The mystery of the vomiting cat:
A granular analysis of splenic and hepatic nodules

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Specimen

Cytology of splenic and hepatic nodules

Signalment

3-year-old spayed female European shorthair cat

History

The cat was presented to the emergency unit at the veterinary teaching hospital of Toulouse, France, with a two-day history of anorexia and two episodes of vomiting.

Clinical findings

Clinical examination was unremarkable. A biochemistry panel revealed mild hyperproteinemia (93g/L [57-89]) and hyperglobulinemia (63 g/L [28-51]). A CBC showed eosinopenia ($0.03x10^9$/L [0.17-1.57]).

Blood gas analysis revealed mild hypokalemia (3.2 mmol/L [3.5-4.8]), ionized hypocalcemia (1.09 mmol/L [1.10-1.33]) and moderate hypochloremia (95.6 mmol/L [116.0-126.0])

Thoracic X-ray was unremarkable. Abdominal ultrasound revealed multiple hepatic nodules (<20mm), a splenic nodule (17mm) and a round, nonobstructive intestinal mass (6mm), suggestive of multiple neoplastic processes.

The cat was sedated and fine needle aspiration of the splenic and hepatic nodules was performed. Samples were submitted to the laboratory for cytological interpretation (Figures 1 and 2).

Follow-up

Splenectomy was performed and the splenic nodule was submitted for histopathological analysis.

The cat showed clinical improvement following splenectomy; however, occasional vomiting persisted. A follow-up ultrasound performed 2-month after splenectomy revealed persistence of the previously observed hepatic nodules and a new 20mm nodule in the right medial liver lobe, a mild enlargement of the intestinal mass (6x7x9mm), and a hypertrophy of the ileo-caecal lymph node. A CBC revealed a moderate leukocytosis ($22.7x10^9$/L [4.0-15.2]) and lymphocytosis ($13.6x10^9$/L [1.2-10.2]) with a moderate number of reactive lymphocytes and very rare granulated cells (Figure 3).

Figure 1. Cytology of the splenic nodule. May-Grunwald-Giemsa, original magnification x10 and x100 oil objectives, respectively

