Splenic extramedullary hematopoiesis in dogs is frequently detected on multiphase multidetector-row CT as hypervascular nodules

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Abstract
Extramedullary hematopoiesis (EMH) is the formation and development of blood cells outside the bone marrow, and in dogs it frequently occurs in the spleen. Although splenic EMH is a relatively common condition, data regarding its appearance in veterinary medicine are lacking. Our aim was to describe different multidetector computed tomographic (MDCT) features of splenic EMH in dogs. In this descriptive retrospective study, dogs with cytological diagnosis of splenic EMH and three-phase MDCT study of the abdomen were included. Multi-detector CT findings recorded were splenomegaly, appearance of the parenchyma, and mean attenuation of the spleen and lesions. Out of 89 dogs included, 55 (62%) presented multifocal nodular aspect, 14 (16%) mass, 12 (13%) diffuse heterogeneous parenchyma, and eight (9%) normal spleen. Most lesions were hyperattenuating to the parenchyma in the arterial (57/89, 64%) and portal (59/89, 66%) phases; whereas in the interstitial phase only 40 of 89 (45%) were hyperattenuating. The mean attenuations of the lesions were higher compared to the values of the adjacent spleen, and the difference of the mean attenuation between the hyperattenuating lesions and the parenchyma was significantly higher in arterial and portal phases than in interstitial phase (P < .0001). The most frequent MDCT aspect of splenic extramedullary hematopoiesis consists of multiple nodules hyperattenuating to the normal spleen, best visualized in the arterial and portal phases.

Keywords
canine, computed tomography, extramedullary hemopoiesis, spleen

1 | INTRODUCTION

Many diseases of the spleen frequently occur in dogs, and the differentiation between clinically relevant abnormalities and benign findings with imaging modalities is challenging. One of the most common conditions is splenic extramedullary hematopoiesis (EMH), but published data regarding its appearance in veterinary medicine are currently lacking. Splenic masses and nodules are frequently observed on imaging in canine patients, and the diagnosis ranges from benign lesions discovered incidentally (e.g., nodular hyperplasia) to malignant neoplasia, such as hemangiosarcoma.¹–⁴ Some studies in veterinary literature described the CT characteristics of splenic masses in dogs.⁵–⁷ Malignant masses were described to have lower Hounsfield Unit (HU) values, with 55 HU in post contrast images as a threshold value to distinguish between malignant (<55 HU) and non-malignant (>55 HU) masses, as benign nodules (nodular hyperplasia) showed the highest enhancement.⁵ In a study regarding two-phases CT characteristics of hepatic and splenic masses, no CT features were found to be significantly associated with malignant or non-malignant splenic lesions, as splenic hemangiosarcoma, hematoma, and nodular hyperplasia showed variable features.⁶

In a recent study, the triple-phase helical CT features of different splenic lesions were described, and in particular, nodular hyperplasia showed a homogeneous normal enhancement pattern, while hematoma and hemangiosarcoma displayed a heterogeneous...
pattern. Extramedullary hematopoiesis is defined as the formation and development of blood cells outside the bone marrow. In adult humans, EMH is seen in case of insufficient bone marrow function or can be incidentally discovered during evaluation for unrelated reasons. The liver and spleen are the two most common abdominal locations of EMH in people, most commonly manifesting as organomegaly and less commonly with focal mass-like lesions.

The spleen is a common site of EMH in dogs. Studies indicate that, in this species, EMH can occur in association with degenerative and inflammatory conditions, including hemolytic anemia, myeloproliferative and lymphoproliferative disorders, and thrombosis; although in most cases can occur independently or without an obvious underlying cause. Despite the frequency with which EMH is found in the spleen of canine patient, studies regarding its CT characteristics are lacking. The aim of the current study was to describe multidetector CT (MDCT) features of splenic EMH in dogs.

2 | MATERIALS AND METHODS

2.1 | Study design, sample, and setting

This was a single-center descriptive retrospective study. The sample population included client-owned dogs that underwent CT examinations for varying purposes. All collection procedures were performed at the Diagnostic and Interventional Radiology Division of the San Marco Veterinary Clinic solely for dog's benefit and for standard diagnostic and monitoring purposes. Previous informed written consent was obtained from all dog owners. All the procedures performed complied with the European legislation “on the protection of animals used for scientific purposes” (Directive 2010/63/EU) and with the ethical requirement of the Italian law (Decreto Legislativo 04/03/2014, n. 26).

