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Case Report

Atypical thymoma in a horse: Diagnostic approach and application of an alternative histological classification system

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Summary

Thymoma is a rare condition in horses. This case of a 24-year-old Warmblood gelding that was presented with oedema and signs of vascular congestion of the left forelimb caused by a thoracic mass is described. The diagnostic work-up included blood chemistry, cytology of pleural effusion, ultrasonography, radiography and the visualisation and collection of a tissue sample by thoracoscopy. Finally, post-mortem findings and histopathology revealed thymic epithelial neoplasia with histomorphologic features previously unreported in horses. The unique mixture of spindle-shaped and epithelioid tumour cells in combination with clear features of malignancy suggested the application of the Moran and Suster histological classification system for thymomas in humans (Moran and Suster, 2008, *Curr. Treat. Options Oncol.*, 9, 288), which has not been reported in an equine case before and fits well to the present case.

Introduction

The clinical signs of thoracic masses are often severe shallow respiration and pectoral oedema due to pleural effusion (Mair *et al*. 2004). Thoracoscopy is a useful technique to obtain clear visuals of the mass and tissue specimens for histopathological examination. Mediastinal lymphoma is the most common neoplasia in the pleural cavity in horses (Sweeney and Gillette 1989; Mair and Brown 1993). Primary neoplasms of the thymus include neoplasia of thymic epithelium (thymoma and thymic carcinoma) and thymic lymphoma (Valli *et al*. 2016). Thymic epithelial neoplasia is rare in domestic animals. It has been reported in dogs, cats, rabbits, cattle, horses, pigs, sheep, goats, monkeys and a Siberian tiger (Migaki 1969; Sandison and Anderson 1969; Kotani *et al*. 2010; Künzel *et al*. 2012; Allan *et al*. 2014; Valli *et al*. 2017). The literature suggests a predisposition in goats (Migaki 1969; Hadlow 1978). Only three individually published cases of thymoma exist in the horse to date (Whiteley *et al*. 1986; Furuoka *et al*. 1987; Shahriar and Moore 2010). Adult or aged animals are most often affected. The neoplasm is typically located in the cranio-ventral thorax, with a nodular gross appearance, encapsulation and haemorrhagic or necrotic areas (Valli *et al*. 2017). Thymic epithelial neoplasia mostly shows a benign biological behaviour, but malignant thymic carcinoma can occur (Valli *et al*. 2016). The diagnosis and subclassification of thymomas can be difficult due to their variable histological appearance (Valli *et al*. 2016). Various histological classification systems have been applied over the years. Classification in veterinary medicine focused for a long time on the cellular composition of the tumour (predominantly lymphocytic, mixed and predominantly epithelial) (Valli and Gentry 2007; Valli *et al*. 2017). The system used in veterinary medicine currently is the 2004 WHO histological classification derived from human medicine (Travis *et al*. 2004; Valli *et al*. 2016), that relies on cell morphology, lymphocyte infiltration and cellular atypia to form the following categories: type A (spindle-shaped cells), types B1 to B3 (epithelioid cells with increasing atypia and decreasing infiltration of lymphocytes), type AB (spindle-shaped and epithelioid cells) and thymic carcinoma (epithelioid cells with prominent malignant features). Controversy regarding the inter-observer concordance, practicability and usefulness of and correlation to the clinical findings and prognosis in human medicine has been raised and several alternative systems proposed in recent years (Rieker *et al*. 2002; Moran and Suster 2008). Moran and Suster (2008) advocated a three-group system which classifies thymic neoplasia into thymoma (comprising WHO categories A, AB, B1 and B2), atypical thymoma (comprising WHO category B3) and thymic carcinoma, thereby allowing for the continuous spectrum of growth patterns often reported that would otherwise make a categorisation extremely difficult (Moran and Suster 2008). Studies to evaluate the usefulness of the WHO classification and the Moran and Suster classification in veterinary medicine, especially regarding the prognosis and survival time, focus mainly on canine thymic epithelial neoplasia (Burgess *et al*. 2016). Such comparative studies on horses are lacking so far. The three existing equine case reports use different classification systems and describe malignant thymoma with cornification (Furuoka *et al*. 1987), malignant squamous cell thymoma (Whiteley *et al*. 1986) and type A thymoma according to the WHO classification (Shahriar and Moore 2010). To the best of the authors' knowledge, the present case report includes the first application of the Moran and Suster classification of thymomas in humans to an equine case.

