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Spontaneous mediastinal myeloid sarcoma in a common marmoset (*Callithrix jacchus*) and review of the veterinary literature

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Abstract

Background—Myeloid sarcoma is a rare manifestation of myeloproliferative disorder defined as an extramedullary mass composed of myeloid precursor cells. A 9-month old, female, common marmoset (*Callithrix jacchus*) had increased respiratory effort.

Methods—A complete necropsy with histology and immunohistochemistry was performed.

Results—The thymus was replaced by a firm, grey-tan mass with a faint green tint, filling over 50% of the thoracic cavity. Sheets of granulocytes, lymphoid cells, nucleated erythrocytes, megakaryocytes, and hematopoietic precursors of indeterminate cell lineage replaced the thymus, perithymic connective tissue, mediastinal adipose tissues, epicardium, and much of the myocardium. The cells demonstrated diffuse strong cytoplasmic immunoreactivity for lysozyme, and strong, multifocal membranous immunoreactivity for CD117.

Conclusion—We report the first case of a myeloid sarcoma in a common marmoset (*Callithrix jacchus*), similar to reported human cases of mediastinal myeloid sarcoma, and present a review of myeloproliferative diseases from the veterinary literature.

1. Introduction

Myeloproliferative disease is defined by the proliferation of one or more bone marrow cell lineages excluding lymphomas and lymphoid leukemias. The classification of myeloid neoplasms falls into four major categories: granulocytic (neutrophilic, eosinophilic, basophilic), monocytic, erythroid, and megakaryocytic. Further division of myeloid neoplasms is based on clinical presentation and rate of proliferation of neoplastic clones into three categories: acute myeloid leukemia (AML), chronic myeloproliferative diseases (includes chronic myeloid leukemia and chronic idiopathic myeloid fibrosis), and myelodysplastic diseases [1]. Myeloid sarcoma (also known as granulocytic sarcoma, chloroma, myeloblastoma, or monocytoma) [2] is an exceedingly rare manifestation of a

myeloproliferative disorder defined in both human and veterinary literature as an extramedullary focal mass composed of myeloid precursor cells. In humans, myeloid sarcoma is typically found in association with acute myeloid leukemia [2, 3]. In domestic animals, the discovery of myeloid sarcoma does not predict the presence of neoplastic cells within the blood, but no studies have tested this potential association [1]. We report the first case of a myeloid sarcoma in a common marmoset (*Callithrix jacchus*) and present a review of myeloproliferative diseases from the veterinary literature.

2. Materials and Methods

2.1 Animal

The marmoset was socially housed in indoor, conventional wire caging, fed a commercial diet (Mazuri Callitrichid diet, Richmond, Indiana, USA) supplemented with grains, vegetables, and fruits and provided water *ad libitum*. All animal care and procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee.

2.2 Pathology

A complete necropsy was performed, and appropriate tissue samples were taken for histologic evaluation. All tissues were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 microns, stained with hematoxylin and eosin, and evaluated by light microscopy by at least one board-certified veterinary pathologist. Histochemical staining for periodic acid-Schiff (PAS), Gomori's methenamine silver (GMS), Giemsa, and Gram's stain were performed according to standard protocol. For immunohistochemical labeling, reagents were procured from Ventana Medical Systems, Tucson, AZ, USA. All stains were completed using the Ventana BenchMark Ultra automatic stainer (Ventana Medical Systems, Inc., Tucson, AZ, USA) with the UltraView DAB detection kit (Ventana Medical Systems, Cat # 760-500). Immunohistochemical labeling was performed on formalin-fixed, paraffin-embedded, 4 µm thick sections of the thoracic mass as well as the myocardium. Slides were deparaffinized, and treated with Hier in CC1 at 95°C for 36 minutes, incubated with primary antibody, and counterstained with Hematoxylin (Ventana catalog number 760–2021)/Bluing (Ventana catalog number 760–2037) for 4 minutes each. The specific primary antibodies and their respective incubation temperatures are listed in Table 1.

2.3 Literature Review

We performed a literature search for all published cases of myeloproliferative disorders in nonhuman primates and for myeloid sarcoma in domestic animals.

3. Case Report

3.1 History

A 9-month old, female, common marmoset (*Callithrix jacchus*) was observed to have increased respiratory effort. The animal was hand captured, became recumbent, and expired.

The marmoset was part of a breeding colony, not used experimentally, and had no prior clinical history.

