellate and possess poorly defined cytoplasmic borders with numerous small, clear punctate vacuoles. Cells are most often observed individually or arranged in small clusters. Nuclei are generally large, with coarsely stippled chromatin and one to three prominent nucleoli. Moderate to marked anisocytosis and anisokaryosis are common, and atypical mitotic figures may be present.

Histology

Histologically, HSA is characterised by irregular, anastomosing vascular-like channels lined by pleomorphic spindle cells that form large, multifocal blood-filled cavities. Areas of tumour necrosis are frequently observed. The neoplastic cells typically demonstrate marked variation in nuclear and cellular size and shape, along with a high mitotic index. With the exception of dermal tumours, most hemangiosarcomas are classified as high-grade malignancies based on histological criteria.

Laboratory Evaluation

Complete blood count

Anaemia is the most commonly identified haematological abnormality in dogs with HSA and is typically regenerative. Associated erythrocyte abnormalities may include schistocytes, acanthocytes, and nucleated red blood cells, findings consistent with red blood cell membrane damage secondary to vasculitis, hepatic dysfunction, and impairment of the reticuloendothelial system. Thrombocytopenia is reported in up to seventy-five percent of dogs with HSA and may result from platelet consumption or sequestration associated with tumour haemorrhage, destruction within abnormal tumour vasculature, or secondary consumptive coagulopathies. Neutrophilic leukocytosis is also frequently observed, particularly in visceral HSA, and is thought to arise as a paraneoplastic effect, secondary to tumour necrosis, or due to expansion of myeloid-derived suppressor cells that inhibit innate antitumour immune responses.

Serum biochemistry and urinalysis

Serum biochemistry and urinalysis findings are generally non-specific and rarely contribute directly to the diagnosis of HSA. In one study evaluating cats with visceral HSA, just over half of the patients demonstrated increased aspartate transaminase activity.

Coagulation profile

Up to fifty percent of dogs with HSA exhibit clinical and laboratory evidence consistent with disseminated intravascular coagulation. Abnormalities may include prolonged prothrombin and partial thromboplastin times, as well as increased concentrations of fibrin degradation products, fibrinogen, and D-dimers.

Diagnostic Imaging

Thoracic radiographs

Pulmonary metastatic disease associated with HSA is most commonly visualised radiographically as a multifocal to coalescing miliary or nodular pulmonary pattern. Reported sensitivity of thoracic radiography for detection of pulmonary metastasis is approximately seventy-eight percent. In dogs with cardiac HSA accompanied by pericardial effusion, thoracic radiographs often reveal a globoid cardiac silhouette.

Abdominal ultrasound

Abdominal ultrasonography is useful for detecting peritoneal effusion and identifying lesions within visceral organs and the omentum. Hemangiosarcoma lesions are frequently cavitated

but may display a wide range of echogenic appearances, including solid, heterogeneous, or anechoic patterns.

Echocardiography

Echocardiography is employed to identify cardiac masses in dogs presenting with pericardial effusion when cardiac HSA is suspected. Its use as a routine staging tool for HSA originating from non-cardiac sites remains controversial, as available data suggest a relatively low overall detection rate for concurrent splenic and cardiac tumours. Echocardiography also provides valuable information regarding cardiac function prior to initiation of chemotherapy and during treatment, particularly in breeds predisposed to dilated cardiomyopathy.

Electrocardiography

Ventricular arrhythmias are relatively common in dogs undergoing splenectomy for HSA, with reported incidence rates of up to forty-four percent. Dogs that develop intraoperative arrhythmias have been shown to carry an increased risk of perioperative mortality compared with those that do not experience arrhythmias.

Advanced imaging

Computed tomography and magnetic resonance imaging may be utilised to evaluate subcutaneous, intramuscular, cardiac, and intra-abdominal forms of HSA. These imaging techniques assist in defining tumour origin, extent, and invasiveness, thereby supporting surgical and radiation therapy planning. Thoracic computed tomography offers superior sensitivity compared with radiography for the detection of early pulmonary metastases. Both computed tomography and magnetic resonance imaging demonstrate high sensitivity and specificity for differentiating benign from malignant splenic and hepatic lesions; however, their routine use is limited by cost considerations and the requirement for general anaesthesia, which may pose significant risk in haemodynamically unstable patients.