All dogs that had undergone CT examination of the abdomen between January 2014 and March 2019 were considered for inclusion in the study. Eligibility criteria and information required were: (a) cytological diagnosis of splenic EMH, (b) multiphase abdominal CT, (c) complete anamnestic, clinical, and clinic-pathological evaluation available (for further study; results will not be reported here). Results of histopathology of the spleen, when available, were also recorded. Patients with concomitant cytological or histological diagnosis of splenic neoplasia were excluded from this study, as well as those having a single phase MDCT examination.

All decisions for dog inclusion or exclusion were made by a consensus of two authors, a veterinary clinical pathologist and a veterinarian with expertise in CT imaging (M.C. and G.B., respectively).

2.2 | Image analyses, interpretation, and CT data registration

The CT examinations were retrieved from the PACS (Picture Archiving Communication System - syngo.plaza, Siemens Healthineers, Milano IT) and analyzed using a dedicated freestanding workstation and vendor-specific postprocessing software (Syngo.Via, Siemens, Germany) by two authors with 2 and 18 years of experience in MDCT imaging (A.C. and G.B.). The reviewers were aware of the diagnosis of splenic EMH (major inclusion criterion) at the time of interpretation of the images, but were unaware of the previous clinical report. Volume CT datasets obtained from the mixed (100-150 kVp) portal venous phase were used for the study. Images were interpreted by both authors together to reach a consensus, using a combination of 2D multiplanar reformations, and 3D volume rendered postprocessing techniques. For image analyses, window settings in different vascular phases were dynamically adjusted to obtain a comprehensive visual estimation of the spleen characteristics (from 190 to 480 window width and from 16 to 90 window level).

The following CT qualitative characteristics were recorded for each dog finally recruited for the study: (a) dimension of the spleen, evaluated subjectively (normal/enlarged); (b) appearance of the parenchyma: normal, diffusely heterogeneous, presence of focal/multifocal nodules (<1 cm) or presence of one (or more) mass (>1 cm). The appearance of the parenchyma was defined "normal," when the spleen showed completely homogeneous enhancement or when it had heterogeneous enhancement in early phases, reflecting variable blood distribution between the red and white pulps and homogeneous enhancement in late phases.

The parenchyma was defined “heterogeneous” when it was heterogeneous in all phases and with focal/multifocal nodular aspect when one or multiple nodules were present within the parenchyma. When lesions were bigger than 1 cm, they were considered as masses, as in previous study. The quantitative assessment of the spleen included: (a) the attenuation value (expressed in HU) of the spleen parenchyma and of the focal areas in all three vascular phases. Measurements were made drawing a round region of interest (ROI) for the focal area and another one, of the same size, for the surrounding splenic parenchyma having normal appearance. The mean, minimum, and maximum attenuation value was each time recorded.

2.3 | Statistical method

Data analyses were selected and performed by one board certified clinical pathologist (M.C., PhD in Clinical Epidemiology and Biostatistics Diplomate) using dedicated analysis software (Microsoft Excel, 1997–2018; Analyse-IT Software LTD). For the statistical analysis, a Shapiro-Wilk test was performed to test the distribution of data. Different factors (age, weight, sex, sexual condition) were tested both with univariable and multivariable analyses (ANOVA-MANOVA) to assess any influence of these factor on the mean attenuation values. Differences between the mean of the means/medians HU of the spleen and mean of the means/medians of the lesions were tested with a Wilcoxon-Mann-Whitney test. Significance level was set at \( \alpha = .05 \).

3 | RESULTS

Eighty-nine dogs met the inclusion criteria; 43 were females and 46 were males. The median age was 10.7 years and median weight 21.7
kg. Twenty-eight of 89 dogs were crossbreed dogs, while nine were Labrador Retrievers, five Golden Retrievers, five Beagles, four Cocker Spaniels, three Boxers, three Yorkshire Terriers, two German Shepherds, two Rottweilers, two Bichon Frises, two Maltese dogs, and two Poodles, and one each of the following breeds: Alaskan Malamute, Boston Terrier, Flat Coated Retriever, Greyhound, Medium Schnauzer, Giant Schnauzer, Scottish Terrier, Siberian Husky, Italian Spinone, Tibetan Terrier, Airedale Terrier, American Staffordshire Terrier, Bo- btail, Bernese Mountain dog, English Bulldog, Pug, Chihuahua, Jack Russell Terrier, Pastore Bergamasco, Weimaraner, Whippet, and West Highland White Terrier.

