



Primary diaphragmatic undifferentiated pleomorphic sarcoma in a cat

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Abstract

Case summary A 5-year-old neutered female domestic shorthair cat was referred for acute onset of dyspnoea. Thoracic radiographs performed by the referring veterinarian revealed the presence of pleural effusion. Upon presentation, the cat was dyspnoeic, and cardiopulmonary auscultation revealed muffled heart sounds and bilaterally increased bronchovesicular sounds. Radiographic study of the thorax revealed bilateral pleural effusion and a soft tissue opacity in the dorsocaudal region of the left hemithorax. A whole-body contrast-enhanced CT scan identified a soft tissue mass arising from the left diaphragmatic crus. Transthoracic ultrasound-guided fine-needle aspiration (FNA) of the mass was performed and the result was consistent with a malignant mesenchymal neoplasia, showing giant cells. Cytoreductive surgery was performed and the histopathology diagnosis of undifferentiated pleomorphic sarcoma was made. Adjuvant chemotherapy was then offered. Ten days after surgery pleural effusion recurred. Thoracic echography revealed the presence of a diaphragmatic thickening in the area of surgical resection. FNA of the thickening was consistent with mesenchymal neoplasia. Even when chemotherapy and supportive treatment with pain relief was instituted, the clinical condition of the cat worsened within a few days and it was euthanased 1 month after surgery.

Relevance and novel information Primary diaphragmatic tumours (PDTs) have been rarely reported in human and in veterinary medicine, where only three cases have been described in the dog. To our knowledge, this is the first report to describe a PDT, specifically an undifferentiated pleomorphic sarcoma, in a cat.

Keywords: Anaplastic sarcoma with giant cells; chemotherapy; primary diaphragmatic tumour; surgery; undifferentiated pleomorphic sarcoma

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Case description

A 5-year-old neutered female domestic shorthair cat weighing 6.5 kg was referred to the Veterinary Hospital i Portoni Rossi for acute onset of dyspnoea. Thoracic radiographs performed by the referring veterinarian revealed the presence of pleural effusion.

At the time of presentation, the patient was dyspnoeic with a respiratory rate of 50 breaths/min. Cardiopulmonary auscultation revealed muffled heart sounds and bilaterally increased bronchovesicular sounds. The remainder of the physical examination was unremarkable. Haematology, biochemistry and coagulation profile were also unremarkable.

After administration of butorphanol (0.3 mg/kg IM [Dolorex 10 mg/ml injectable solution; MSD]), thoracocentesis was performed to stabilise the cat's condition before performing other diagnostic procedures and 180