Case history

A 24-year-old Warmblood gelding was presented with a 2-week history of left forelimb swelling, intermittent lameness, pyrexia (38.5–39°C) and lethargy. Previous treatments for suspected cellulitis with bandaging, administration of

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nonsteroidal anti-inflammatory drugs and various antimicrobials showed no improvement.

Clinical findings

The horse demonstrated normal behaviour at presentation, and vital parameters were within normal limits. The gelding had a marked oedematous swelling of the entire left forelimb, which was the largest proximally. It was neither warm nor painful. In addition, mild sternal and pectoral oedema was evident (**Fig 1**). Distension of both jugular veins and subcutaneous facial vessels was visible.

Laboratory findings

Haematology revealed signs of a nonspecific inflammatory response with a total leucocyte count within the normal limits (9.23×10^9/L, reference range [rr] $5.0–10.0 \times 10^9$/L), an increased neutrophilic granulocyte count (8.22×10^9/L, rr: $1.6–6.4 \times 10^9$/L) and a decreased number of lymphocytes (0.57×10^9/L, rr: $1.5–4.0 \times 10^9$/L). The acute-phase protein serum amyloid A was increased (1008 μg/L, rr: 0–2.7 μg/L). Serum biochemistry and electrolytes showed no abnormalities.

Ultrasonography

Ultrasonography of the thorax revealed signs of a moderate, anechoic pleural effusion on both sides of the thorax with a maximum height of 12 cm in the 8th intercostal space (ICS). Moreover, there was a mass with mixed echogenicity at the cranial aspect of the heart (**Fig 2**). The size of this mass could not be determined, but it was visible from both sides of the thorax. The superficial cervical lymph nodes were neither enlarged nor had an abnormal echogenicity. Echocardiography did not show any pericardial effusion or structural abnormalities.

Fig 1: Clinical presentation of the gelding with oedema of the left front limb including the left pectoral region and distended jugular veins.

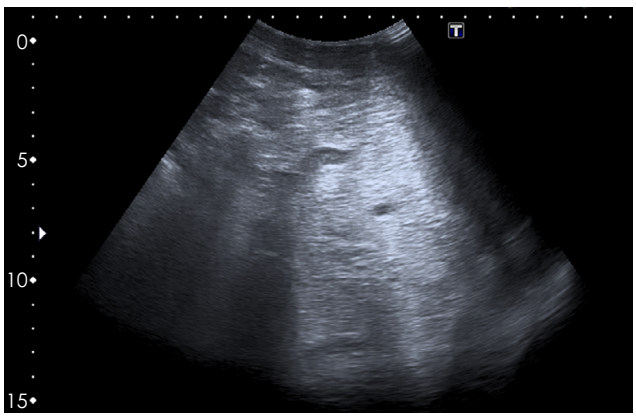

Fig 2: Ultrasound image of the left thorax in the 4th intercostal space with an inhomogeneous hyperechogenic mass. Dorsal is to the right side.

Radiography

Standard left lateral–lateral radiographic projections of the thorax showed a well-circumscribed radiodense structure that superimposed the silhouette of the heart. There was no evidence of further isolated structures with increased opacity. The lung showed a mild generalised increased opacity with interstitial pattern.