3.1 CT scanning techniques

Multiphase CT data were obtained with a second or third generation dual-source CT (128 × 2 or 192 × 2 dual-source CT; Somatom Definition Flash or Force; Siemens, Erlangen, Germany). Three-phases tomo- graphic studies of the abdomen were consistently obtained with the patient in the sternal recumbency on the CT table, head first and scanning in cranio-caudal direction. An iodinated contrast agent (iohexol 370 mgI/mL, 2 mL/kg dosage followed by a saline flush) was each time injected in a cephalic vein at an injection rate varying between 1.5 and 5 mL/s depending on the dog size (from 1.5 to 2 mL/s for dogs <15 kg and from 2 to 5 mL/s for larger dogs) using a dual barrel injector system. A bolus tracking technique was always used to tailor the arterial phase on the patient. With the bolus-triggering technique used, an ROI was placed in the descending aorta, at diaphragmatic level; a series of low-dose, nonincremental scans were obtained and the attenuation within the ROI constantly automatically monitored. The acquisition of the arterial phase started automatically when a pre- set enhancement of 100 HU was reached within the aorta. A standard delay of 20 s was preset between the arterial and the portal phase; interstitial phase was acquired between 3 and 5 min after the end of the contrast agent injection. Computed tomography settings were as follows: one tube for arterial and interstitial phase (120 kVp) and two tubes for portal venous phase at 100/140 kVp. For all phases, 400 mAs/rotation (0.28 s), collimation 128/192 × 0.6 mm; images were reconstructed at 0.3 mm using a soft-tissue reconstruction algorithm.

3.2 CT findings

The first qualitative feature considered was the dimension of the spleen, evaluated subjectively with the use of both 2D-multiplanar reformation (Figure 1A–C) and 3D-volume rendering (Figure 1D) tech- niques: 26 of 89 dogs (29%) showed subjective splenomegaly, while in the remaining 63 of 89 (71%) dogs, the size of the spleen was considered normal. The focal/multifocal nodular aspect (Figure 2D) was the most frequent one, present in 55 of 89 dogs (62%). In the remaining cases, the appearance of the parenchyma was considered normal in eight of 89 dogs (9%) (Figure 2A), heterogeneous in 12 of 89 dogs (13%) (Figure 2B), and in 14 of 89 dogs (16%), a splenic mass was present (Figure 2C). No dogs with more than one mass were included. Most of the lesions appeared hyperattenuating to the surrounding parenchyma, especially in arterial (57/89, 64%; Figure 3A) and portal phases (59/89, 66%; Figure 3B), while in interstitial phase, 40 of 89 (45%) dogs were hyperattenuating and 39 of 89 (44%) dogs were isoat- tenuating (Figure 3C). In 10 of 89 (11%) cases, the lesions were hypoattenuating with respect to the splenic parenchyma in the three phases. The medians/means of the mean attenuations of the lesions and the spleen in all phases are reported in Table 1. The difference of the mean attenuation between the lesions and the parenchyma was significantly higher in arterial and portal phases than in interstitial phase (P < .0001; Figure 4). Attenuation was not influenced by age, weight, sex, and sexual condition neither in univariable nor in multi- variable analyses. When considering the masses alone, the majority of them were hyper or hypoattenuating to the surrounding splenic parenchyma in all phases; three of 14 were heterogeneously hypoattenuating, but showed a hyperattenuating peripheral rim of enhance- ment (Figure 5). The results regarding the appearance of the splenic masses are reported in detail in the Tables 2 and 3. Four out of the 14 dogs with splenic masses were subjected to splenectomy, and the fol- lowing histological examination confirmed the diagnosis of EMH, without underlying neoplastic causes.

4 DISCUSSION

The multiphase-MDCT features of EMH in the spleen of dogs were for the first time described in this study. According our results, splenic EMH in dogs can show different presentations. The presence of multiple hyperattenuating nodules, especially visible in arterial and portal phases, was the most frequent finding. Other features, less frequent, were the presence of diffusely heterogeneous parenchyma, splenic mass, and splenomegaly, although also cases with normal appearance of the spleen were recorded.

The most frequent MDCT aspect of EMH was a multifocal nodular aspect, hyperattenuating to the normal spleen: due to the hematopoietic activity, the nodules appeared markedly hypervascular with respect to the surrounding parenchyma. This result is in agreement with previous studies, in which benign lesions were described to be hyperattenuating to the remaining splenic parenchyma after contrast administration, although EMH nodules were not described in these studies.

