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SHORT COMMUNICATION Clinical Case Report

Characterization of canine hemangiosarcoma by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography

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Abstract

Our objective was to characterize the use of ^{18}F-fluorodeoxyglucose (FDG)-PET/CT in the diagnosis of primary splenic hemangiosarcoma in combination with histopathology and immunohistochemistry. A 7-year-old castrated male mixed breed dog weighing 6 kg was presented with the complain of recurring pruritus, ulceration, and alopecia. X-ray and ultrasonography confirmed the splenic nodule of 0.5 cm in the abdominal cavity. Further FDG-PET/CT staging showed a hypermetabolic splenic mass with increased glucose uptake with SUV_{max}= 10.69 and $SUV_{average}$= 5.172 with no distant metastases. Histopathology was consistent with splenic hemangiosarcoma. Tumor cells were strongly positive for CD31, a strong marker of cells with endothelial-origin. Thus, we report the first case that describes the utility of FDG-PET/CT in diagnosis of canine primary splenic hemangiosarcoma.

Key Words: FDG-PET/CT, hemangiosarcoma, immunohistochemistry

Hemangiosarcomas (HSA) are the most common malignant tumors originated from endothelial cells and mostly affect larger breed middle-aged dogs than any other species [11)]. The most common primary site in the dog is spleen which in the severe case may rupture and cause sudden and severe internal bleeding eventually metastasizing to the right atrium of the heart (8.7-25%), liver, lung, omentum in particular followed by skin and subcutis. Prognosis is quite variable as it is very frequently associated with metastasis.

Clinical symptoms may include weight loss, lethargy, anorexia, and anemia. Splenic HSA is characterized by 3 stages. In stage 1, tumors are confined to spleen without any metastases. Stage 2 is characterized by the presence of ruptured spleen with or without lymph node involvement. Tumors are large and invasive with distant metastases in stage 3. Histologically, it is reported to be of three types in dogs: capillary, cavernous, and solid.

Diagnosis and staging of HSA has been done by ultrasonography, radiography, computed tomography (CT) scan, and surgeries in veterinary field. Whole body ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT is the technology that combines PET with CT to put function and form metabolically active malignant lesions by FDG uptake [10)] and because tumor cells

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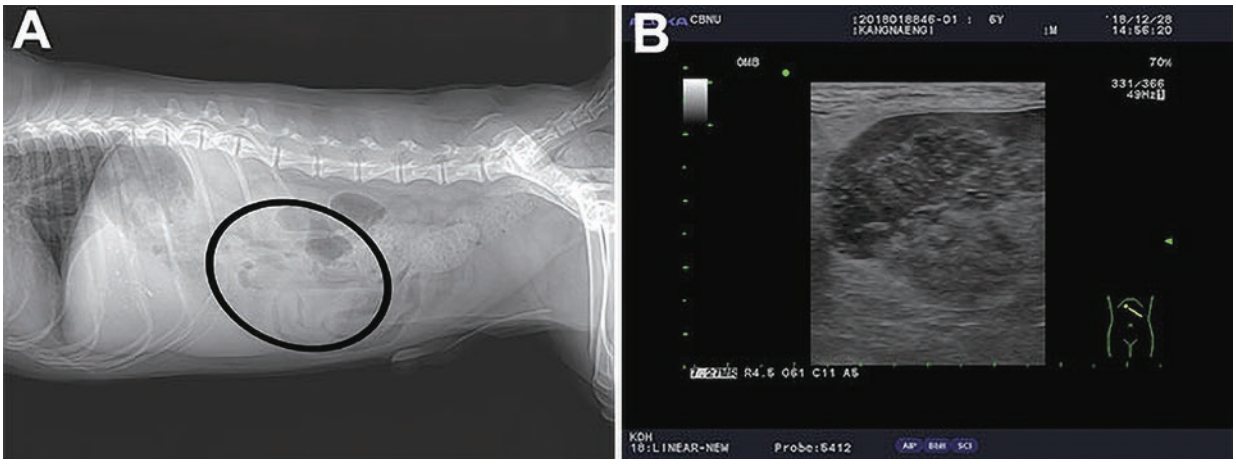

Fig. 1 Radiological evaluation in a dog.
(A) X-ray showed the presence a soft tissue mass with length of 5.7 cm behind the caudal margin of liver (circle). The LL/T11 ratio was increased to 8.14. Hepatomegaly was also observed. (B) Ultrasonography showed a large amorphous irregular round-shaped hypoechoic splenic mass. Mild angiogenesis was found.

