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Multiple myeloma in an Amur tiger (*Panthera tigris altaica*)

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Abstract

The Amur tiger (*Panthera tigris altaica*) is an endangered tiger subspecies. An adult zoo-bred female was found collapsed, and died despite supportive treatment. Hematology and biochemistry showed pancytopenia and hyperglobulinemia, and serum protein electrophoresis revealed a monoclonal band in the β -globulin region. Necropsy demonstrated hemoabdomen, multifocal lytic bone marrow lesions, splenomegaly, and hemorrhagic hepatic nodules, with left medial lobe rupture. There were multifocal hemorrhages in the subcutis, lung, epicardium, and intestinal mucosa. Histopathology demonstrated plasmacytoid cells infiltrating the bone marrow, liver and spleen, and circulating within blood vessels. On immunohistochemistry, cell infiltrates of the three tissues were positive for λ light chains, bone marrow infiltrates were positive for MUM-1 and bone marrow and spleen infiltrates were positive for CD20. These findings indicate that this animal died of hemoabdomen subsequent to multiple myeloma. This is the first time this disease has been reported in a tiger.

Keywords: Amur tiger, Immunohistochemistry, Multiple myeloma, *Panthera tigris altaica*, Serum protein electrophoresis.

Introduction

The Amur (Siberian) tiger is classed as 'Endangered C2a(i); D' (International Union for Conservation of Nature, 2011). In 2007, there were an estimated 428 - 502 surviving wild individuals, with another 421 housed in zoos/wildlife parks in Europe and North America (Henry *et al.*, 2009). This subspecies has very low genetic diversity, but zoo-housed individuals retain genetic material that has been lost in wild populations (Henry *et al.*, 2009). Therefore the maintenance of a healthy zoo population may be critical to this species' survival. To date, a variety of different tumors have been reported sporadically in zoo-housed tigers of different species (Junginger *et al.*, 2005).

Multiple myeloma (MM) is a clonal proliferation of malignant plasma cells that arises in the bone marrow, secretes monoclonal immunoglobulin (paraprotein) and produces lytic bone lesions (Thompson and Dittmer, 2017). MM is infrequently reported in domestic cats, with one study estimating them to comprise < 1% of feline neoplasms (Patel *et al.*, 2005). Affected domestic cats have a mean age of 12.5 years (median 14 years) and males are overrepresented (Patel *et al.*, 2005). Non-specific presenting signs (lethargy, weakness, anorexia) are common, and lameness or paresis may occur due to osteolysis. (Patel *et al.*, 2005).

A number of paraneoplastic syndromes may occur secondary to MM, including the Bence Jones proteinuria (free immunoglobulin light chains in the

urine), hypercalcaemia, AL amyloidosis and bleeding diathesis. (Thompson and Dittmer, 2017). Immunohistochemistry may act as a valuable tool in differentiating MM from other round cell tumours, and in subclassifying it based on the type of immunoglobulins produced (Thompson and Dittmer, 2017).

MM has been reported once in a jaguar, but to the authors' knowledge, never in an Amur tiger (Port *et al.*, 1981). Given the endangered status of Amur tigers, it is important to build up knowledge of diseases that affect these animals, their associated clinical signs, clinicopathological features, and useful diagnostic aids.

Case Details

This 13-year-old, zoo-bred, female Amur tiger was found collapsed in its habitat. Anaesthesia was carried out via remote delivery (2.3 ml Tiletamine hydrochloride and Zolazepam hydrochloride/'Zoletil 100' combined with 2.3 ml Medetomidine/'Domitor'). Fluid (2.5 l compound sodium lactate), antibiotic (12 ml Enrofloxacin/'Baytril Max' via subcutaneous injection), and non-steroidal anti-inflammatory (5 ml Meloxicam/'Metacam' via subcutaneous injection) therapy was administered, and blood was sampled for hematology and biochemistry.