Thoracocentesis

After aseptic preparation and local anaesthesia, thoracocentesis was performed in the 7th ICS, approximately 12 cm proximal to the olecranon under ultrasonographic guidance using a Tuohy cannula (120 mm, 18G). A cloudy orange fluid was aspirated. Laboratory findings showed a nonspecific pyogranulomatous exudate with a few eosinophils and mild mesothelial cell hyperplasia. As the diagnostic tests were not specific for either a neoplastic or an inflammatory process, further investigations were deemed necessary, but an ultrasound-guided biopsy was not performed because of the location of the mass close to the heart and the associated unpredictable risk.

Thoracoscopy

Prior to surgery, the gelding received flunixin–meglumine (Phlogoxin)[1] (1.1 mg/kg bwt i.v.) and amoxicillin (Belamox)[2] (10 mg/kg bwt i.v.).

The horse was sedated with detomidine (Cepesedan®)[3] (0.01 mg/kg i.v.) and butorphanol (Butorgesic®)[3] (0.01mg/kg i.v.) followed by a constant rate infusion (0.03 mg/kg/h of detomidine and 0.03 mg/kg/h of butorphanol). An arterial catheter was placed in the right facial artery for blood gas analysis. Ringer's lactate solution was infused (5 mL/kg/h), and supplementary oxygen (15 L/min) administered via nasal insufflation.

The horse was restrained in stocks. After surgical preparation of the left thorax, local infiltration was performed with mepivacaine (Mecain®)[4] subcutaneously and in the deeper layers of the intercostal muscles at the site of each portal.

An optical portal was created in the standard fashion at the level just below the coxal tuberosity in the 10th ICS using a No. 11 scalpel blade to create an approximately 10-mm-long stab incision for introduction of a blunt trocar. Before inserting the trocar, negative pressure of the pleural cavity was revoked by placing a teat cannula in the thorax and insufflating room air (Peroni *et al*. 2001; Röcken and Scharner 2013). Loss of the negative pressure resulted in the collapse of the ipsilateral lung. A 57-cm-long, 10-mm-diameter rigid scope with a 30° optic was inserted.

A mild hydrothorax with a cloudy orange fluid was present. The normal anatomical structures of the oesophagus, thoracic aorta, diaphragm, ribs, vessels and nerves were apparent. An encapsulated, nodular mass with blood vessels on its surface was observed cranio-dorsally in the thorax (**Fig 3**). The mass seemed attached to the pericardium and the surrounding left cranial lung lobes. An instrument portal was created in the 9th ICS with a 5-mm trocar under optic guidance. A biopsy from the mass was taken with Blakesley laparoscopic biopsy forceps. A surgical suction device was used to evacuate the pneumothorax and allow the re-expansion of the lung under visual guidance. All portals were closed in two layers with interrupted sutures using polyglycolic acid 2-0 USP. The surgical time was approximately 40 min, and the post-operative phase was uneventful.

A presumptive diagnosis of neoplasia was made. The owner elected to euthanise due to the overall poor prognosis, prior to the histological interpretation of biopsy samples.

Post-mortem findings

Gross pathology

Post-mortem examination revealed a light brown, nodular, fibrous mass, measuring approximately 40 × 30 × 30 cm, in the mediastinum cranial to the heart extending to the cranial thoracic aperture. Firm, fibrous attachment to the pericardium and the pleura of lung and costae was present. Sternal and mediastinal lymph nodes and cranial vena cava were embedded within the mass (**Fig 4a**).