often use more glucose than normal cells, ^{18}F-FDG is an excellent tool to detect malignant neoplastic tissue. It is well-established and routinely used in staging and monitoring cancer in human medicine. However, in veterinary medicine, it is still innovative, and not many tumor cases have been reported using this technique. HSA is a malignant neoplasm that shows noticeably high metabolic activity area due to anaerobic glycolysis needed for energy consumption. Glucose transporters (GLUT) are present on a cell membranes and especially enhanced on tumor cells membranes [8, 12]. FDG is internalized via this GLUT, phosphorylated to ^{18}F-FDG-6-phosphate (^{18}F-FDG-6-p) and trapped inside the cells since, unlike glucose, it cannot proceed to the glycolytic pathway [5]. Earlier mRNA sequencing studies have shown high expression of GLUT1 and GLUT3 in all canine HSA samples analyzed suggesting that HSA will likely take up glucose avidly and thus FDG as well [6]. FDG-PET/CT has also been described as a promising tool for staging and monitoring of dogs with HSA [3], but no studies using PET-CT to detect splenic HSA in dogs have been reported yet.

This study aims to describe the clinical, FDG-PET/CT and histopathologic findings of splenic HSA in a dog. To our knowledge, this is the first report to assess the potency of FDG-PET guided method in canine patients with naturally occurring primary splenic hemangiosarcoma.

A 7-year old, mixed breed, castrated male dog with the complain of anorexia, recurring pruritus, ulceration, alopecia and history of long-term steroid medication was admitted to Veterinary Medical Center, Chungbuk National University, Republic of Korea. Physical examination showed mild dehydration. Other clinical symptoms were normal with slight anorexia. CBC showed leukocytosis (WBC: 32.97 × 10^8/μL), increased CRP, ALP, and anemia (Hb:8.8gm/dl). Abdominal X-ray revealed the presence of mass of around 5.7 cm behind the caudal margin of liver (Fig. 1A). Ultrasonography confirmed the presence of large amorphous round-shaped hypoechoic splenic mass (Fig. 1B) with no other visible lesions in other abdominal organs. Hepatomegaly was also observed. We decided to further stage and characterize the nodule with whole-body FDG-PET/CT.

The PET/CT system used in this study was a DiscoverySTE (General Electric Medical Systems, Waukesha, WI, USA). The dog was fasted for at least 12 h before the induction of anesthesia. General anesthesia was induced with intravenous administration of propofol (6 mg/kg; Provive, Myungmoon Pharm, Seoul, Republic of Korea) and maintained by inhalation of 2.0% isoflurane