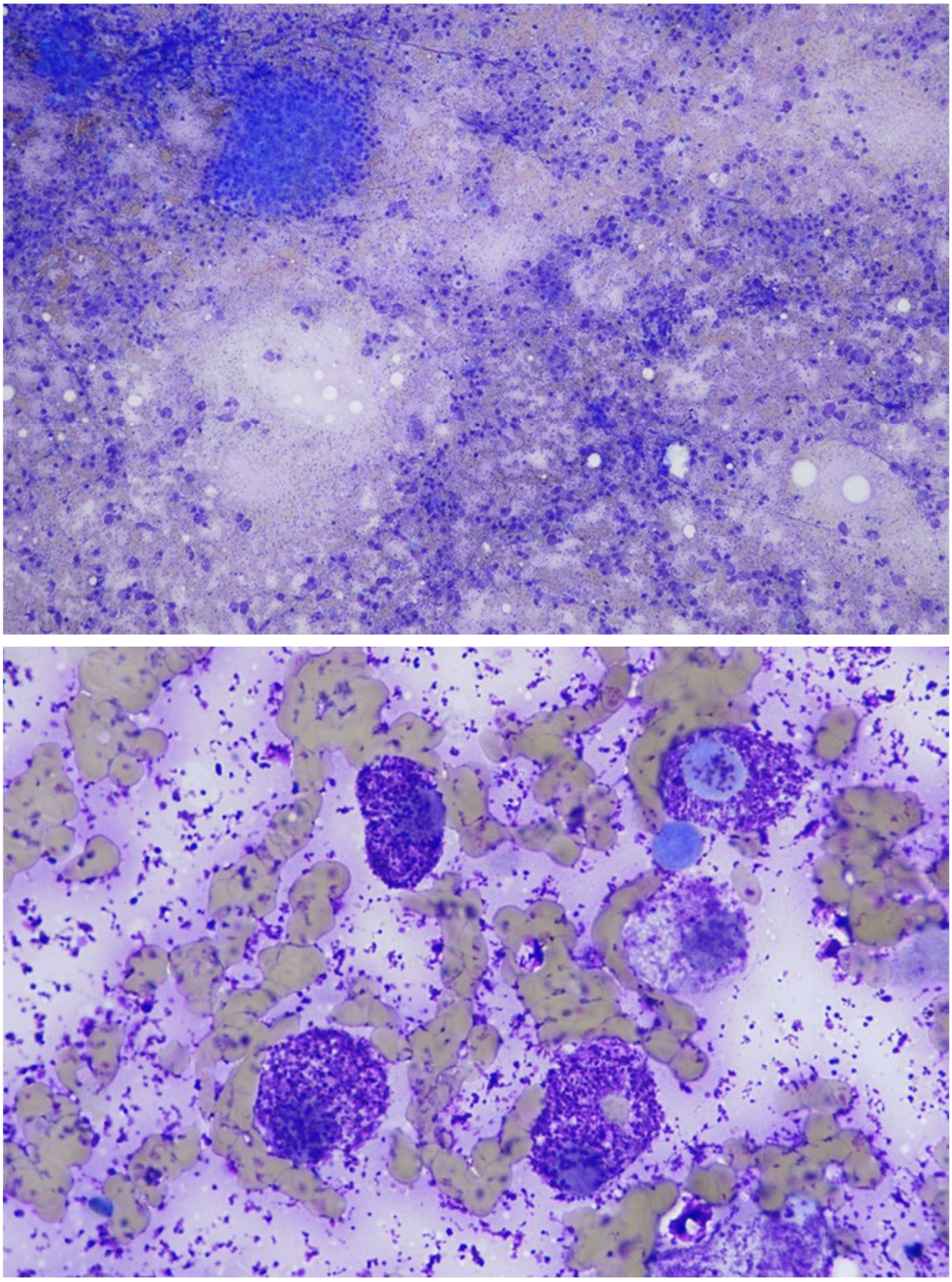


Figure 2: Cytology of one hepatic nodule. May-Grünwald-Giemsa, original magnification x20 and x100 oil objectives, respectively

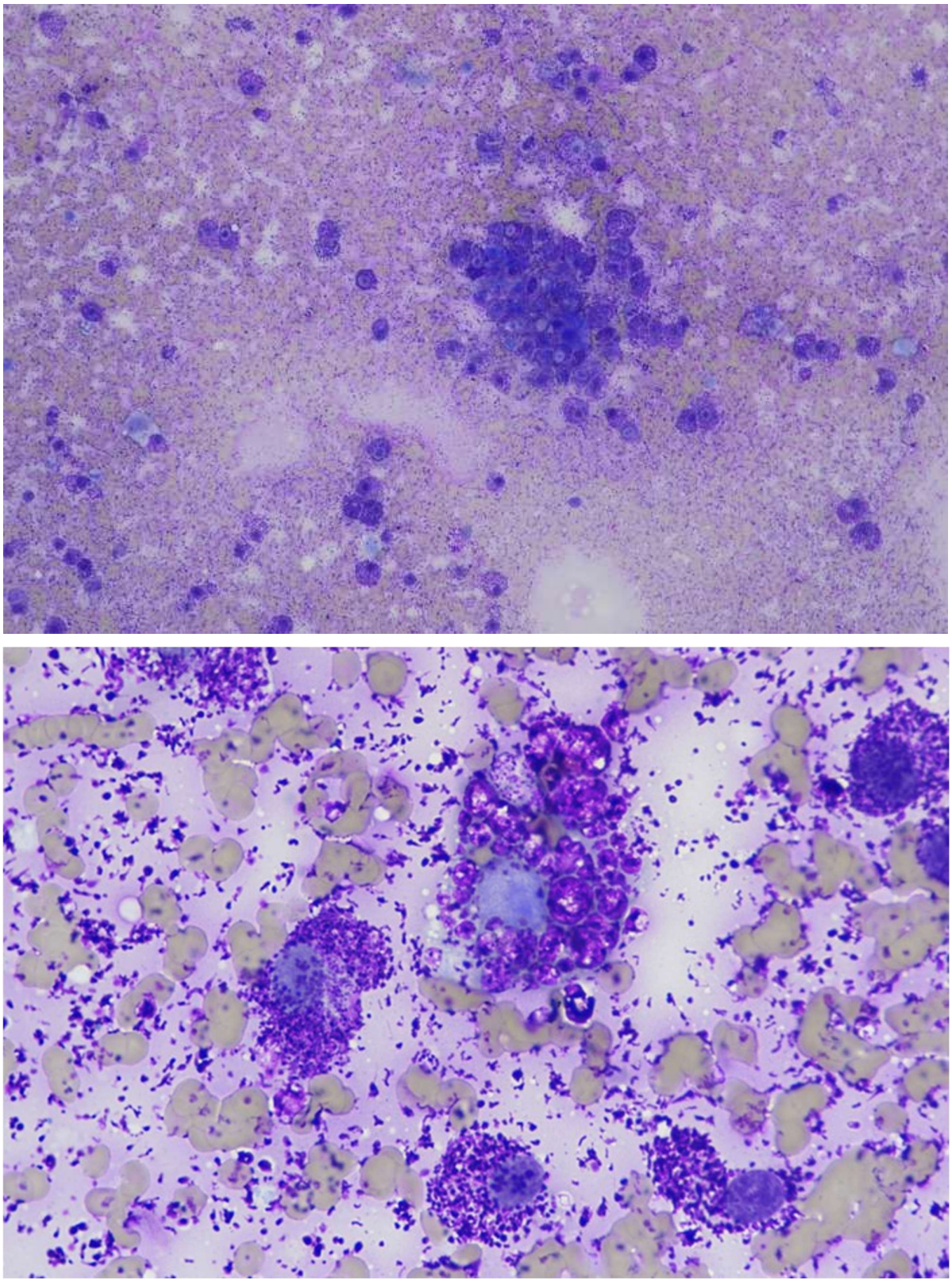
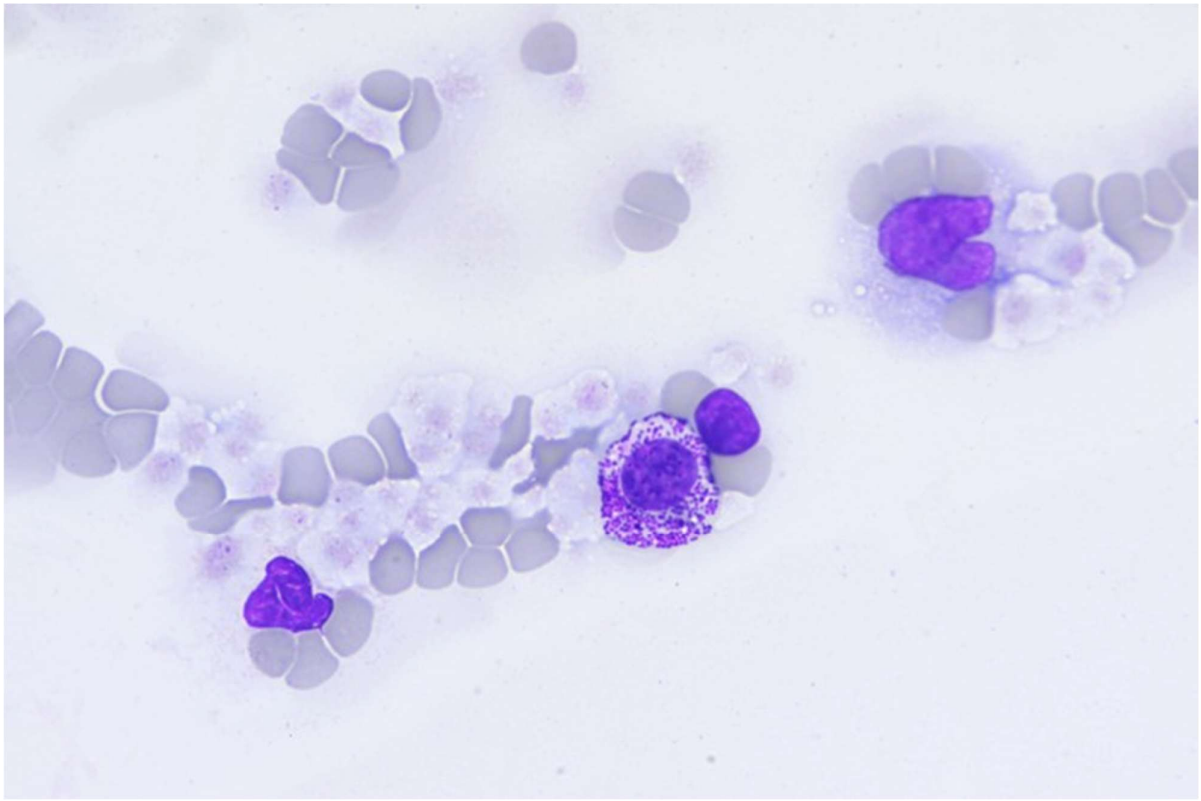