Nodules of EMH in the spleen were more hyperattenuating compared to the rest of the parenchyma in the arterial and portal phases, as the difference of the mean attenuation between the hyperattenuating lesions and the parenchyma was significantly higher in arterial and portal phases than in interstitial phase (P < .0001). This result supports the theory of active nodules, in which the blood supply is higher in early phases due to the hematopoietic activity; in the equi- librium phase, these nodules tend to become isoattenuating to the rest of the parenchyma, and are subsequently less visible. A normal post- contrast splenic enhancement was found in 9% of the dogs of this study, and 13% showed a diffusely heterogeneous pattern of enhancement. These two conditions could reflect the fact that EMH in the spleen of dogs can be diffuse, and not only nodular.
**FIGURE 1** Example of splenomegaly. Two different 3D image volume techniques were used: multiplanar reformation (MPR), in which the three orthogonal imaging planes are seen (A, transverse plane; B, dorsal plane; C, sagittal plane) and permit to identify the enlargement of the spleen in all three planes (width, height, length), and volume rendering (VR) technique (ventral view) (D), helpful to display anatomical structures in an interactive and 3D way. In this case, the spleen was subjectively considered enlarged because was bigger than expected for a patient under general anesthesia, and tend to displace the intestinal loops, as seen in the VR image. Abbreviations: S, spleen; LK, left kidney; L, liver [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 2** Different appearances of splenic parenchyma (transverse sections). A, Normal enhancement of splenic parenchyma, homogeneous. B, Diffusely heterogeneous enhancement of the spleen, no focal lesion detected. C, Splenic mass: a rounded, well-defined, heterogeneously enhancing mass is deforming the splenic profile at the level of the head (arrow). D, Multifocal nodular aspect: multiple, rounded, well-defined, hyperattenuating nodules are visible throughout the whole splenic parenchyma (arrowheads). Abbreviations: S, spleen; LK, left kidney; RK, right kidney

In 16% of the cases, a splenic mass was present. In humans, the EMH in the spleen can present as a focal mass, but is much less common than the diffuse presentation\(^{10,11}\) and CT appearance of EMH can consist of heterogeneous, hypovascular soft-tissue masses\(^ {11}\) or of well-defined, highly and heterogeneously enhanced lesion.\(^ {16,17}\) Also, in this study, both hypervascular and hypovascular masses were seen, and this result is in agreement with previous study in dogs in which malignant and non-malignant splenic masses showed variable CT features.\(^ {6}\) In another study, benign splenic masses showed homogeneous normal enhancement while malignant masses were heterogeneously poorly to remarkably enhancing,\(^ {7}\) although in these studies only nodular hyperplasia was described and no patients with extramedullary hematopoiesis were included.\(^ {6,7}\)

In some cases, EMH appeared as a mass hypoattenuating to the adjacent splenic parenchyma in all three phases, with a peripheral rim of enhancement. The presence of hypoattenuating areas could be explained with the presence of inactive EMH lesions, in which iron deposition and fatty infiltration are the predominant features, as described in human medicine.\(^ {16,18}\) The hypervascular masses, as well as the hypervascular rim, are most likely consistent with active hematopoietic areas in the spleen.\(^ {16,18}\)

Splenic enlargement is the most frequent imaging appearance of intra-abdominal EMH reported in in people.\(^ {10,11}\) The spleen was subjectively evaluated “larger than expected” only in 29% of the dogs included here. This difference could reflect biological differences in EHM between the two species as well as technical issues. Indeed, the presence of splenomegaly in dogs is normally subjectively evaluated, because standardized ranges for different breed and sizes are lacking. Again, all dogs included in this study underwent MDCT examination under general anesthesia, condition that can affect the size of the spleen, depending on the protocol used.\(^ {19,20}\)

This study has some limitations. First of all, the cytological diagnosis of EMH and the histological confirmation in a limited number of cases. Cytology can be considered as the gold standard for the diagnosis of EMH in dogs,\(^ {8,12}\) but with histology it is also possible to exclude other conditions (as neoplasia) involving the spleen at the same time. Another limitation is the ultrasound guided samples of the lesions we found in CT; sometimes, due to the vascular origin of the nodules, they are not visible on ultrasound. We tried to minimize this limitation performing the samples directly on CT table, immediately after the MDCT exam.

In conclusion, based on our review of the literature, this is the first published study describing the MDCT features of splenic EMH in dogs and the use of a three-phase, bolus-triggered MDCT technique for the evaluation of the spleen. The most frequent appearance consisted
Figure 3  Different aspects of the same spleen in three vascular phases. On top, different enhancement of the liver and great vessels in the three phases (transverse sections): A<sub>1</sub>, arterial phase; B<sub>1</sub>, portal phase; C<sub>1</sub>, interstitial phase. Abbreviations: Ao, aorta; PV, portal vein; CVC, caudal vena cava. Below, the appearance of the same spleen in the three phases (dorsal sections): A, arterial phase; B, portal phase; C, interstitial phase. Note that the multiple hyperattenuating nodules, well seen in late arterial and portal phases, are not visible in interstitial phase.