Contrast Harmonic Ultrasound

Contrast harmonic ultrasonography has been shown to improve detection of hepatic and splenic HSA lesions. In small studies, this modality identified hepatic nodules that were not visible on conventional grey-scale ultrasonography. Evaluation of splenic lesions using contrast-enhanced techniques has demonstrated that hypoechogenicity during both early and late vascular phases is strongly associated with malignancy. Despite these advantages, limited availability has restricted widespread clinical application.

Biomarkers

The identification of HSA-specific biomarkers has the potential to facilitate earlier disease detection, improve monitoring of treatment response, and provide surrogate indicators of disease burden. At present, the development and clinical use of such biomarkers remain in early stages.

Cardiac troponin I

Cardiac troponin I is a highly sensitive and specific biomarker of myocardial injury. Dogs with cardiac HSA have been shown to exhibit significantly higher plasma concentrations of cardiac troponin I compared with dogs with pericardial effusion arising from non-neoplastic causes.

Serum collagen XXVII peptide

Collagen XXVII peptide is a degradation product associated with invasive and angiogenic processes. Serum concentrations of this peptide have been reported to be significantly elevated in dogs with HSA, particularly those with extensive metastatic disease, compared with healthy control dogs. Decreases in collagen XXVII peptide levels following surgical tumour removal, followed by subsequent increases with tumour recurrence, support its potential utility as a biomarker for disease monitoring.

Thymidine kinase

Thymidine kinase is a cytosolic enzyme involved in DNA synthesis and is expressed predominantly in proliferating cells. Dogs with HSA have been shown to have significantly higher serum thymidine kinase activity than healthy dogs. However, the absence of a clearly defined diagnostic cutoff value limits its usefulness for distinguishing benign splenic masses from HSA.

TREATMENT

Initial Emergency Therapy

Because the majority of dogs with hemangiosarcoma present in a critical condition secondary to acute haemorrhage, immediate treatment priorities focus on patient stabilisation. Intravenous fluid therapy using crystalloids, colloids, and blood products is indicated to address anaemia and hypovolaemic shock. In patients presenting with pericardial effusion and cardiac tamponade due to suspected cardiac HSA, urgent therapeutic pericardiocentesis is required and typically results in rapid clinical improvement.

Local Therapy

Surgery

Cardiac hemangiosarcoma

Although isolated case reports and small series describing surgical excision of cardiac HSA have been published, complete resection of these tumours is rarely achievable and is therefore not routinely attempted. Surgical intervention most commonly consists of pericardiectomy, which may be performed via open thoracotomy or minimally invasive thoracoscopic techniques. Removal of the pericardium can prevent recurrence of cardiac tamponade but is considered a palliative measure, as it does not directly address the underlying tumour.

Splenic, hepatic, and renal hemangiosarcoma

Once haemodynamic stability has been achieved, exploratory laparotomy is recommended to facilitate removal of the affected organ and to obtain biopsies from additional tissues, particularly the liver. In dogs undergoing splenectomy for splenic HSA, gross abnormalities of the liver are common, and approximately half of dogs with visibly abnormal hepatic tissue have been shown to harbour histological evidence of metastatic disease. Consequently, any abnormal tissues identified at the time of surgery should be biopsied.

Dermal hemangiosarcoma

Wide-margin surgical excision is the treatment of choice for dermal HSA and is generally curative for individual lesions.

Subcutaneous and intramuscular hemangiosarcoma

Wide surgical excision remains the preferred treatment approach for subcutaneous and intramuscular HSA. In certain cases, radical surgical procedures, including limb amputation, may be required to achieve adequate margins.

Radiation Therapy

Hypofractionated external beam radiation therapy may be used for palliative management of nonresectable subcutaneous or intramuscular HSA. This approach is associated with high response rates in terms of tumour control but has not consistently demonstrated a survival benefit. Hypofractionated radiation therapy has also been evaluated in dogs with cardiac HSA and has been shown to reduce the frequency of recurrent cardiac tamponade. In this context, reported median survival times approximate two and a half months.

