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Case Report

Use of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography in a Miniature Pig (*Sus scrofa domestica*) with Pneumonia

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A 1-y-old male miniature pig housed in our laboratory facility was evaluated for weight loss and rough coat condition. CBC results revealed neutrophilia. Radiography of the thoracic area showed increased opacity throughout the thoracic cavity except for the right caudal lobe. ^{18}F-labeled fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET–CT) revealed elevated standard uptake values in the area corresponding to the radiologic findings. Follow-up thoracic radiography taken 2 wk after FDG-PET–CT showed several interval changes, including markedly decreased opacity throughout the entire thoracic cavity. Necropsy revealed adhesions between the upper portion of the caudal lobe of the left lung and thoracic wall. ELISA for several closely related infectious species confirmed the presence of antibody to *Actinobacillus pleuropneumoniae* serovar V.

Abbreviations: FDG-PET–CT, ^{18}F-labeled fluorodeoxyglucose positron emission tomography–computed tomography; NOS2, nitric oxide synthase 2; SUV, standard uptake value.

Functional imaging by using ^{18}F-labeled fluoro-2-D-deoxyglucose in positron emission tomography–computed tomography (FDG-PET–CT) is useful for the diagnosing and staging malignant diseases, planning image-guided therapy, and monitoring treatment.[16] This visual assessment tool has been used mainly in clinical oncology. However, the capability of FDG-PET–CT to detect biologic activities in tissues might also be applied in cases of benign diseases related to infection or inflammation. In miniature pigs, few cases of metastatic cancer have been evaluated by FDG-PET–CT,[3] and no reports describe the use of FDG-PET–CT to assess infection or inflammation in this species.

Porcine pleuropneumonia is one of the most important respiratory diseases of intensively raised swine. This disease causes enormous economic losses in the swine industry in many countries[22] and has been the focus of veterinary scientific research for several decades.[7] However, most research in this area has focused on farm pigs; to date, pleuropneumonia has not been studied in miniature pigs.

Miniature pigs are important models in biomedical research and are used predominantly for preclinical studies involving surgical and interventional methods. The number of miniature pigs reared in laboratory facilities has been increasing consistently.[30] Here we report the use of FDG-PET–CT in a laboratory miniature pig presumed to be infected with *A. pleuropneumoniae* serovar V. We describe the possible misinterpretation of FDG-PET–CT data in the differential diagnosis of lung lesions of miniature pigs and the potential value of FDG-PET–CT for the evaluation of infectious pneumonia.

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Case Report

In July 2010, a 1-y-old, crossbred (Yucatan miniature pig × Vietnamese pot-bellied pig × Pygmy hog × Korean native pig) miniature pig (PWG micropig; Medi Kinetics Korea, Pyeongtaek, Korea) housed in an indoor laboratory animal facility presented with weight loss and rough coat condition. This boar was part of a research project approved by the IACUC of Konkuk University and had been procured from a vendor that maintains miniature pigs within an SPF barrier system. This pig was negative for pseudorabies virus, porcine reproductive and respiratory syndrome virus, and *Haemophilus parasuis*. It had remained within the closed miniature pig colony at our facility. Due to its assignment to research evaluating anesthesia monitoring protocols for miniature pigs, the pig underwent one episode of general anesthesia with medetomidine (Domitor, Pfizer Animal Health Korea, Seoul, Korea) and tiletamine–zolazepam (Zoletil, Virbac, Carros, France) administered via intramuscular injection; the pig had not been enrolled in any other study prior to the appearance of clinical signs.

On physical examination, the boar appeared quiet and slightly depressed and exhibited mild weight loss (1.5 kg from the initial 17 kg), but its appetite was not altered. The periocular and snout skin region was dirty with clear nasal discharge present. CBC and leukocyte differential counts revealed moderate leukocytosis ($21.00 \times 10^3/\mu L$), neutrophilia ($17.94 \times 10^3/\mu L$, 85.41%), and lymphopenia ($0.94 \times 10^3/\mu L$, 4.48%).[23,24] AST levels were slightly