Table 1  Means (or median) of the mean attenuations of the lesions and the respective splenic parenchyma in all phases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean (SD) (HU)</th>
<th>Min (HU)</th>
<th>Max (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spleen</td>
<td>Lesions</td>
<td>Spleen</td>
</tr>
<tr>
<td>Arterial</td>
<td>74 (12.7)</td>
<td>109 (52.3)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>56</td>
</tr>
<tr>
<td>Portal</td>
<td>92.8 (13.4)</td>
<td>122.2 (29.5)</td>
<td>54</td>
</tr>
<tr>
<td>Interstitial</td>
<td>93 (11.2)</td>
<td>106.7 (22.9)</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>*</sup>Data not normally distributed, presented as Median (IQR) instead of Mean (SD).

Abbreviations: SD, standard deviation; IQR, interquartile range; Min, minimum; Max, maximum; HU, Hounsfield Units.

of multiple nodules, hypervascular to the rest of the parenchyma, reflecting an active hematopoietic activity. These nodules were best visualized in the arterial and portal phases, underlying the importance to evaluate the spleen, as well as other abdominal organs, in different vascular phases. Other aspects of splenic EMH included normal and diffusely heterogeneous enhancement, reflecting the possibility of a diffuse EMH in dogs, as well as presence of splenic masses. For this reason, authors believe it is important to also include EMH as differential diagnosis for splenic masses in dogs. Further investigations are needed to compare the findings described in this study and MDCT features of other splenic diseases (neoplastic, inflammatory, vascular), in order to assess the differences between EMH and other conditions, and to establish key features that could permit the differentiation of benign and malignant processes in the spleen.
**FIGURE 4** Boxplot with whiskers from minimum to maximum graphic showing the degree of dispersion of the data inside each group. In ordinate are reported the differences between the mean values of mean attenuation (HU) between the lesions and the corresponding splenic parenchyma, and in abscissa the three different vascular phases (groups): 0, arterial phase; 1, portal phase; 2, interstitial phase. The difference between the differences of the mean attenuation between lesions and parenchyma is statistically significant when comparing groups 0 and 2 (arterial-interstitial) ($P < .0001$) and groups 1 and 2 (portal-interstitial; $P < .0001$).

**FIGURE 5** Three examples of splenic masses with hypervascular rim (dorsal views). Rounded, well-defined, heterogeneously hypoattenuating masses are seen in the spleen (arrow), in two cases deforming the splenic profile (A, B) and in the other case within the parenchyma (C), in all three cases, surrounded by a markedly hyperattenuating rim (arrowheads). Abbreviations: S, spleen; L, liver; RK, right kidney.

**TABLE 2** Appearance of splenic masses (total: 14) compared to the splenic parenchyma in the three phases

<table>
<thead>
<tr>
<th></th>
<th>Hyperattenuating</th>
<th>Isoattenuating</th>
<th>Hypoattenuating</th>
<th>Hypoattenuating + rim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Portal</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Interstitial</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**TABLE 3** Medians/means of the mean attenuations of the 14 masses and the respective splenic parenchyma in all phases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean (SD) (HU)</th>
<th>Min (HU)</th>
<th>Max (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spleen Masses</td>
<td>Spleen</td>
<td>Masses</td>
</tr>
<tr>
<td>Arterial</td>
<td>70.7 (11.8)</td>
<td>61</td>
<td>83</td>
</tr>
<tr>
<td>Portal</td>
<td>98.8 (12.5)</td>
<td>80</td>
<td>127</td>
</tr>
<tr>
<td>Interstitial</td>
<td>96.7 (11.3)</td>
<td>86</td>
<td>116</td>
</tr>
</tbody>
</table>

*Data not normally distributed, presented as Median (IQR) instead of Mean (SD). Abbreviations: SD, standard deviation; IQR, interquartile range; Min, minimum; Max, maximum; HU, Hounsfield Units.
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Category 1
(a) Conception and Design: Bertolini
(b) Acquisition of Data: Cordella
(c) Analysis and Interpretation of Data: Caldin, Bertolini, Cordella

Category 2
(a) Drafting the Article: Cordella
(b) Revising Article for Intellectual Content: Bertolini, Caldin

Category 3
(a) Final Approval of the Completed Article: Bertolini, Caldin, Cordella

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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