Systemic Therapy

Given the highly metastatic nature of HSA and the overall poor prognosis associated with nondermal forms, adjuvant chemotherapy is recommended following surgical intervention. Chemotherapy may also be administered in cases involving nonresectable subcutaneous or intramuscular tumours, cardiac HSA, or advanced-stage visceral disease.

Chemotherapy

Doxorubicin is the most widely utilised and effective chemotherapeutic agent for the treatment of HSA. It is administered intravenously at a dose of thirty milligrams per square metre in dogs weighing more than fifteen kilograms, or one milligram per kilogram in cats and smaller dogs, every two to three weeks. When used as adjuvant therapy following splenectomy, doxorubicin is associated with median survival times ranging from five to eight months. It has also demonstrated activity in dogs with nonresectable cardiac and subcutaneous HSA, with reported response rates between thirty-eight and forty-one percent.

Vincristine, administered intravenously at doses of 0.5 to 0.7 milligrams per square metre weekly, and cyclophosphamide, given orally or intravenously at doses of two hundred to two hundred and fifty milligrams per square metre weekly, may be used together as a rescue protocol or combined with doxorubicin as part of a first-line vincristine, doxorubicin, and cyclophosphamide protocol.

Dacarbazine has been evaluated in dogs with HSA using two dosing strategies: intravenous administration of eight hundred to one thousand milligrams per square metre every three weeks, or two hundred milligrams per square metre daily for five consecutive days. When combined with vincristine and doxorubicin in dogs with advanced-stage disease, dacarbazine was associated with a response rate of forty-seven percent. In another study, the addition of dacarbazine to doxorubicin significantly improved both time to metastasis and median survival time compared with doxorubicin and cyclophosphamide.

Epirubicin may be substituted for doxorubicin in dogs with underlying cardiac disease due to its reduced cardiotoxicity. Administered intravenously at a dose of thirty milligrams per square metre every three weeks, epirubicin demonstrated efficacy comparable to doxorubicin when used as adjuvant therapy for splenic HSA.

Ifosfamide has been administered either as a single agent or in alternating combination with doxorubicin at doses of three hundred and fifty to three hundred and seventy-five milligrams per square metre every two to three weeks, accompanied by saline diuresis and mesna for uroprotection.

Metronomic cyclophosphamide, administered orally at twelve and a half to fifteen milligrams per square metre every twenty-four hours, may be combined with a nonsteroidal anti-inflammatory drug such as piroxicam, deracoxib, or carprofen. This regimen may be used following doxorubicin therapy, concurrently with chemotherapy, or as an alternative approach. While early pilot studies suggested comparable outcomes to adjuvant doxorubicin in selected cases, subsequent investigations failed to demonstrate a clear survival advantage.

Thalidomide has been evaluated as maintenance therapy at oral doses ranging from two to three milligrams per kilogram every twenty-four to forty-eight hours, or approximately 8.7 milligrams per kilogram daily. Studies have reported prolonged time to metastasis and improved survival in dogs receiving thalidomide following doxorubicin, as well as improved outcomes when used as a single adjuvant agent after splenectomy.

Metronomic chlorambucil, administered orally at four milligrams per square metre every twenty-four hours with or without concurrent nonsteroidal anti-inflammatory drugs, has been associated with stable disease in a subset of dogs with macroscopic HSA.

Targeted Therapy

Toceranib phosphate has been evaluated as maintenance therapy following splenectomy and doxorubicin chemotherapy in dogs with early-stage HSA. This treatment did not result in significant improvement in disease-free interval or overall survival.

A bispecific epidermal growth factor receptor–urokinase angiotoxin, eBAT, has been investigated in a small cohort of dogs prior to adjuvant doxorubicin therapy. Treatment was associated with improved median survival time and six-month survival rate compared with historical controls. This agent is not currently commercially available.