Anaesthesia was reversed with 2.3 ml Atipamazole/'Antisedan'. Abnormal hematological findings included neutropenia ($0.46 \times 10^9/L$, ref: 2.5-12.5), non-regenerative anemia (hematocrit of 0.23 I/L,

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ref: 0.24 – 0.45), lymphopenia ($0.21 \times 10^9/L$; ref: 1.5-7) and thrombocytopenia ($21.00 \times 10^9/L$, ref: 180-550). Biochemistry showed hyperproteinemia (121.5 g/L, ref: 59-78) with hyperglobulinemia (100.7 g/L, ref: 24-40), hypoalbuminemia (20.8 g/L, ref: 25-35) and hypercreatinemia ($237 \mu\text{mol/L}$, 40-170). Serum protein electrophoresis (SPEP) revealed a monoclonal band in the β -globulin region with γ -globulin depletion. Although some recovery was observed, the animal remained dull and died naturally four days after presentation, before further diagnostics were carried out.

At necropsy, the carcass weighed 109 kg. Subcutaneous fat was diffusely depleted, and the oral mucosae were markedly pale and slightly icteric. There were focal, subcutaneous and intramuscular hemorrhages at the right olecranon, within the left forelimb and hind limb musculature, and the cranial thoracic region (T2-T3). There were multifocal, oval, dark red nodules in the medullary cavities of the right humerus and right and left tibias (Fig. 1A). Surrounding marrow was yellow and fatty. The abdomen contained approximately three litres of sanguinous fluid, and several large blood clots. There were multifocal, small, irregularly-shaped, flat, dark, hemorrhagic foci affecting all liver lobes (Fig. 1B), continuing into the parenchyma to a depth of 0.5 - 1 cm. There was a linear, 4 cm rupture on the diaphragmatic surface of the left medial liver lobe, with an adherent blood clot (Fig. 1B).

The spleen was diffusely enlarged and pink (Fig. 1C), with soft, wet parenchyma. All lung lobes were covered in multifocal-coalescing, variably-sized (0.2 - 1 cm) hemorrhages (Fig. 1D). There were multifocal subendocardial hemorrhages and fibrosis, and multiple jejunal and ileal mucosal petechiae. Additionally, there was moderate-marked bilateral degenerative joint disease (DJD) of the stifles. No significant abnormalities were present in other organs.

On histopathology, the bone marrow consisted of sheets of small, round cells, with scant to moderate amounts of eosinophilic cytoplasm and eccentric, round nuclei (Fig. 2A), which occasionally displayed marginated chromatin and intranuclear inclusions (Dutcher bodies).

There were occasional binucleate and apoptotic cells, and one to two mitotic figures per high-power-field. Similar cells infiltrated the spleen and hepatic cords, associated with hemorrhage and necrosis. Microscopically, the subcutaneous hemorrhagic lesions revealed hemorrhage with necrotic skeletal muscle. Hemorrhagic areas contained occasional individual and clustered round cells with large, eccentric, round nuclei and occasional prominent or bizarre mitotic figures. There were multifocal-coalescing areas of pulmonary hemorrhage and intra-alveolar edema, associated with intra-alveolar macrophages.



Fig. 1. Organs removed at necropsy from an Amur tiger (*Panthera tigris altaica*) with multiple myeloma. (A): Tibia, longitudinal section: multifocal to coalescing haemorrhagic nodules infiltrating the yellow discoloured bone marrow. (B): Liver; multifocal irregularly shaped dark red foci. The capsule over left medial lobe is ruptured, with adherent blood clot. (C): Spleen: diffuse marked splenomegaly. (D): Opened thorax, lung in situ: Multifocal, variably-sized haemorrhages scattered over the pleural surface.

There were bands of dissecting myocardial fibrosis. Both kidneys exhibited moderate membranous depositions in the glomerular tufts, basement membranes and Bowman's capsules, and protein casts in tubules, with multifocal, mild, lymphoplasmacytic interstitial nephritis. Immunohistochemistry for various B-cell and immunoglobulin markers was carried out (Table 1). Antibodies were chosen based on their known cross-reactivity with feline tissues. Each antibody labelled occasional round cells, confirming that specific epitopes were detected. All cells infiltrating the bone marrow, liver and spleen were strongly, diffusely positive for λ light chains (Fig. 2B). Eighty per cent of the neoplastic bone marrow cells exhibited moderate nuclear staining for MUM-1 (Fig. 2C). Ninety per cent of cells infiltrating the bone marrow and the spleen exhibited cytoplasmic CD20 staining (Fig. 2D). These findings indicated a diagnosis of MM.