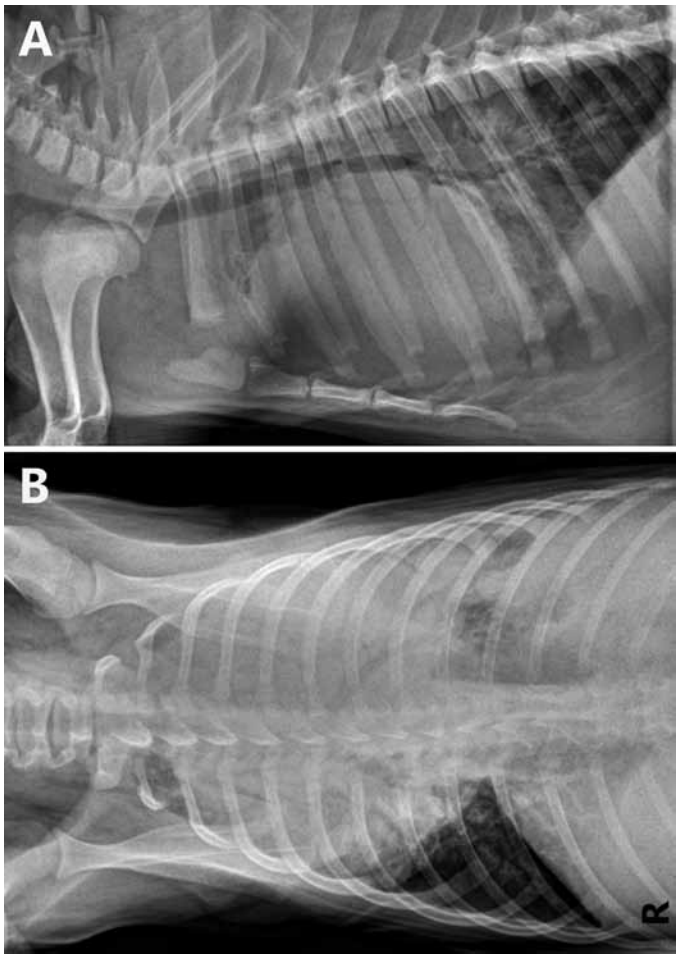

Figure 1. Radiographs taken before FDG-PET–CT scan. (A) Lateral thoracic view demonstrating an obscured cardiac silhouette and narrow, elevated trachea. (B) Ventrodorsal thoracic radiograph, demonstrating increased opacity throughout the thoracic cavity except for the right caudal lung lobe.

elevated, but other serum biochemical parameters measured were unremarkable.

Radiographs showed increased opacity throughout the thoracic cavity except for the right caudal lobe; discrimination between lung lobes was therefore difficult (Figure 1). In the caudal lung lobes, a mixed radiographic pattern (bronchial, alveolar, and interstitial) was evident. The trachea was narrow and elevated. A differential diagnosis list based on the results from radiography and hematology included pulmonary inflammation and pleural effusion. Furthermore, the possibility of lung cancer that coincided with inflammation was considered in view of the severely increased opacity, which covered the cardiac silhouette, even though the boar was young.

For diagnostic accuracy, FDG-PET–CT scanning (Gemini System, Philips Medical System, Eindhoven, The Netherlands) was performed. The pig was fasted for 12 h prior to the scanning process, with free access to drinking water, and was anesthetized by using medetomidine (0.2 mg/kg IM) and tiletamine–zolazepam (4.4 mg/kg IM). A catheter was placed in the marginal ear vein for administration of FDG (4 mCi), after which the pig was kept in a preparation room for 1 h to minimize excitement and allow