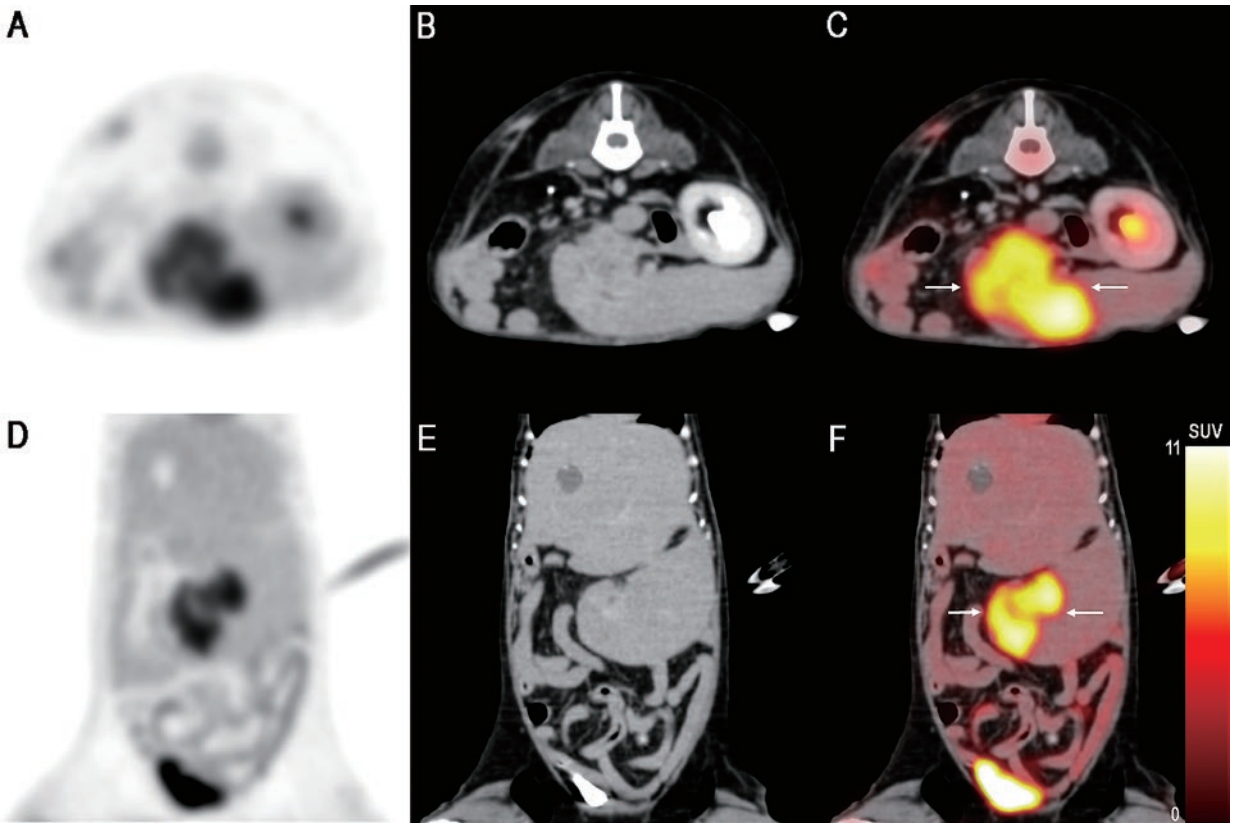

Fig. 2 PET, CT, and PET/CT fusion images in a dog.
(A) Transverse PET image. (B) Transverse CT image. (C) Transverse PET/CT fusion image. (D) Dorsal PET image. (E) Dorsal CT image. (F) Dorsal PET/CT fusion image. The PET (A, D) and PET/CT fusion (C, F) images show a hypermetabolic region (arrows) in the splenic mass which was proven to be hemangiosarcoma. On PET image, high and low FDG uptakes were represented as blackish and whitish color, respectively. On PET/CT fusion image, high and low FDG uptakes are represented as yellowish and blackish to reddish color, respectively.

(Terrell; Piramal Critical Care, Bethlehem, PA, USA) in a circle rebreathing circuit. FDG (6.29 MBq/kg) was administrated intravenously into a saphenous vein, followed by 5 ml of 0.9% normal saline for flushing of residual FDG. Low-dose computed tomography (CT) images were acquired prior to the PET scan to use as an anatomical background. Thirty-minute PET scans were obtained one hour after FDG injection. The images were reconstructed with iterative techniques (four iterations with 28 subsets) with a slice thickness of 3.27 mm, matrix size of 256 × 256, with pixel sizes of 1.95 mm for the emission scan. Corrections for attenuation and scatter were applied. A Gaussian post-reconstructing smoothing filter with a 5-mm full width at half-maximum was used to achieve uniform image resolution across sites. PET image analysis was conducted using OsiriX MD v10.0 (Pixmeo Sarl, Geneva, Switzerland). The regions of interest (ROIs) were drawn manually on PET/CT fusion images. Metabolic activity of ROI was converted to a standardized uptake value (SUV) as follows: SUV = average tissue concentration of FDG (MBq/ml)/injected dose (MBq) per body weight (g).

FDG-PET/CT showed a hypermetabolic splenic mass with increased glucose uptake with SUV_{max}= 10.69 and $SUV_{average}$= 5.172 (Fig. 2(A-F)) confirming the mass as malignant tumor. Distant metastases to heart or nearby tissues were not observed indicating the mass as primary tumor. However, hypermetabolic area (SUV_{max} = 3.593 and $SUV_{average}$ = 1.996) was observed in the middle gluteal skin along the muscle of left iliac bone due to the presence of granulation tissue. Thus, increased