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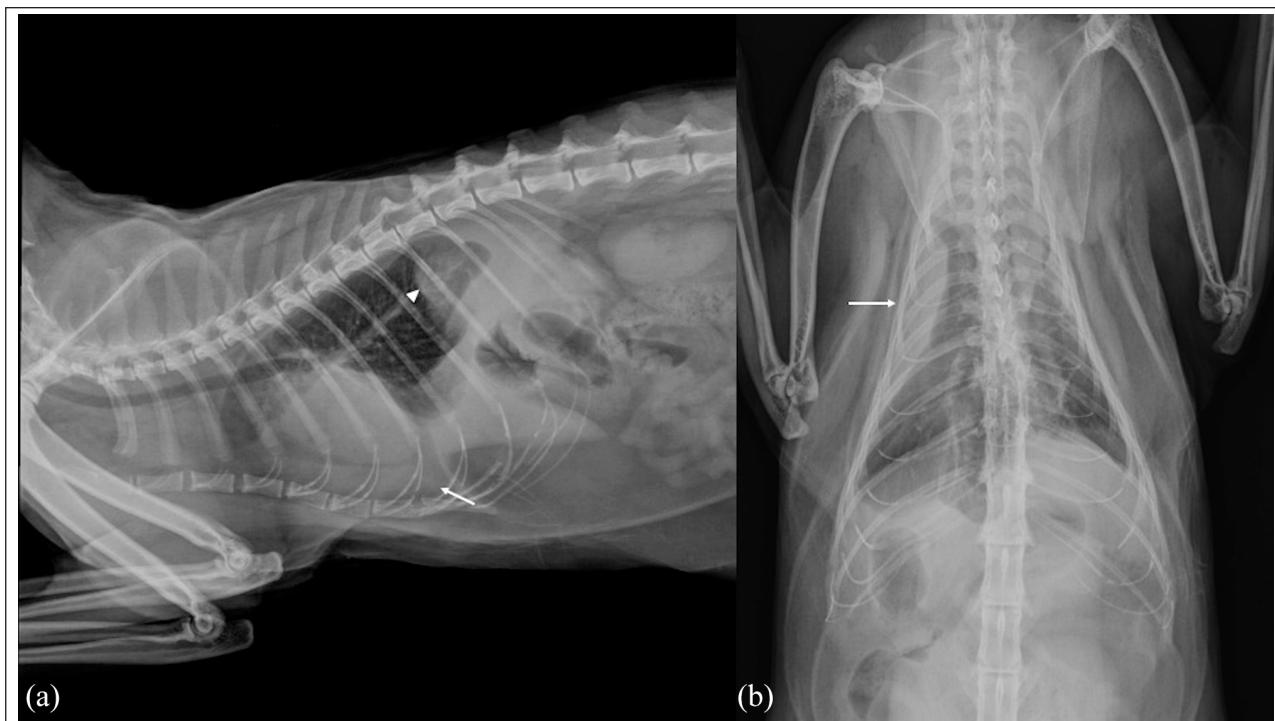


Figure 1 (a) Laterolateral and (b) dorsoventral view of the thorax: residual bilateral pleural effusion (arrows) and soft tissue opacity (arrowhead) in the dorsocaudal area of the left hemithorax are noted

and 80ml of serosanguineous fluid, respectively, were drained from the left and right hemithorax. Cytological analysis of pleural fluid was compatible with a modified transudate; on cytological evaluation, primary cell types included neutrophils and macrophages. After thoracentesis, an echocardiographic examination was performed and ruled out any cardiac abnormalities, while two-view thoracic radiographs revealed the presence of residual pleural effusion and a soft tissue opacity in the dorsocaudal region of the left hemithorax at the level of T10–T13. The cranial margins of the mass were rounded and well-defined, while the caudal margins were superimposed with the left diaphragmatic crus (Figure 1).

To better evaluate the extent of the disease, a whole-body contrast-enhanced CT scan was performed. A 16-slice multidetector CT (Somatom Emotion; Siemens Healthcare) was used. CT findings confirmed the presence of bilateral pleural effusion and a well-defined, lobulated, soft tissue mass arising from the left diaphragmatic crus. The mass showed a moderate ring enhancement with an hypoattenuating centre. The mass protruded cranially into the thoracic cavity, displacing the left caudal lung lobe and compressing the thoracic caudal segment of the oesophagus; caudally, the mass also compressed the fundus and body of the stomach, and the left medial and left lateral hepatic lobes (Figure 2). Thoracic and abdominal CT showed no evidence of

metastasis. A transthoracic, ultrasound-guided fine-needle aspiration (FNA) of the mass was performed using a 5ml syringe and a 27G needle. The sample was highly cellular and composed of spindle-shaped cells interspersed with giant multinucleated cells and round cells; the result was consistent with a malignant mesenchymal neoplasia (Figure 3a).

Treatment options, including cytoreductive surgical removal and adjuvant chemotherapy, palliative radiotherapy or palliative chemotherapy, were discussed, and the owner agreed to proceed with surgical removal.