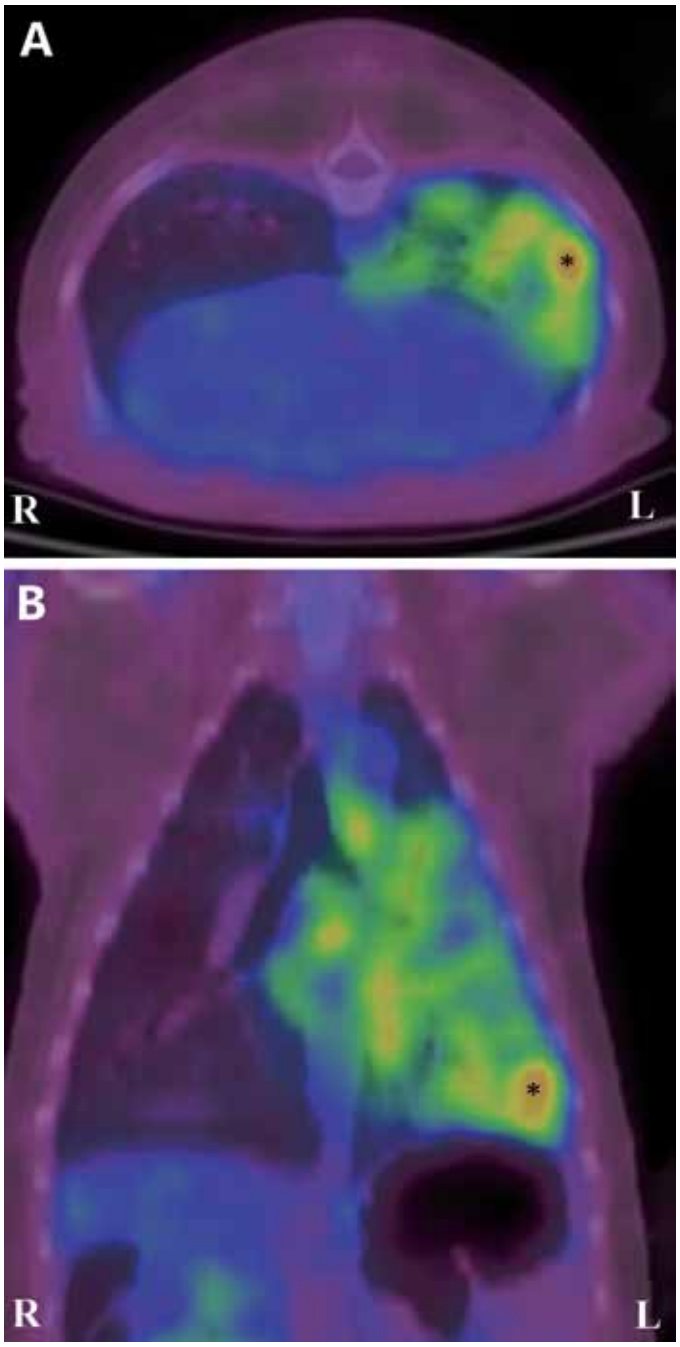

Figure 2. FDG-PET–CT images. The site of maximal FDG uptake value (asterisk) was the focus point for (A) axial and (B) coronal images. Increasing FDG uptake values are expressed as green, yellow, and orange colors.

FDG uptake. FDG uptake was calculated as a standard uptake value (SUV) within the region of interest drawn on the scanned image. Whole-body scanning showed that the left thoracic cavity (SUV [mean ± 1 SD], 2.42 ± 0.51) exhibited increased FDG uptake compared with the right thoracic cavity (SUV, 0.68 ± 0.16); in particular, the maximal SUV within the caudal lung lobe adjacent to the left thoracic wall and diaphragm was 4.44 (Figure 2). The high PET–CT scan signal indicated hypermetabolic activity in the left lung, suggesting possibilities including inflammation and