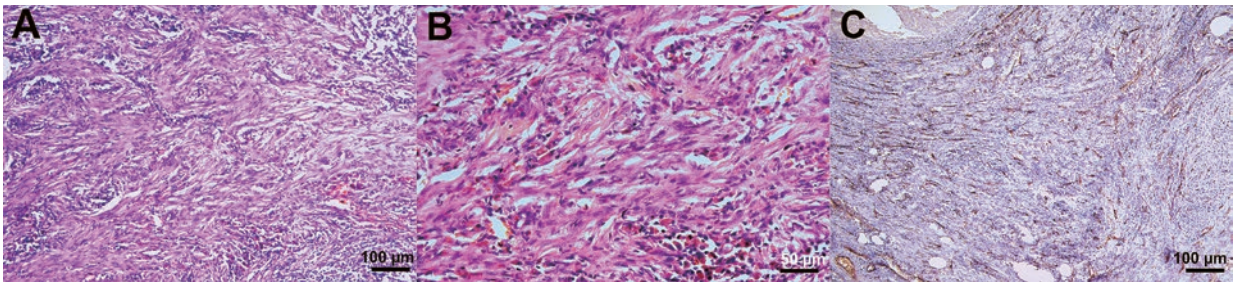

Fig. 3 Histopathological and immunohistochemical evaluation of the splenic lesions in a dog.
(A) The mass showed endothelial-like, fusiform cells forming tortuous vascular channels of different seizes separated by fibrous stroma. Variable amounts of eosinophilic cytoplasm without distinct borders with pleomorphic nuclei containing small amounts of chromatin were found. H&E stain. (B) High magnification of histopathological evaluation of the splenic HSA shown in Fig. 3A. H&E stain. (C) Immunohistochemical staining of the splenic mass showed that the tumor cells were stained strongly positive for anti-CD31 antibody, indicating the endothelial origin of tumors.

FDG uptake of the mass was divided into two parts with different SUVmax values.

To alleviate the risk of metastasis, surgical resection of the spleen was done instead of fine needle aspiration (FNA). Laparoscopic splenectomy revealed the mass of size 5.7 x 5 x 5 cm. Grossly, the spleen has a well-defined, irregularly shaped mass replaced by severe multifocal to coalescing hemorrhagic nodules with some cystic spaces. Histopathologic examination revealed that the mass consisted of erratic streams of pleomorphic, fusiform or spindle cells forming the linings of tortuous vascular channels of different seizes supported by fibrous stroma (Fig. 3A and 3B). The neoplastic cells had variable amounts of eosinophilic cytoplasm with pleomorphic nuclei containing small amounts of chromatin. Mild anisocytosis and anisokaryosis were found. Immunohistochemistry revealed strong reactivity to rabbit polyclonal anti-CD31 antibody (Abcam, Cambridge, UK) confirming the endothelial origin of this tumor (Fig. 3C).

Primary HSA is a vascular tumor and its close association with endothelial cells causes extravasation and metastases lending to very aggressive biologic behavior and poor prognosis [11]. Primary splenic HSA tends to show variable morphological features and may be mistaken for other benign vascular tumors complicating the diagnosis both histologically and radiologically [4].

Use of FDG-PET/CT in the diagnosis and staging of splenic HSA is very rarely reported even in human [1, 7, 13]. Combined PET/CT provides considerably more information on regional and distant lymph node metastases. Thus, PET/CT can dependably differentiate between benign and malignant solid splenic masses [9]. Few reports have been done in veterinary medicine to characterize the various tumors using whole-body FDG PET/CT [10] with no cases reported with primary splenic HSA till date. A pilot study had just shown the use of FDG-PET/CT in diagnosing metastasis after splenectomy in a dog with stage 2 splenic HSA [3]. So, we could not make a direct comparison with other studies. In the present case, spleen had solid tumors and showed avid FDG uptake. In contrast to our report, the use of FDG PET/CT in a human patient with solid splenic masses showed highly negative predictive value [9]. However, there is a correlation between the tumor size and the intensity of FDG uptake. Combining the use of FDG-PET/CT with other techniques would lead to a definitive diagnosis of primary splenic HSA.

The CBC and histopathology were constant with HSA [2, 13, 14]. Blood cells pooled in the newly formed vessels and formed clots. These clots are known to prevent blood and nutrients from reaching tumor cells causing the cells to die. CD31, a specific and most reliable marker for differential diagnosis with other tumors such as histiocytic sarcoma, mast cell tumor, and lymphoma [13], confirmed the splenic HSA.

Untimely splenectomy is a great threat to spleen that causes spontaneous rupture and intra-abdominal hemorrhage due to increased friability. Splenic HSA may be impossible to identify if the resulting hemorrhage, ischemia, and necrosis erase or displace the actual tumor. The treatment protocol and prognosis were significantly changed due to the results of FDG-PET/CT in ten canine patients with various cancers [10] suggesting that the use of FDG-PET/CT would help us to plan and monitor the treatment protocol leading to improving the quality of life.

In conclusion, earlier recognition of tumors by improving diagnostic techniques is essential in veterinary medicine for successful therapeutic interventions. PET/CT is very limited in veterinary medicine but could be an attractive and useful tool for minimally invasive diagnosis, staging, restaging and monitoring of highly metastatic primary splenic HSA. Our study could be used as a promising data to provide a major impact on treatment and prognosis of primary splenic HSA using FDG-PET/CT imaging technique in veterinary medicine.

Acknowledgments

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