The cat was premedicated with alfaxalone (1mg/kg IM [Alfaxan 10mg/ml injectable solution; Dechra]), methadone (0.2mg/kg IM [Semfortan 10mg/ml injectable solution; Dechra]) and midazolam (0.1mg/kg IM [Midazolam 5mg/ml injectable solution; Hameln Pharmaceuticals]). Alfaxalone (Alfazalan 10mg/ml injectable solution; Dechra) was then administered at 2mg/kg intravenously (IV) titrated to effect for anaesthetic induction, the trachea was intubated and anaesthesia was maintained using sevoflurane (Sevoflo; Zoetis) carried by oxygen throughout general anaesthesia. An intercostal right and left locoregional block was performed with ropivacaine (Ropivacaina 10mg/ml injectable solution; Galenica Senese) at a dose of 1.1mg/kg. A continuous rate infusion of remifentanil (Ultiva; Aspen Pharmacare) at a dosage of 0.1 mg/kg/h was performed as intraoperative analgesia.

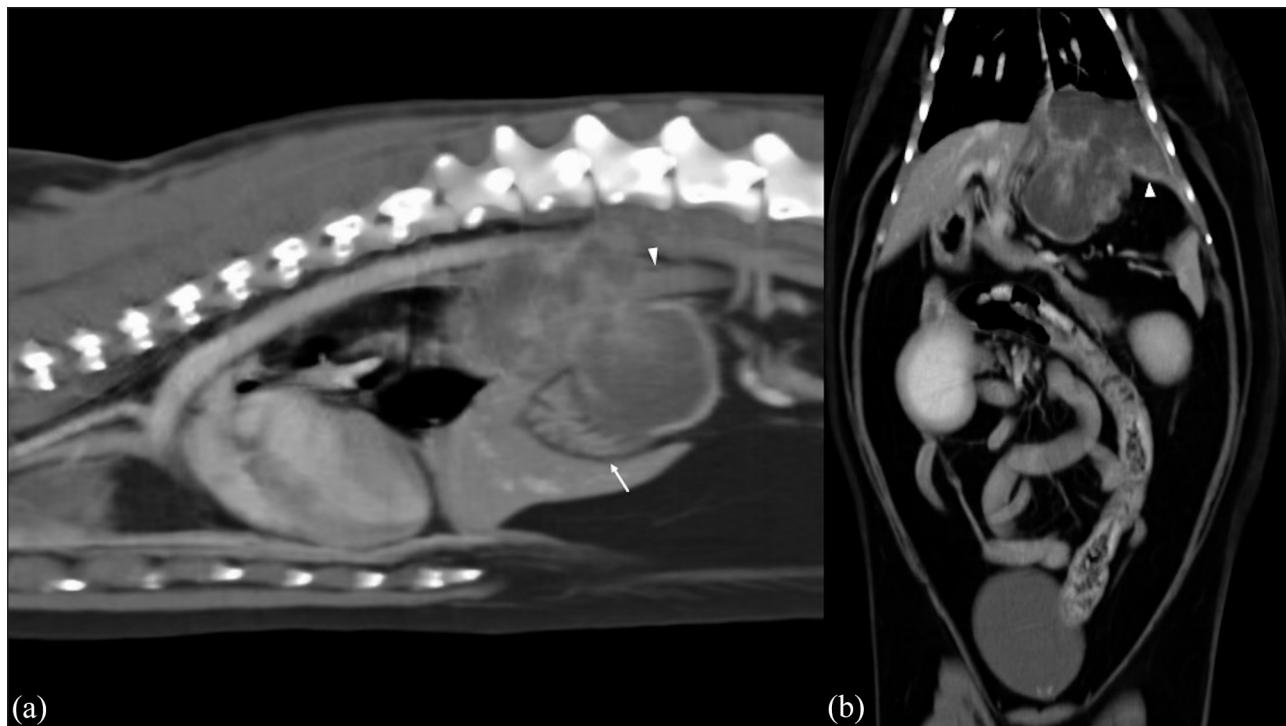


Figure 2 (a) Volume-rendering sagittal reconstruction and (b) dorsal reconstruction of the diaphragmatic mass. A large, ring-enhancing, soft tissue mass arising from the left crus is shown (arrowheads); the mass is causing ventral compression of the stomach (arrow)