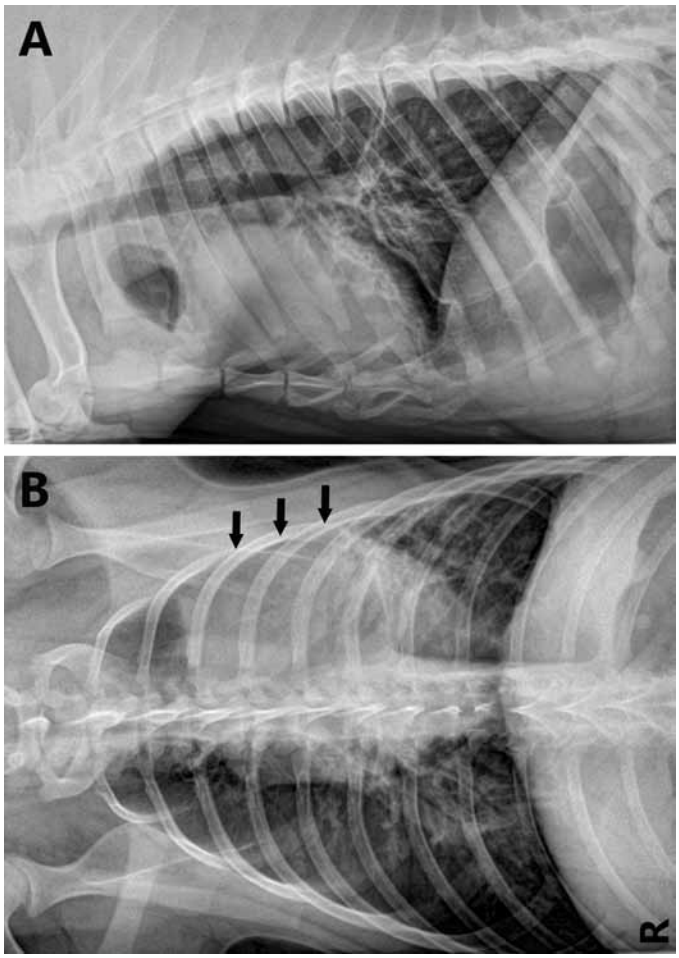

Figure 3. Radiographs taken after administration of antibiotics. (A) Lateral thoracic view demonstrates the return of correct tracheal position and diameter. Radiographic pattern of inflammation is present in the caudal lobes of the lung. (B) Ventrodorsal thoracic view demonstrating the noticeable regression of opacity in the overall thoracic cavity, with arrows pointing to focal opacity in the left aspect of the thoracic cavity adjacent to the thoracic wall.

metastatic malignancy. However, an SUV of 2.5 generally has been used as a cutoff value for diagnosing pulmonary malignancies with FDG-PET–CT,[1,9,20] and an SUV higher than 1.59 is associated with a 62% to 77% probability of pulmonary malignancy.[11] Consequently, in light of the hematologic data, the preliminary diagnosis was lung cancer with concurrent inflammation, although the boar was young.

After the FDG-PET–CT scan, enrofloxacin (5 mg/kg IM daily; Baytril, Bayer Korea, Seoul, Korea) was administered for 3 d to rule out infectious inflammation and to selectively acquire subsequent images that were more focused on the presumed tumor. Follow-up thoracic radiography 2 wk after FDG-PET–CT revealed that the increased opacity of the left lung remained in contact with the thoracic wall, making discrimination of the cardiac silhouette difficult. In addition, a vascular pattern was present in the caudal lung lobes. However, opacity throughout the thoracic cavity had decreased considerable and the tracheal position and diameter had returned to normal (Figure 3). Despite its short course, the antibiotic treatment markedly ameliorated

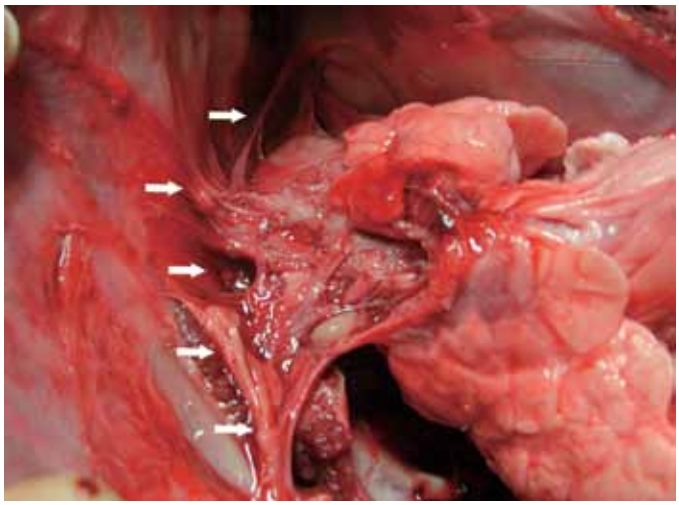

Figure 4. View of the thoracic cavity. Firm adhesions (arrows) were present between the dorsocranial portion of the left caudal lobe and thoracic wall.

the radiologic signs of disease, suggesting that the increased FDG uptake was due to infection and not a tumor.