Immunotherapy

Liposomal muramyl tripeptide phosphatidylethanolamine, a synthetic macrophage activator derived from mycobacterial cell wall components, has been shown to improve survival when administered concurrently with a doxorubicin and cyclophosphamide protocol. This immunotherapeutic agent is not currently available for routine clinical use in the United States.

Complementary and Alternative Therapy

Yunnan Baiyao, a traditional Chinese herbal preparation, has been used anecdotally to manage haemorrhage in dogs with HSA. In vitro studies demonstrated dose- and time-dependent induction of apoptosis in HSA cell lines; however, controlled laboratory studies

failed to show modulation of coagulation parameters in healthy dogs. Retrospective clinical evaluations have not demonstrated a clear survival benefit or reduction in recurrence of pericardial effusion. Dosing recommendations remain anecdotal.

Polysaccharopeptide, the bioactive compound derived from the mushroom Coriolus versicolor and marketed as I'm-Yunity, has been evaluated in a small double-blind, randomised pilot study. High-dose administration at one hundred milligrams per kilogram per day was associated with delayed metastatic progression and improved survival in dogs following splenectomy when compared with historical control populations.

FOLLOW-UP

Dogs diagnosed with hemangiosarcoma are routinely reassessed through regular physical examinations and laboratory testing. Periodic restaging is performed using thoracic and abdominal imaging modalities, which may include radiography, ultrasonography, echocardiography, computed tomography, or magnetic resonance imaging, depending on the anatomical form and distribution of disease. The frequency and scope of follow-up evaluations are tailored to tumour location, stage, and treatment modality.

PREVENTION

Dermal Hemangiosarcoma

For lightly pigmented, short-haired breeds such as Salukis, Whippets, Italian Greyhounds, and Greyhounds, limitation of sun exposure is recommended to reduce the risk of developing dermal hemangiosarcoma.

PROGNOSIS

Prognosis for hemangiosarcoma varies substantially according to tumour location and extent of disease at diagnosis. In cases of dermal HSA, wide surgical excision is frequently curative, and reported median survival times exceed two years following complete removal. For subcutaneous and intramuscular forms of HSA, long-term outcomes differ among studies; median survival times for dogs treated with surgery followed by adjuvant chemotherapy range from approximately nine months to more than three years.

Dogs with splenic hemangiosarcoma treated with surgery alone typically have median survival times of less than one month to approximately two and a half months. The addition of adjuvant doxorubicin-based chemotherapy extends median survival to five to eight months. Despite chemotherapy, the one-year survival rate remains below ten percent. For renal HSA, dogs undergoing nephrectomy with or without adjuvant chemotherapy have a reported median survival time of approximately nine months.

In cases of cardiac hemangiosarcoma, dogs that do not receive chemotherapy have a median survival time of roughly two weeks, whereas treatment with doxorubicin extends median survival to approximately four months. A small subset of dogs treated with surgical tumour excision followed by adjuvant doxorubicin chemotherapy achieved a median survival approaching six months.

Survival data for feline hemangiosarcoma are limited. Cutaneous forms in cats are generally associated with a more favourable prognosis, with reported median survival times ranging from nine months to four years, whereas visceral presentations carry a poorer prognosis, with median survival times of approximately two and a half months.

SUMMARY

Histiocytic sarcoma and hemangiosarcoma continue to represent two of the most aggressive malignant neoplasms encountered in companion animal medicine. Over the past two decades, however, meaningful progress has been achieved in several key areas. Advances in the understanding of the genetic abnormalities underlying these diseases, along with the recognition of specific breed predispositions, have substantially improved diagnostic precision and disease characterisation.

Therapeutic outcomes for histiocytic sarcoma have improved with the incorporation of surgical intervention and adjuvant chemotherapy, shifting its clinical perception from that of an immediately fatal malignancy to one that, in selected cases, can be managed for extended periods measured in months or even years. In contrast, nondermal forms of hemangiosarcoma remain uniformly fatal despite multimodal treatment approaches.

Ongoing efforts to identify driver mutations and molecular subtypes in both diseases hold promise for the development of more targeted therapeutic strategies. Such advances may ultimately lead to further improvements in prognosis for patients affected by these challenging cancers.

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