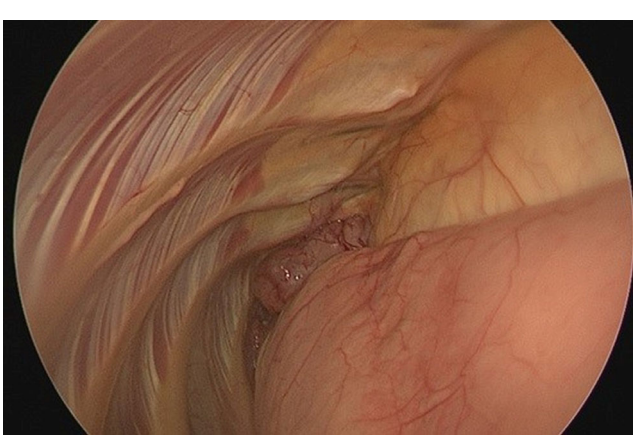

Fig 3: Thoracoscopic image: cranial view with margo dorsalis of the lung (right ventral), ribs (left), mediastinum (right dorsal) and the thymic neoplasia (central).

Histopathology

Histology of the thoracoscopic biopsy and tissue specimens collected during post-mortem examination revealed a densely cellular, encapsulated, neoplastic proliferation with compression of the surrounding tissue and early capsular invasion (**Fig 4b**). The cell morphology varied within the neoplasm. Two different growth patterns were noticeable: (1) polygonal to pleomorphic cells with a moderate amount of eosinophilic cytoplasm, centrally located round nuclei with a vesicular chromatin structure and one nucleolus, marked anisocytosis and anisokaryosis, and a high mitotic rate (up to ten often bizarre mitoses per high-power field) (**Fig 4c**); and (2) spindle-shaped cells arranged in bundles and streams with a scarce amount of eosinophilic cytoplasm, indistinct cell borders, oval nuclei with invisible nucleoli, mild-to-moderate anisocytosis and anisokaryosis, and only a few mitoses (**Fig 4d**). In addition, there were clusters of a moderate number of small, mature lymphocytes. Multifocal coagulative necrosis and haemorrhage with fibrin thrombi in larger blood vessels were present, especially in the periphery of the neoplasm, and a chronic-active suppurative inflammation characterised by neutrophils and fewer plasma cells. Cervical, sternal and axillary lymph nodes were oedematous with interstitial fibrosis and granulation tissue but without metastasis.

Immunohistochemistry was performed using a 2-day protocol with incubation of primary antibodies at 4°C overnight and using 3,3′-diaminobenzidine as chromogen (see **Table 1** for antibodies and detection systems used). Most neoplastic cells of either shape stained positive for the epithelial marker cytokeratin (**Fig 4e**) and negative for the mesenchymal marker vimentin. The small lymphocytes were positive for CD3, consistent with T lymphocytes (**Fig 4f**). CD79 alpha-positive B lymphocytes were not detected. A thyroid origin could be ruled out due to the negative staining for thyroglobulin.

Therefore, thymic epithelial cells were determined as the origin of the neoplasm based on the morphology and immunohistology.

Discussion

The clinical signs of thoracic neoplasia are often shallow respiration and pectoral oedema due to pleural effusion (Mair *et al*. 2004). In addition, masses in the pleural cavity can lead to signs of congestion when they compress vessels, especially the cranial vena cava (Knottenbelt *et al*. 2015b; Unger *et al*. 2016). Potential consequences are a varying degree of venous congestion of the facial and jugular veins, pectoral oedema and hydrothorax (Knottenbelt *et al*. 2015b; Unger *et al*. 2016), such as in the case presented. In addition, the compression of cardiac vessels such as the pulmonary artery can consequently cause cardiac disorders (Smith *et al*. 2019), but in our case, echocardiography and post-mortem revealed no abnormalities. In this case, the owner noticed only pyrexia and lethargy, while depression, inappetence, weight loss and pyrexia have been described in the literature as general clinical signs in horses with neoplasia (Mair *et al*. 2004; Knottenbelt *et al*. 2015a).