To identify the infectious agent, we performed ELISA (National Veterinary Research and Quarantine Service, Korea) for the detection of antibodies to several specific respiratory infectious organisms including *Actinobacillus pleuropneumoniae* serovar II, *A. pleuropneumoniae* serovar V, *Mycoplasma hyopneumoniae*, and *M. hyorhinis*. Blood samples were collected at the time of both radiologic analyses (interval of 2 wk), and both samples were assayed in duplicate. The presence of antibodies was evaluated by using the sample-to-positive ratio, defined as:

(sample OD – negative control OD) / (positive control OD – negative control OD).

A ratio of 0.4 or greater was considered to indicate the presence of antibody to the test organism. Consequently, antibody to *A. pleuropneumoniae* serovar V was detected in both serum samples, and the mean of the sample-to-positive ratio increased slightly from 0.655 in the first sample to 0.727 in the second. *A. pleuropneumoniae* is the cause of contagious pleuropneumonia in pigs.[4] The pig was maintained without further treatment until euthanized for pathologic evaluation.

One month after the second radiographic session, the pig was euthanized by exsanguination while deeply anesthetized by using xylazine and tiletamine–zolazepam. Gross lesions on necropsy were limited to the left lung with mild atrophy. The caudal part of the left cranial lobe was congested; in particular, there were firm adhesions between the dorsocranial part of the left caudal lobe and the thoracic wall (Figure 4). These adhesions are frequent sequelae to pleuropneumonia.[12,25,26] Bacterial culture, isolation of the organism, and identification by other means were not performed. Each lung lobe and all lesion areas including adhesions were evaluated histologically. Lung tissue samples were immersion-fixed in 10% phosphate-buffered formalin and embedded in paraffin wax. Sections were cut and stained with hematoxylin and eosin. Histology revealed accumulation of peribronchial inflammatory cells (Figure 5 A). In addition, inflammatory cells had infiltrated into interstitial tissue (data not shown). There was no evidence of pulmonary malignancy detected by macroscopic and microscopic analyses.