3.2 Gross pathology

At necropsy, the animal had adequate muscle mass, hydration, and adipose tissue. The abdominal subcutis was edematous. The thoracic cavity contained approximately 3 mL of clear to red, watery fluid. The thymus was enlarged (measuring approximately $2 \times 1 \times 2 \text{ cm}^3$ and filling over 50% of the thoracic cavity), grey-tan with a faint green tint, and firm (Figure 1A).

3.3 Histology

A pleocellular infiltrate of round cells expanded and largely replaced the thymus (Figure 1B and C), perithymic connective tissue, mediastinal adipose tissues, epicardium, and much of the myocardium (Figure 1D, E and F). The infiltrate was composed of sheets of granulocytes, lymphoid cells, nucleated erythrocytes, megakaryocytes, and hematopoietic precursors of indeterminate cell lineage (Figure 1E and F) with high mitotic activity (Figure 1F inset). Under oil immersion, moderate numbers of the smaller segmented cells contained small, pink cytoplasmic granules (Figure 1C inset). Intravascular neoplastic hematopoietic cells were not visualized in any tissue sections. Scattered extramedullary hematopoiesis was observed within the kidney, spleen and adrenal gland.

3.4 Immunohistochemical Staining

The neoplastic round cells demonstrated diffuse strong cytoplasmic immunoreactivity for lysozyme, in both thymus (Figure 2A and B) and heart (Figure 2C and D) which support a myeloid origin. Neoplastic cells also demonstrated strong, multifocal membranous immunoreactivity for CD117 (c-KIT), indicating the presence of hematopoietic precursors in thymus (Figure 2E and F), and myocardium. There were scattered immunopositive cells for CD61 (platelets/megakaryocytes) and hemoglobin, consistent with hematopoiesis. There were scattered or rare CD20 and CD3 immunopositive cells in the thoracic mass and heart. Immunohistochemical staining for CD34 (hematopoietic stem cell marker), CD15 (hematopoietic stem cell and granulocyte marker), and myeloperoxidase (granulocyte marker) did not work on this marmoset tissue. Special histochemical stains (PAS, GMS, Giemsa, and Gram) failed to identify any etiologic agents in the heart or thymic tissue.

4. Literature Review

4.1 Myeloproliferative Disease in Nonhuman Primates

Recent reviews of all nonhuman primates species revealed that hematopoietic neoplasms (lymphomas and leukemias) are the most commonly reported malignancies, however, myeloproliferative disorders are less common [4, 5]. Table 2 shows reported cases, spontaneous and experimental, of myeloproliferative diseases in nonhuman primates. In nonhuman primates, the term “myeloid sarcoma” is infrequently used. Two other case reports demonstrating gross lesions similar to this marmoset were identified [6, 7]. In an owl monkey, a cranial mediastinal mass occupying the space where the thymus is normally located has been described [6]. Histologically, diffuse sheets of immature eosinophils with

several criteria of malignancy were found in the thymic mass, lung, heart, liver, gall bladder, spleen, adrenal gland, ovary, uterus, and retroperitoneal connective tissue. The presence or absence of leukemic cells within blood vessels was not noted [6]. In contrast, an ileocecal mass found in a cotton top tamarin was diagnosed as a megakaryocytic leukemia based on Factor 8 positive cells (marker for megakaryocytes or precursors) and the presence of neoplastic cells within capillary beds [7]. Histological features were consistent with immature granulocytic cells and blast cells of indeterminate origin found in the ileocecal mass and lamina propria of the stomach, small intestine, and colon. The only reported myeloproliferative disorder in a common marmoset was a single case of idiopathic myelofibrosis in a 8 year old animal [8]. While there is a case of myeloid sarcoma reported in a rhesus macaque [9], it was presumed that the myelomonocytic tumor resulted from retroviral vector insertion into the BCL2-A1 gene (a TaqMan assay revealed a vector copy number of at least one per cell in the tumor) [9].

4.2 Myeloid Sarcoma in Domestic Species

Myeloid sarcoma has been reported in several domestic species (Table 3). While the etiology remains unknown, it has been shown that myeloproliferative disease can be induced in domestic cats by inoculation with feline leukemia virus (FeLV) [10]. Similarly in domestic dogs, a viral origin and genetic susceptibility have been implicated [11].

5. Discussion

Myeloid sarcoma is a rare neoplasm (2/1,000,000 in human adults) and usually accompanies the diagnosis of acute myeloid leukemia, but can also be associated with other myeloproliferative diseases (myelodysplastic syndromes or myeloproliferative syndromes). In rare cases where hematologic malignancies are absent in the bone marrow, lesions are classified as nonleukemic, primary, or isolated myeloid sarcomas [3], however the disease typically progresses to bone marrow involvement weeks to months later [2]. Myeloid sarcoma is an aggressive disease in humans and while the recommended treatment is systemic chemotherapy, the prognosis of the underlying leukemia is generally poor [2, 12].