Cytoreductive surgery was performed via a ventral midline coeliotomy to the abdomen and a vertical trans-diaphragmatic approach to the thorax; at the abdominal level the mass adhered to the muscles and the left diaphragmatic pillar, while the thoracic side of the mass was larger than the abdominal side. Medially and dorsally, the mass was close to the oesophagus and to the thoracic aorta artery. The left internal thoracic artery, which was infiltrated by the tumour, was closed with titanium clips and then resected. The entire left diaphragm was removed with the mass and, for anatomical reconstruction, a flap with transversus abdominis muscle was performed. Using the thirteenth rib as the base, we created the flap by incising the muscle in rectangular shape that was 4.5 cm long and 3 cm wide. The flap was turned over so that the superficial layer became the thoracic side, while the deep layer became the abdominal side. The flap was sutured to the diaphragm using polypropylene 3-0 in a simple interrupted pattern without traction. The coeliotomy wound was sutured routinely. Thoracic drainage was placed and the patient was hospitalised for postoperative care, including IV fluid therapy (lactated Ringer's 18 ml/kg/h), analgesia with methadone (0.2 mg/kg/q4h IM [Semfortan 10 mg/ml injectable solution; Dechra]) and monitoring of blood gases, blood pressure, urine output, and thoracic fluid volume and character.

The postoperative recovery was uneventful; the drainage was removed 96 h after surgery because the

cat's respiratory rate and pattern were normal, and fluid production was minimal. The patient was discharged the next day in good clinical condition.

The surgically resected tumour was fixed in 10% neutral buffered formalin and submitted for histopathological evaluation. Macroscopically, the tumour was 5 × 5 × 5 cm and multilobular, embedding the diaphragm. In section, it was whitish and with necrotic haemorrhagic areas (Figure 3b). Histopathology showed a non-encapsulated, poorly demarcated, highly cellular neoplasia with infiltrative growth in adipose tissue and skeletal muscle. The neoplasm was composed of spindle cells organised in interlacing bundles and streams, mixed with multinucleated giant cells, supported by a fine-to-moderate fibrovascular stroma. The spindle cells had indistinct borders, eosinophilic cytoplasm, vesicular round nuclei with 1–2 small nucleoli. Anisocytosis and anisokaryosis were moderate. The mitotic count was 22 in 2.37 mm². Multinucleated giant cells with distinct cell borders, abundant eosinophilic cytoplasm and around 20 nuclei were present, and cells ranged from 20 to 50 µm in diameter (Figure 4a). Multifocally, there were large areas of coagulative and colliquative necrosis, haemorrhage and lymphoplasmacytic inflammation. Masson's trichrome staining was useful to highlight the collagen stroma present in the neoplasm (Figure 4b). Spindle neoplastic cells and multinucleated giant cells were strongly vimentin positive (strong and cytoplasmic positivity in