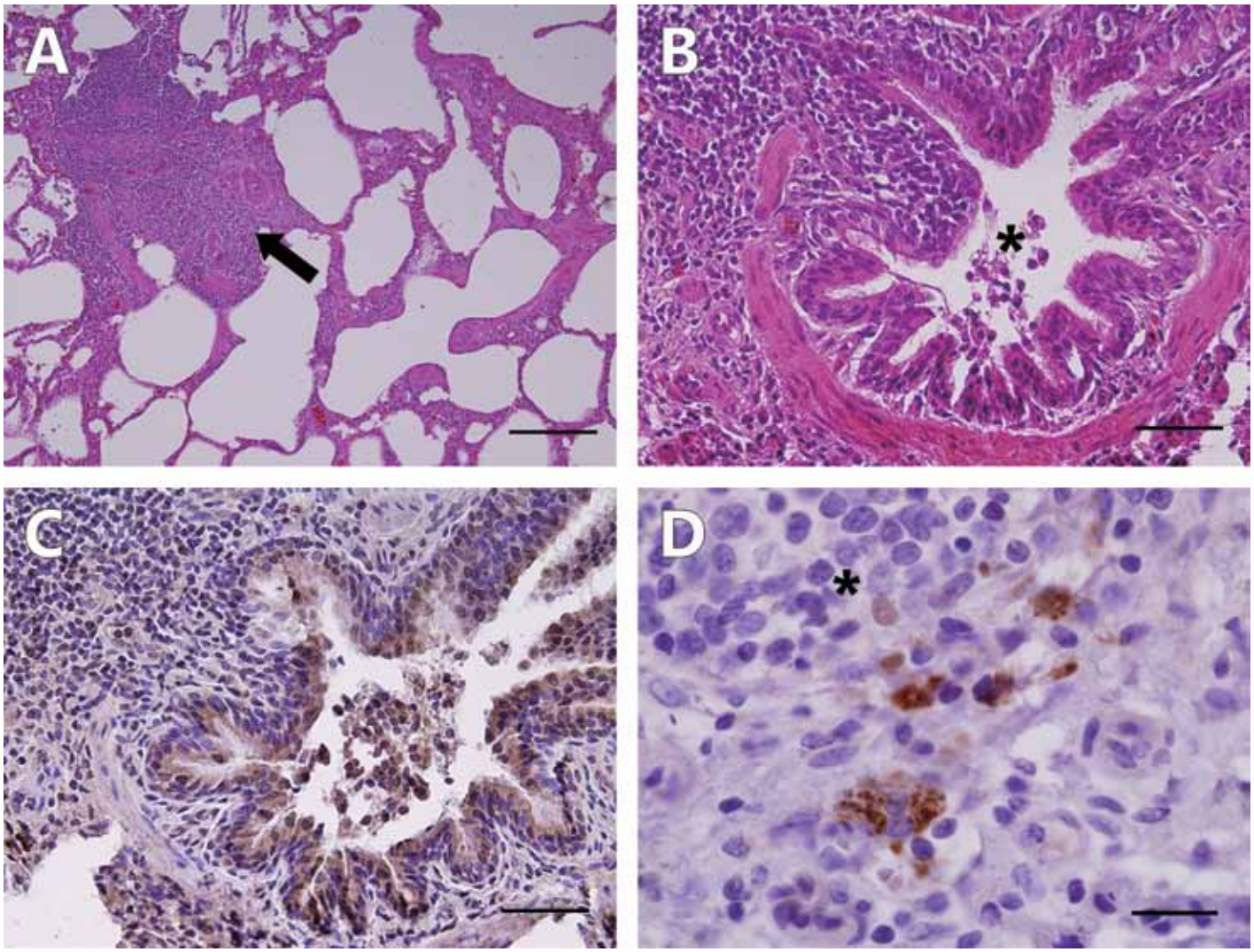

Figure 5. Photomicrographs of lung tissue. (A) Accumulation of peribronchial inflammatory cells (arrow). Bar, 200 µm. (B) Inflammatory cells including neutrophils and macrophages in the bronchiole lumen (asterisk). Bar, 50 µm. (C) Serial section showing positive immunohistochemistry staining with NOS2 in the lumen and epithelium of the bronchiole. Bar, 50 µm. (D) NOS2 expression adjacent to an intrapulmonary lymph node (asterisk). Bar, 20 µm.

Immunohistochemistry of the lung tissue was conducted by using antibodies to nitric oxide synthase 2 (Santa Cruz Biotechnology, Santa Cruz, CA). Avidin–biotin–peroxidase complex (Vector Laboratories, Burlingame, CA) was used as the detection system. NOS2-labeled sections were evaluated and compared with serial sections stained with hematoxylin and eosin. Expression of NOS2 protein was greater in tissue of the left lung compared with the right lung and was particularly intense in areas with adhesions. NOS2 expression is related to inflammatory cells[8,15,17] and was intense in alveolar spaces and interstitial tissues. In addition, bronchiole lumens (Figure 5 B and C) and adjacent connective tissues (Figure 5 D) were infiltrated markedly with neutrophils and macrophages that stained positively for NOS2.

Discussion

Pleuropneumonia is a major swine respiratory disease but had not previously been reported in miniature pigs. The current case is the first report of a presumptive infection of *A. pleuropneumoniae* serovar V in a miniature pig in a research environment. During the diagnostic process, primary intrathoracic malignancy was considered in light of the intense FDG uptake corresponding to radiologic changes. Nevertheless, pleuropneumonia was eventually strongly suggested by ELISA analysis in addition to the progression of radiographic changes over time.

In addition to accumulating in malignant tissues, FDG accumulates in nontumor sites, including inflamed tissues, granulomatous tissues, and tissues involved in autoimmune diseases.[19,28,31] In human medicine, FDG-PET–CT is a valuable diagnostic tool for the evaluation of children with unexplained signs of inflammation.[14] Moreover, pulmonary uptake values of FDG assessed with PET have been used to evaluate the metabolic activity of inflammatory lesions in the lung.[27] It is important, however, to distinguish inflammatory lesions from malignant tumors for accurate diagnosis, especially when cancer is suspected. As seen in the current case, reliance on increased FDG uptake in inflammatory

and adhesive lesions resulted in an initial misdiagnosis. Dual time-point FDG-PET–CT imaging has been proposed as a feasible and promising method for distinguishing benign lesions from malignancies.[33] In the current case, instead of dual time-point FDG-PET–CT imaging, only radiographic changes were determined over time. Although short-term antibiotic administration did not completely eliminate inflammatory signs on follow-up radiography, the differences in radiographic signs were sufficient to exclude a diagnosis of lung cancer. However, dual time-point PET–CT is still considered to be useful in complicated conditions, such as the coexistence of granulomatous inflammation or infection and cancer.[18,32]