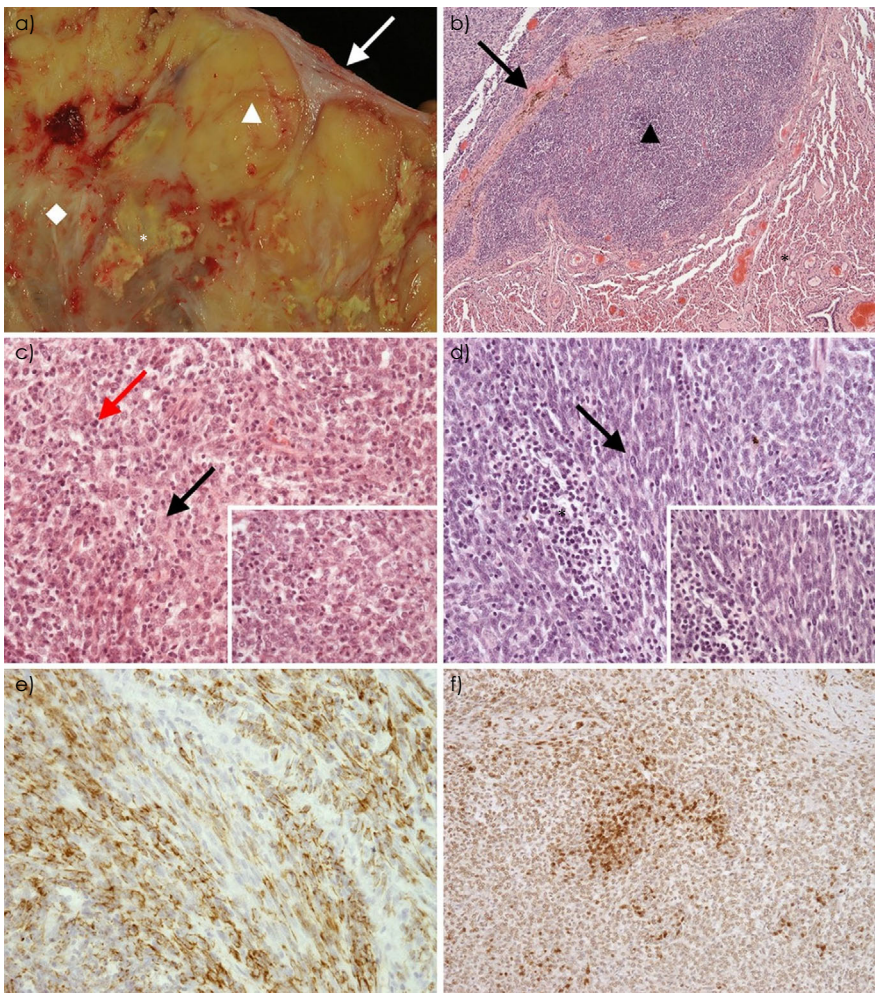

***Fig 4:** a) Macroscopic view of the cut surface with tumour capsule (arrow), neoplastic tissue (triangle), stroma (rhomb) and areas of necrosis (asterisk). b) Microscopic view of infiltration and compression of the lung. Lung (asterisk), infiltrating neoplastic cells (triangle) and tumour capsule (arrow). Haematoxylin and eosin (HE). 40×. c) Pleomorphic neoplastic cells (black arrow) with interspersed T lymphocytes (red arrow). Haematoxylin and eosin (HE). 200×. Inset: higher magnification. 400×. d) Spindle-shaped neoplastic cells (arrow) and cluster of T lymphocytes (asterisk). Haematoxylin and eosin (HE). 200×. Inset: higher magnification. 400×. e) Pancytokeratin-positive cytoplasm of neoplastic cells (brown signal). IHC for pancytokeratin, counterstained with Papanicolaou solution. 200×. f) Cluster of CD3-positive T lymphocytes (brown signal). IHC for CD3-antigen, counterstained with Papanicolaou solution. 100×.*