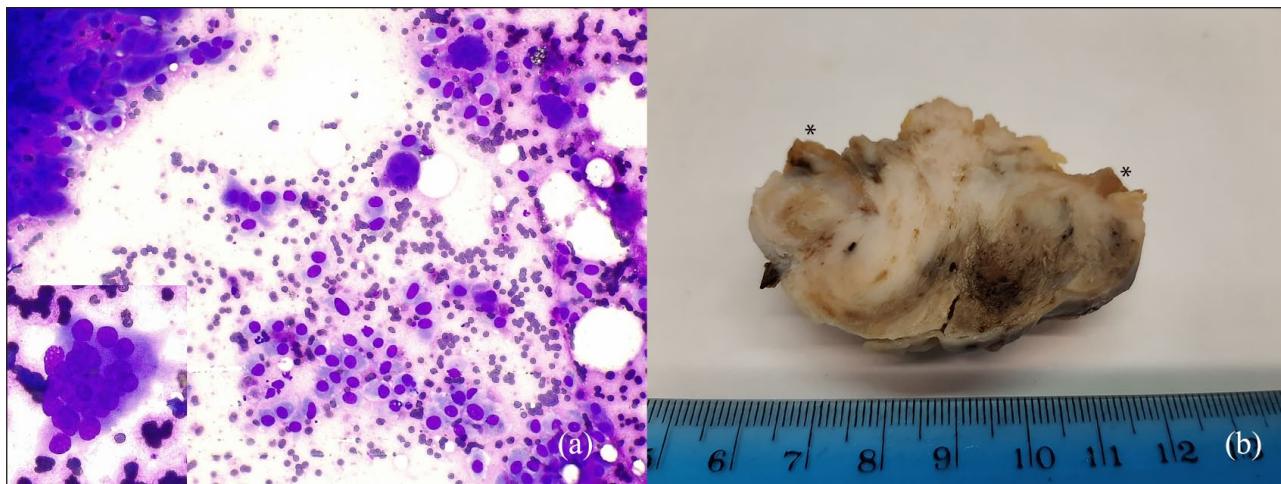


Figure 3 (a) Cytological smear of undifferentiated pleomorphic sarcoma, with round cells interspersed with giant multinucleated cells and spindle-shaped cells. Romanowsky quick stain, $\times 20$ magnification. Inset: a giant cell with multiple nuclei. Romanowsky quick stain, $\times 40$ magnification. (b) Macroscopic appearance of the neoplasm after fixation in formalin. In cross section, the neoplasm is multilobular, embedding the diaphragm (asterisks), whitish and with multifocal necrotic haemorrhagic areas

100% of cells) and negative to antibodies against alpha smooth muscle actin (α -SMA), desmin and S-100. The myofibroblasts present in the fibrovascular stroma were α -SMA positive (strong and cytoplasmic positivity in 100% of myofibroblast cells) (Figure 4c). Multinucleated giant cells were also slightly positive for Iba-1 (Figure 4d), as well as some rare round histiocytoid cells present in the neoplasia (weak and cytoplasmic positivity in around 10% of cells).

Owing to the lack of complete surgical excision and the risk of development of metastatic disease, a chemotherapy protocol including carboplatin alternating with doxorubicin was offered. At the time of the first chemotherapy session, 10 days after surgery, physical examination revealed bilaterally increased bronchovesicular sounds. Three-view thoracic radiographs were performed and revealed the presence of a moderate amount of bilateral pleural effusion. Thirty millilitres of serosanguineous fluid were drained from the left hemithorax and fluid analysis was compatible with a modified transudate. Ultrasound of the thorax revealed the presence of a diaphragmatic thickening in the area of surgical resection. FNA showed the same cell population of the original primary tumour that was removed, consistent with a malignant mesenchymal neoplasia. Based on clinical signs, diagnostic imaging findings and cytological result, a recurrence was diagnosed. Carboplatin (Carboplatino Teva; Teva Pharma) was then administered at a dose of 240 mg/m^2 as a slow (10 mins) IV infusion following premedication with maropitant (Cerenia; Zoetis) at a dose of 1 mg/kg IV.

A few days after chemotherapy the clinical condition of the cat worsened considerably owing to the

presence of pleural effusion, requiring thoracentesis every 3 days. Owing to the sudden worsening of the clinical condition of the cat, euthanasia was performed 1 month after surgery. The owner declined a necropsy.

Discussion

Primary diaphragmatic tumours (PDTs) are a rare entity in veterinary, as well as human, medicine, with <200 cases reported in people.¹ Several benign and malignant PDT histotypes have been described in humans: lipomas are the most common benign tumours, while malignant tumours, such as fibrosarcoma, rhabdomyosarcoma and leiomyosarcoma, are the most frequently reported.² Some patients with PDT may be asymptomatic, while others can manifest cough, dyspnoea, dysphagia, anorexia, nausea and vomiting as a consequence of gastric compression.³ PDTs are generally surgically removed if patients are symptomatic or if there is a doubt about the diagnosis.