Several studies have suggested the diagnostic utility of imaging tools for infectious disease in pigs. Portable radiography was used to determine when the pneumonia induced by *Mycoplasma hyopneumoniae* involved the greatest percentage of the lung.[29] The diagnostic significance of radiographic and ultrasonographic results from a pig experimentally infected with *A. pleuropneumoniae* have been compared. Alterations in pleura and lung surfaces were could not be evaluated clearly on radiographs, and ultrasonographic examination showed less reliable results associated with deep-tissue alterations.[13] In our case, FDG-PET–CT was not practically helpful for diagnosis of pleuropneumonia, and it might ultimately have led to a misdiagnosis of malignancy. Nonetheless, for the first time, we were able to partially overcome the drawbacks of existing imaging tools in regard to the evaluation of pleuropneumonia by detecting functional activity by using FDG PET–CT. In addition, localization and quantification of volumetric and metabolic changes of inflammatory lesions were conducted noninvasively.[5,21]

Porcine pleuropneumonia is characterized by fibrinohemorrhagic to necrotizing lesions.[10] In the current case, gross lesions including fibrous adhesion formations were correlated with areas localized by FDG-PET–CT. Accumulation of newly recruited inflammatory cells was verified in these lesions. Immunohistochemical staining of NOS2 protein was particularly intense in the adhesion area. Upregulation of NOS2 protein indicates increased production of nitric oxide and its microbicidal activity.[17] NOS2 protein has been shown to be overexpressed in *A. pleuropneumoniae*-infected lungs, and staining was especially strong in neutrophils and macrophages within the alveolar spaces. Therefore, evidence of NOS2 expression in pleuropneumonic areas indicates the activation of antimicrobial defense mechanisms as part of the inflammatory process.[6] This correlation between FDG-PET–CT imaging and NOS2 expression supports the use of FDG-PET–CT for the evaluation of pneumonic lesions.

In the current case, the route of infection was not investigated in depth. This boar had been procured from a vendor that had provided certified health monitoring results. Although *A. pleuropneumoniae* was not included in the vendor's list of excluded agents, the prolonged time between procurement of the pig and occurrence of pleuropneumonia argues against the vendor as the infection source. Transmission from farm pigs reared in an adjacent room within the research facility or workers who managed both rooms was presumed. No other miniature pigs in the same room manifested any symptoms of the disease. However, antibody to *A. pleuropneumoniae* serovar V was detected by ELISA analysis in 3 (38%) miniature pigs housed in the same room of the facility, and the fact that the time until the appearance of signs of pleuropneumonia among pigs can vary may have contributed to unawareness of the disease outbreak. Furthermore, additional organisms might be involved in the pathogenesis of this case, because bacterial culture, isolation of the organism, and identification by other means were not performed. As the number of facilities holding SPF pigs increases, more attention to infections in pigs housed at research facilities as well as on farms is needed.

This case suggests that FDG-PET–CT is a valuable imaging technique for the evaluation of infection and inflammation in miniature pigs. Although FDG thoracic uptake with pneumonia infection mimicked the appearance of a pulmonary tumor, dual time-point imaging likely would have prevented misdiagnosis.[33] In addition, after a final diagnosis is established, FDG-PET–CT could be used to monitor the effect of therapy for infectious and inflammatory diseases that cannot easily be visualized by conventional techniques.[2,14] As the use of miniature pigs in biomedical research and as pets increases, FDG-PET–CT can be considered a tool for evaluation of lesion location, analysis of inflammatory patterns, and quantification of inflammation associated with various diseases in these animals.

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