Discussion

The non-specific clinical signs exhibited by this tiger (tachypnea and collapse) may have been secondary to anemia and dehydration, and are fairly typical of felids affected with MM (Patel *et al.*, 2005). The fluid therapy and pain relief may have caused the brief improvement noted prior to death. There was no history of lameness, despite the osteolytic lesions and DJD. A number of changes suggestive of MM were evident on hematology and biochemistry. Hematology revealed non-regenerative anemia, neutropenia, and thrombocytopenia, findings which have been reported in cats with MM (Patel *et al.*, 2005). Pancytopenia may result from myelophthisis secondary to bone marrow infiltration with neoplastic cells (Brockley *et al.*, 2012).

Table 1. Methodology details and results of immunohistochemical examination of various tissues from an Amur tiger (*Panthera tigris altaica*) with multiple myeloma.

Marker	Source	Concentration	Pre-treatment	Bone marrow	Spleen	Liver
MUM-1	M7259, Dako,	1:100	FLEX TRS HIGH pH 9 (Dako)	+++	-	-
CD20	RB-9013-P Thermo-Scientific	1:1500	FLEX TRS LOW pH 6.1 (Dako)	+++	+++	ND
CD45R	MAK1258G, LINARIS	1:2000	FLEX TRS LOW pH 6.1 (Dako)	-	-	-
Pax5	610863, BD BioSciences,	1:40	Microwave-EDTA	-	-	ND
IgG	Polyclonal A042301-2, Agilent	1:20,000	HIER pH6	-	-	-
IgM	Polyclonal A042501-2, Agilent	1:2000	HIER pH6	-	-	-
IgA	Polyclonal A026201-2, Agilent	1:8000	HIER pH6	-	-	-
IgD	Polyclonal A009302-2, Agilent.	1:1000	HIER pH9	-	-	-
λ light chains	Polyclonal A019302-2, Agilent.	1:3000	HIER pH6	+++	+++	+++
κ light chains	Polyclonal A019102-2, Agilent.	1:2000	HIER pH6	-	-	-

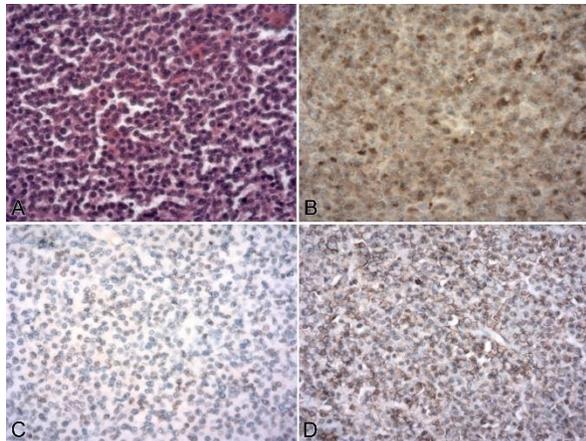


Fig. 2. Photomicrograph of round cell neoplasm in the bone marrow of an Amur tiger (*Panthera tigris altaica*) with multiple myeloma. (A): Densely-packed, round cells with eosinophilic cytoplasm and eccentric nuclei (malignant plasma cells) (Hematoxylin and eosin; 200X magnification). (B): Neoplastic cells exhibit diffuse, strong brown cytoplasmic labelling for λ light chains. λ light chain immunohistochemical staining, hematoxylin counterstain (200X magnification). (C): MUM-1 intranuclear expression in eighty per cent of neoplastic cells. MUM-1 immunohistochemical staining, hematoxylin counterstain (200X magnification). (D): Ninety per cent of neoplastic cells exhibit brown membranous labelling for CD20. CD20 immunohistochemical staining, hematoxylin counterstain (200X magnification).

On necropsy, hemorrhage was present in the lungs, gastrointestinal tract, liver, subcutis, myocardium, and abdomen. This was likely secondary to the marked thrombocytopenia. It has also been suggested that such

bleeding diatheses may occur in MM due to clotting factor and platelet disruption by paraprotein (Patel *et al.*, 2005).

Paraproteinemia, a characteristic feature of MM, is apparent on SPEP as a narrow spike in the α₂, β or γ region (monoclonal or occasionally biclonal) with M-protein levels of > 30 g/l. (O’Connell *et al.*, 2005). In one study, all cats with MM displayed a mono- or biclonal gammopathy on SPEP (Patel *et al.*, 2005). This tiger displayed hyperglobulinemia, hypoalbuminemia (likely compensatory, to maintain osmotic pressure), with an increased albumin-to-globulin ratio. SPEP revealed a monoclonal peak in the β-globulin region.