Identifying the site of origin can be challenging; on imaging, most PDTs present as homogeneous masses that appear as mediastinal or thoracic masses with a contour abnormality of the diaphragmatic leaves, suggesting herniation or eventration. Large tumours may sometimes pose a diagnostic difficulty and can mimic mediastinal or upper abdominal masses; for this reason, a combination of ultrasound, CT scan and MRI may be needed.¹ In our case, a CT scan revealed the anatomical origin of the mass, confirming the usefulness of advanced imaging in this uncommon clinical situation.

Surgery is considered the treatment of choice for PDTs, with wide surgical excision being the goal to minimise the risk of local recurrence.¹ In the case of large

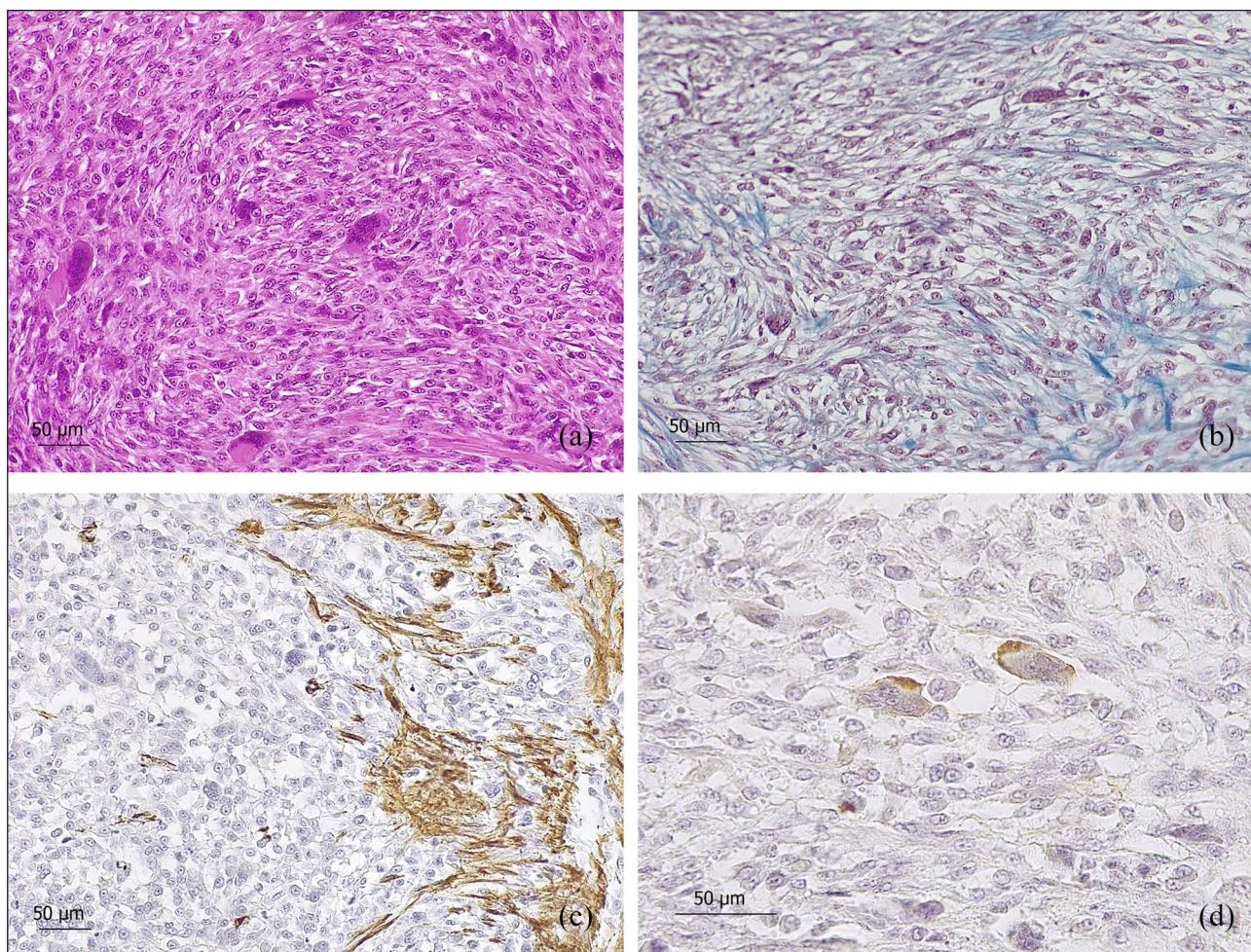


Figure 4 Photomicrographs of feline undifferentiated pleomorphic sarcoma: (a) interlacing bundles of spindle cells mixed with multinucleated giant cells were shown. Haematoxylin and eosin stain, scale bar 50 µm. (b) A thin fibrovascular stroma, stained in blue, is present between the bundles of spindle cells. Masson's trichrome stain, scale bar 50 µm. (c) In another area where the fibrovascular stroma was moderate, the myofibroblasts were positive with antibody anti- α -smooth muscle actin. Immunohistochemistry, scale bar 50 µm. (d) Giant cells showed mild and focal positivity with anti-Iba-1 antibody. Immunohistochemistry, scale bar 50 µm

and infiltrative tumours removed with dirty margins, a multimodal approach is recommended.

Data regarding PDTs in the veterinary literature are lacking and, to the best of our knowledge, they have been reported only in three dogs, namely a peripheral nerve sheath tumour in two,^{4,5} and a mesothelioma in one.⁶ To the best of our knowledge, this is the first report of a PDT in cats.

The diagnosed histotype was a feline undifferentiated pleomorphic sarcoma (or anaplastic sarcoma with giant cells), which is an uncommon tumour of the skin and subcutaneous tissue, usually affecting middle-aged to old animals (mean age 9.5 years).⁷

Undifferentiated pleomorphic sarcoma, previously known as malignant fibrous histiocytoma or anaplastic sarcoma with giant cells, is a still controversial entity in human and veterinary medicine;^{8,9} in our case, the