Differential diagnoses for masses in the thorax include abscess formation (Griffin 2002) or neoplastic processes. Abscesses can occur subsequent to pleuropneumonia (Byars *et al*. 1991). Even in horses with no signs of respiratory distress or a history of respiratory disease, as in the current case, abscesses should be considered as a potential diagnosis. An additional diagnostic work-up to distinguish inflammatory processes from neoplasia could have included serum protein electrophoresis, which may have provided further information on the character of the mass. It may reveal hyperfibrinogenaemia, hyperglobulinaemia or monoclonal gammopathy. However, serum protein electrophoresis is a non-invasive but not very specific diagnostic tool (Knottenbelt *et al*. 2015a). Mediastinal lymphoma is the most common neoplasia in the pleural cavity (Sweeney and Gillette 1989; Mair and Brown 1993). However, intrathoracic neoplasia can originate from the lung and surrounding anatomical structures, for example, regional lymph nodes, or consist of metastases deriving from a distant primary neoplasia (Knottenbelt *et al*. 2015b). The most common primary lung tumour in horses is granular cell tumour (Mair *et al*. 2004; Caswell and Williams 2016). Other tumours of the lung are pulmonary and bronchial carcinomas, adenocarcinomas, bronchogenic squamous cell carcinomas, bronchial myxomas and pulmonary chondrosarcomas (Knottenbelt *et al*. 2015b). Furthermore, melanoma, mesothelioma (Knottenbelt *et al*. 2015b) and neoplasia of the oesophagus must be considered (Ford *et al*. 1987).

The systematic examination in cases with a suspected pleural mass includes ultrasonography and radiography of the thorax and thoracocentesis. Since results obtained by these diagnostic tools were inconclusive in the current case, a biopsy was presumed necessary for a final diagnosis. An ultrasound-guided percutaneous biopsy may lead to diagnosis (De Clercq *et al*. 2004) but was not chosen because of the close proximity of the mass to the heart. The

TABLE 1: Antibodies and detection systems used for immunohistochemistry

Primary antibody	Dilution	Blocking	Antigen retrieval	Secondary antibody	Detection system
Cytokeratin (monoclonal mouse anti-human clone AE1/AE3*)	1:50	Horse serum	EDTA	Biotinylated horse anti-mouse IgG†	ABC†
Vimentin (monoclonal mouse anti-vimentin clone V9*)	1:50	Horse serum	–	Biotinylated horse anti-mouse IgG†	ABC†
CD3 (polyclonal rabbit anti-human*)	1:100	20% pig serum	Target retrieval pH9 ready to use*	Pig anti-rabbit IgG†	Rabbit PAP*
CD79alpha (monoclonal mouse clone HM57‡)	1:100	Horse serum	Citrate pH 6	Biotinylated horse anti-mouse IgG†	ABC†
Thyroglobulin (polyclonal rabbit anti-human*)	1:5000	20 % pig serum	–	Pig anti-rabbit IgG†	Rabbit PAP*

ABC, avidin–biotin complex method; PAP, peroxidase antiperoxidase method.
Sources
* DAKO Deutschland (Hamburg, Germany).
† Vector Laboratories (Burlingame, California, USA).
‡ Acris Antibodies GmbH (Herford, Germany).

mass was deemed to be located too axial for a right-sided biopsy. Consequently, it was decided to take a tissue sample under direct optical guidance during thoracoscopy (Vachon and Fischer 1998; Fry *et al*. 2003). Minimal invasive endoscopic visualisation of the thorax has proven to be a valuable diagnostic tool for inflammatory processes of unknown origin with masses or fluid accumulation (Rossier *et al*. 1990; Fischer and Vachon 2002; Pollock and Russell 2006; Lee *et al*. 2013) and for potentially therapeutic interventions (Vachon and Fischer 1998). A therapeutic intervention was considered impossible in the present case, as resection of the mass would not have been possible because of its size and localisation. Potential complications of thoracoscopy, for example, damage to the lung, a residual pneumothorax or infection (Mackey and Wheat 1985), did not occur in this case.