Myeloid sarcoma is difficult to diagnose in humans and is misdiagnosed in 25–57% of cases as large cell lymphoma [2, 12, 13] or other malignant lymphoproliferative disorders [3]. Although routine hematoxylin and eosin frequently reveal a cell population of myeloblasts, immunohistochemistry, flow cytometry, fluorescence *in situ* hybridization (FISH), and molecular analysis are the preferred diagnostic modalities [3]. Common myeloid markers include lysozyme, myeloperoxidase (MPO), chloroacetate esterase, and various clusters of differentiation [2, 3, 12]. Immature myeloid cells or myeloid precursors in the thymus can be detected by CD34, CD43, CD117, and TdT (Terminal deoxynucleotidyl transferase), while more differentiated myeloid cells are detected by CD13, CD15, and CD33 [12]. A recent review of human literature suggests that the majority of myeloid sarcomas (in formalin-fixed, paraffin-embedded tissue specimens) can be diagnosed using an immunohistochemical panel including CD43, MPO, CD117, CD68 (or CD163), CD3 and CD20 [14]. For a more detailed discussion of various immunohistochemical stains used in

the diagnosis of myeloid sarcoma, the reader is directed to Alexiev *et al* [14] and Hagen *et al* [15].

The greenish appearance of the mass, a commonly reported feature of myeloid sarcomas, is attributed to the high level of myeloperoxidase present in granulocytes [1]. Histologically, the differential diagnoses include extramedullary hematopoiesis (EMH), myelolipoma, leukemia, and an atypical inflammatory process. EMH is a common finding in many tissues of young marmosets [16], including in the heart [17], and there appears to be scattered EMH in the heart and thymus in this young animal (indicated by the presence of low numbers of cells immunopositive for CD61 (platelets/megakaryocytes) or hemoglobin) in addition to EMH in the spleen, adrenal gland, and kidney. However, age-associated physiologic EMH in young marmosets is not expected to efface the thymus or extensively infiltrate the ventricular myocardium. The presence of EMH in the neoplastic tissues, along with cellular and nuclear pleomorphism, granular cytoplasm, and high mitotic index, contributed to the heterogeneity observed in the neoplasm.

Myelolipomas are fairly common in callitrichids, including common marmosets and cotton top tamarins. They most commonly arise in the adrenal gland and occasionally occur at other locations, including liver and lymphoid tissues [18]. The composition of myelolipomas can vary from being primarily adipocytes to predominantly hematopoietic. Though they have not been previously described in the mediastinum of nonhuman primates, they can occur at this location in humans [19]. Myeloproliferative disorder is favored over myelolipoma in this case because of disruption of the perithymic connective tissue capsule at multiple locations and invasion into the adjacent myocardium, findings which would not be expected in cases of myelolipoma.

Although a complete blood count and bone marrow aspirate would have been helpful to completely exclude the presence of myeloid leukemia, blood samples and bone marrow were not collected at the time of necropsy. We did not observe intravasacular neoplastic hematopoietic cells in any tissue. While an underlying inflammatory process was also a consideration, we would expect to see greater recruitment of CD3 immunopositive T-cells and CD20 immunopositive B-cells, which is not apparent in this case.

In conclusion, we report the first case of a myeloid sarcoma in a common marmoset (*Callithrix jacchus*). While CD34, CD15, and myeloperoxidase would have been helpful diagnostics, the pattern of infiltration in the heart, effacement of the thymus, and disruption of the thymic capsule are consistent with extramedullary myeloproliferative disease. The cell morphology and immunoreactivity for lysozyme and CD117 further support the diagnosis. The gross findings in this marmoset are similar to reported human cases of mediastinal myeloid sarcoma. In humans, gross lesions can occur at any site in the body, but a recent literature review revealed that the mediastinum was the most common extramedullary site of myeloid sarcoma [20]. Similar to the presentation seen in this marmoset, myeloid sarcoma has been noted in the thymus in the absence of circulating leukemic cells [21].

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Figure 1.

Gross appearance and histopathological features of neoplastic mass. A) Green-tan neoplastic mass measuring $2 \times 1 \times 2 \text{ cm}^3$ occupying about 50 % of the pulmonary cavity by volume. B) The thymic follicular architecture is severely effaced and replaced by neoplastic round cells. A remnant of Hassall's corpuscle is present in the center of the photomicrograph (40 $\times$, H&E). C) Higher magnification of thymus with inset showing neoplastic cells with granular cytoplasm (60 $\times$, H&E). D) Infiltration and effacement of the epicardium and myocardium by neoplastic round cells (2 $\times$, H&E). E) Higher magnification of myocardium showing

fragmented and degenerate cardiac myocytes and increased interendomysial spaces infiltrated with neoplastic myeloid cells, megakaryocytes, and erythrocytes (40×, H&E). F) Myocardium with numerous neoplastic cells often with reniform nucleus and pink cytoplasm. Inset showing neoplastic cells with mitotic figures (100×, H&E).