Hypercreatininemia has been occasionally reported in affected cats, likely due to renal insufficiency secondary to glomerular paraprotein loss (Patel *et al.*, 2005). Bence-Jones proteinuria occurs in up to 65% of affected cats (Thompson and Dittmer, 2017). Urinalysis was not carried out in this case, but renal tubular protein casts seen on histological examination indicate proteinuria may have occurred. Paraneoplastic hypercalcemia has been reported in cats with MM, but this tiger’s total calcium levels were normal (Patel *et al.*, 2005). Ionised calcium was not measured.

On necropsy, neoplastic plasma cells infiltrated the medullary cavities of the humerus and tibia, the liver and the spleen. In cats and dogs, vertebrae, femur, pelvis, humerus and ribs are the skeletal sites most frequently involved in MM, and single or multiple bones may be affected (Patel *et al.*, 2005; Thompson and Dittmer, 2017). The liver and spleen are common sites of visceral involvement in cats (Patel *et al.*, 2005). MM appearing grossly as hepatic and splenic

hemorrhagic nodules has been reported in a felid, but appears to be an uncommon mode of presentation (Hribernik *et al.*, 1982).

On histology, the neoplastic cells' appearance was typical of well-differentiated MM, despite the relatively high mitotic rate (Mellor *et al.*, 2008). Additionally, circulating neoplastic-appearing plasmacytoid cells were frequently seen in blood vessel lumens, which has rarely been reported in felids with MM (Mellor *et al.*, 2006), and indicates a worse prognosis (Valli *et al.*, 2017). Amyloidosis is another pathological process that occurs secondary to MM, with AL amyloid deposited in splenic, renal, and hepatic vessels (Thompson and Dittmer, 2017). Congo red stains were carried out on multiple tissues in this case, but were negative.

On immunohistochemistry, neoplastic cells in the bone marrow, spleen and liver were positive for λ light chains. Previous reports investigating light chain expression in feline MM and plasmacytomas found the majority were positive for λ light chains, consistent with the fact that λ light chains are expressed in 90% of normal feline plasma cells (Arun *et al.*, 1996; Majzoub *et al.*, 2003; Mellor *et al.*, 2008).

Immunohistochemistry in the same tissues for heavy chains (IgG, IgA, IgM and IgD) was negative. This may indicate that this neoplasm represents a light-chain myeloma, which has rarely been reported in cats. However, this is unlikely, as these neoplasms rarely present with paraproteinemia. Other immunohistochemical studies conducted on feline plasmacytomas reported tumors that were light-chain positive but heavy-chain negative (Majzoub *et al.*, 2003). It is possible that aberrant immunoglobulin heavy chains were synthesized by the neoplastic cells that were not labelled by commercial antibodies. IgG and IgA are the heavy chains most commonly expressed in feline MM (Patel *et al.*, 2005).

Immunohistochemistry was also carried out for plasma and B-cell markers (Table 1). MUM-1 is required for lymphoid development and immune response regulation (Ramos-Vara *et al.*, 2007), and MUM-1 positive plasma cells and memory B-cells are found in normal bone marrow (Tsuboi *et al.*, 2000). Its expression has been demonstrated in plasma cell tumors of dogs and cats (Ramos-Vara *et al.*, 2007). Eighty per cent of nuclei of the bone marrow infiltrates in this case were strongly positive for MUM-1, while expression was not found in the spleen or liver. It is possible that these cell populations were less differentiated than the bone marrow cells, and lost expression of MUM-1. CD20 is another common pan-B-cell marker. Here, it was weakly-moderately expressed in neoplastic cells of the bone marrow and spleen (the liver was not tested). Its expression has been reported in neoplastic feline B-cells (Brockley *et al.*, 2012). All three tissues were negative for lymphocyte

markers Pax-5 and CD45R. Antibodies used have not been validated for tigers, so false negative staining cannot be excluded.