The histopathological and immunohistochemical examination revealed the neoplasm to be of thymic epithelial origin. The nodular gross appearance of the tumour, with its partial encapsulation, and areas of haemorrhage and necrosis were in accordance with previous descriptions in literature (Valli *et al*. 2017). The pathohistological examination revealed no signs of vascular invasion of the tumour or lymph node metastases. Venous congestion and subcutaneous oedema were most probably caused by mechanical compression of the cranial vena cava (Knottenbelt *et al*. 2015b). Whiteley *et al*. (1986) also describe oedema of the forelimb and ventral chest in a horse with thymoma. The chronic fibrosis in regional lymph nodes is suggestive of a chronic mechanical compression of lymphatics and probably contributed to the oedema. The results of thoracocentesis were inconclusive due to the presence of inflammatory cells without detection of neoplastic cells in the fluid. The chronic-active inflammation of the tumour, as detected histologically, explains the presence of neutrophils and macrophages that can be mistaken for a pure pyogranulomatous inflammatory process. The presence of eosinophils in thoracocentesis is in accordance with descriptions of thymomas in other species previously (Sandison and Anderson 1969; Burgess *et al*. 2016). The absence of neoplastic cells may have been due to the encapsulation of the mass, preventing exfoliation of tumour cells.

The neoplasm in our case showed various features different from any of the other three cases published (Whiteley *et al*. 1986; Furuoka *et al*. 1987; Shahriar and Moore 2010) and did not fit easily into any of the WHO categories (Travis *et al*. 2004; Valli *et al*. 2016). On the one hand, it showed several features of benign AB thymoma, according to the WHO classification, that is the coexistence of spindle-shaped and epithelioid cells. On the other hand, it had marked features of malignancy, such as the extremely expansile growth with the compression of neighbouring anatomical structures and early capsular infiltration. These findings are mostly correlated with B3 thymoma, according to the WHO classification. Furthermore, the extremely high mitotic rate fits with thymic carcinoma, as described by the WHO classification, although the cell morphology does not show the corresponding amount of atypia (Travis *et al*. 2004; Valli *et al*. 2016). The cases of equine thymic carcinomas described in literature previously showed prominent histological features of squamous cells with cornification. Metastases were found in the cervical lymph nodes, ribs, lungs and thyroid gland (Whiteley *et al*. 1986); lung, pulmonary and mediastinal lymph nodes; and surrounding the abdominal aorta close to the left kidney, respectively (Furuoka *et al*. 1987). Shahriar and Moore (2010) describe clear histological features of type A thymoma, according to the WHO classification, with spindle-shaped cells. Moreover, heart metastases were present in their case.

The neoplasm in the present case clearly had malignant potential, even in the absence of lymph node or distant metastases, due to the high mitotic rate and capsular invasion. Regarding the histological appearance, the diagnosis atypical thymoma, as proposed by Moran and Suster (2008), seems to be most appropriate. The criteria are in accordance with those applied in the only veterinary study on classification systems performed in the dog (Burgess *et al*. 2016). The authors found an increase in mitotic figures, cellular pleomorphism and capsular invasion in atypical thymomas compared with thymomas. There was no correlation between the classification

and the expression of certain immunohistochemical markers that were used in human medicine. They concluded that histomorphology is the main criterion for classification but found no statistically significant difference in survival between the tumour subgroups.

In conclusion, the present case illustrates a systematic diagnostic approach to an atypical thymoma and exemplifies the morphologic heterogeneity of equine thymomas. The application of a human classification system of thymoma to the current equine case revealed that histological findings correspond well. It is currently unknown which classification system is most suitable to assess disease progression, treatment options and prognosis due to the low number of cases described.

Authors' declarations of interest

No conflicts of interest have been declared.

Ethical animal research

The owner was informed and signed an informed consent form.

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Authorship

All authors contributed to this case and preparation of the manuscript. All authors gave their final approval.

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