Figure 2.

Immunohistochemistry results from thymus and myocardium against lysozyme and CD117/c-KIT proteins. A) Sub-gross view of the thymus showing diffuse positive labeling of the mass for lysozyme (1×, DAB). B) Higher magnification of the thymus shows neoplastic cells with diffuse intracytoplasmic positive labeling for lysozyme (40×, DAB). C) Sub-gross view of myocardium showing significant positive labeling for lysozyme (1×, DAB). D) Higher magnification of the myocardium showing intracytoplasmic labeling of the neoplastic cells in the interendomysial space; myocytes are not immunoreactive (40×, DAB).

E) Sub-gross view of thymus showing multifocal scattered labeling for CD117/c-KIT (1×, DAB). F) Higher magnification of the previous slide showing scattered aggregates of cells with membranous labeling for CD117/c-KIT (40×, DAB).

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Table 1

Primary antibodies used for immunohistochemistry

Target Protein	Primary Antibody	Clone	Supplier	Incubation time and temperature
CD3	Rabbit anti-human, Monoclonal antibody	2GV6	Ventana (Cat # 790–4341)	37°C, 48 min
CD20	Mouse anti-human, Monoclonal antibody	L26	Ventana (Cat # 760–2531)	37°C, 32 min
CD61	Mouse anti-human, Monoclonal antibody	2f2	Ventana (Cat # 760–4249)	37°C, 32 min
C-KIT	Rabbit anti-human Monoclonal antibody	9.7	Ventana (Cat # 790–2951)	37°C, 60 min
Lysozyme	Rabbit anti-human Polyconal antibody	Polyclonal	Ventana (Cat # 760–2656)	37°C, 40 min
Hemoglobin	Rabbit anti-human, Monoclonal antibody	EPR3608	Cell Marquee (Cat # 360R-18)	37°C, 32 min

Table 2

Myeloproliferative diseases in nonhuman primates.

Diagnosis	Species	Reference
Erythroleukemia	Chimpanzee (<i>Pan troglodytes</i>)	[22]
Eosinophilic myelocytoma	Owl monkey (<i>Aotus trivirgatus</i>)	[6]
Granulocytic leukemia	Gibbon (<i>Hylobates</i> spp.) Whitehanded Gibbon (<i>Hylobates lar</i>)	[23, 24]
Idiopathic Myelofibrosis (agnogenic myeloid metaplasia)	Marmoset (<i>Callithrix jacchus</i>)	[8]
Megakaryocytic leukemia	Cotton top tamarin (<i>Saguinus oedipus oedipus</i>)	[7]
Monocytic leukemia	Greater Bushbaby (<i>Galago crassicaudatus argentatus</i>)	[25]
Myelogenous leukemia	Rhesus macaque (<i>Macaca mulatta</i>)	[26]
Myelomonocytic leukemia	Orangutan (<i>Pongo pygmaeus</i>) Capuchin (<i>Cebus apella</i>)	[27, 28]
Myeloid sarcoma	Rhesus macaque (<i>Macaca mulatta</i>)	[9]
Unspecified myeloproliferative disease	Pygmy marmoset (<i>Cebuella pygmaea</i>) Talapoin (<i>Miopithecus</i> spp.)	[29]

Table 3

Myeloproliferative diseases in domestic species.

Diagnosis	Gross Lesions	Species	Reference
Myeloid sarcoma	Lung, gastrointestinal tract, lymph nodes, liver, skin	Domestic dog (<i>Canis lupus familiaris</i>) and cat (<i>Felis catus</i>)	[1]
	Lung, lymph nodes, liver, kidney, spleen	Cattle (<i>Bos taurus</i>) and pigs (<i>Sus scrofa</i>)	[30, 31]
Myelomonocytic disease	Liver, kidney, spleen, lung, lymph nodes, heart	Quarter horse (<i>Equus caballus</i>)	[32]
Eosinophilic granulocytic sarcoma	Bone marrow	Mixed breed domestic pig (<i>Sus scrofa domesticus</i>)	[33]
	Perianal mass	New Zealand White rabbit (<i>Oryctolagus cuniculus</i>)	[34]