Had the spleen been biopsied at the time of immobilisation and examined histologically, a diagnosis of round cell tumour suspicious of plasmacytic origin would have been considered, based on the cell morphology and the concurrent hyperglobulinemia and paraproteinemia. However, had IHC been carried out for B-cell and plasma cell markers, a B-cell lymphoma may have been included as a differential due to the positive CD20 expression. CD20 is not usually expressed on plasma cells, but rather on earlier developmental stages of B-lymphocytes (Brighenti *et al.*, 2005). However, CD20 expression has been shown in plasma cell neoplasia in dogs, meaning that MM remains a differential (Ramos-Vara *et al.*, 2007).

Clinically, the hematology and biochemistry results, when interpreted in light of the SPEP results, were suggestive of MM. However, on gross examination, the multiple hemorrhagic lesions and hemoabdomen were suggestive of a multicentric hemangiosarcoma, which has been reported previously in a Bengal tiger (Kang *et al.*, 1996). However, the histological findings confirmed MM as the most likely diagnosis, which was confirmed with immunohistochemistry.

Other lymphoma types have been shown to express MUM-1 in humans, namely diffuse large B-cell lymphoma (DLCLB), marginal zone lymphoma (MZL), and small lymphocytic lymphoma (SLL) (Tsuboi *et al.*, 2000). The production of antibodies of DLBCL is relatively rare and it is not typically included on the list of differentials for paraproteinemia (Kumar *et al.*, 2010). DLBCLs would usually only secrete IgM immunoglobulin heavy chain, whereas neoplastic plasma cells have the potential to secrete any heavy chain type (IgA, IgD, IgE, IgG, or IgM). The type of heavy chain produced in this case was not determined. On serum gel electrophoresis, the spike was visible in the beta region, which may indicate excess IgA, IgG or IgM production. MZL form characteristic nodules centred around germinal centres, which was not seen in this case. Additionally, MZL is rarely associated with macroglobulinemia (Valli *et al.*, 2017). SLL, also known as B-cell chronic lymphocytic leukemia, is characterised by severe lymphocytosis, but in this case, a lymphopenia was evident. Although an IgM macroglobulinemia may occur with this condition, this is again very rare (Valli *et al.*, 2017).

The diagnostic criteria for MM in cats are a) presence of plasma cell tumor, either in bone marrow or abdominal organs, and b) monoclonal proteins in serum or urine (Thompson and Dittmer, 2017). These are likely not strict enough to exclude B-cell tumors which may also infiltrate bone marrow, viscera and cause

paraproteinemia, such as those listed above. Diagnosis of lymphocytic neoplasms is often not straightforward, as is evidenced by another case in which a cat with similar lesions to this tiger was diagnosed with B-cell lymphoma (Brockley *et al.*, 2012). However, taken together, the cellular size and morphology, typical bone marrow lesions, visceral involvement, and bone marrow nuclear MUM-1 expression, indicate MM is the most likely diagnosis in this case.

Had the animal lived, recommended diagnostics would include skeletal radiography for detection of lytic lesions, and urinalysis for Bence-Jones proteins. However, the prognosis for MM is poor, with most cats being euthanised within six months of diagnosis (Thompson and Dittmer, 2017) The findings described in this case fulfill the criteria which have been suggested to confirm diagnosis of feline MM (Thompson and Dittmer, 2017). This is the first reported case of MM in this endangered species.

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Conflict of interest

The authors declare that there is no conflict of interest.

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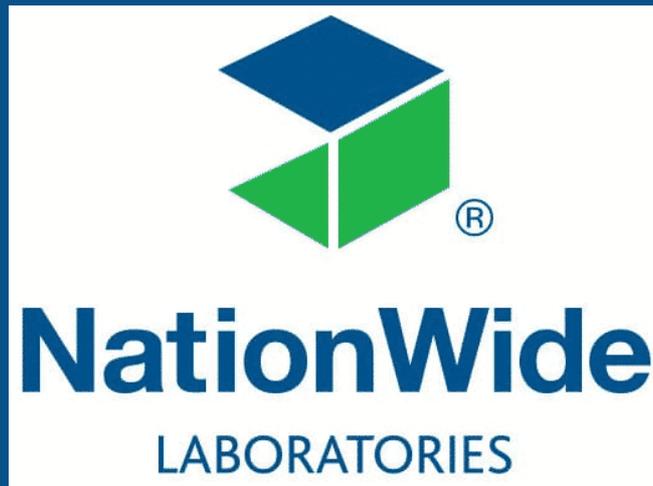
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