histological variant was 'giant cell', with numerous giant cells and many spindle cells (fibroblast/myofibroblast-like) and very few mononuclear histiocytoid cells. Histiocytic sarcoma (HS) is the main differential diagnosis to consider; in our case, both the morphological aspect and the immunohistochemical results were not compatible with a HS. Monocyte/macrophage lineage antibodies (such as CD18 and Iba-1) can be used to identify HS: all cells are strongly positive to antibodies against CD18 and Iba-1.⁸⁻¹⁰ In our case, rare histiocytoid cells and multinucleated giant cells were weakly positive and all the spindle neoplastic cells were negative; for this reason, a diagnosis of HS was ruled out. Similar results were reported by De Cecco et al,⁷ who described 13 cases of feline pleomorphic sarcoma, in which the labelling for Iba-1 was mild to marked in histiocytoid cells and multinucleated giant cells, while the spindle cells were

negative. It is not clear if histiocytoid and giant cells have neoplastic or inflammatory behaviour in undifferentiated pleomorphic sarcoma; in fact, both antibodies (CD18 and Iba-1) mark neoplastic, as well as non-neoplastic, cells.⁸ In some of the cases described by De Cecco et al.,⁷ spindle cells were negative for antibodies against α -SMA and desmin, as in the case described herein. In other cases, the spindle cells were positive to antibodies against α -SMA and desmin, suggesting a fibroblastic/myofibroblastic phenotype. S-100 antibody was used to rule out the diagnosis of malignant peripheral nerve sheath tumours.

Feline pleomorphic sarcomas have been described in several anatomical locations, including the dermis and subcutis in non-vaccine sites.⁸ Cytological, pathological and immunohistochemical characteristics have also been described, while treatment, prognosis and outcome have not been extensively characterised,⁷ even if the expected outcome is possibly similar to other soft tissue sarcomas, characterised by local invasiveness and a low-to-moderate metastatic rate.

Conclusions

To our knowledge, this is the first report of a PDT in cat. Diaphragmatic tumours, even if rare, should be considered in the differential diagnosis of patients presenting with a radiographic evidence of a mass in the area of the caudal thorax or cranial abdomen.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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