Figure 3. Peripheral blood smear. May-Grünwald-Giemsa, original magnification x100 oil objective



Questions

1/ How would you describe the cytological samples (Figures 1 and 2)? What is the most probable diagnosis?

2/ What would you recommend to confirm the diagnosis?

3/ Identify the granulated cells on peripheral blood smear (Figure 3) and give the differential diagnosis.

Interpretation/Diagnosis

Cytological examination of the splenic and hepatic nodules revealed numerous round to ovoid granulated cells, either free or arranged in large aggregates. The cytoplasm was abundant and contained numerous variably sized and shaped granules —ranging from round to slightly elongated— which stained purple to magenta. A large number of these granules were also present in the background. Microvacuoles were frequently observed in the cytoplasm, their number appearing inversely proportional to the quantity of granules. Nuclei were round and located paracentrally to eccentrically, with pale, loosely clumped chromatin. These cells exhibited moderate anisocytosis and anisokaryosis. Occasionally, a single erythrocyte was observed within the cytoplasm of these granulated cells (Figure 1). A few heterogenous aggregates —composed at least in part of altered or necrotic granulated cells— were also noted. In addition, a few larger cells with bigger and more heterogenous granules were observed (Figure 2); These were suspected to be either neoplastic cells or macrophages.
In the liver samples, rare and small clusters of moderately atypical hepatocytes were observed. These showed multiple nucleoli (some large), along with moderate anisocytosis and anisokaryosis. Numerous granulated cells were also present.

The most probable diagnosis was splenic and hepatic infiltration by a mast cell tumor.

A CBC performed one month after splenectomy revealed leukocytosis and lymphocytosis, which may have been related to adrenergic stress or antigenic stimulation. Very rare granulated cells were observed. These cells were large, round to columnar, with a moderate amount of cytoplasm containing numerous small purple to magenta granules. The nucleus was round with coarse chromatin and no visible nucleoli. The primary suspicion was circulating mast cells, most likely of neoplastic origin in this context, given the cytological findings in the spleen and liver.

Additional examination

Histopathological examination of the splenic nodule revealed a 2cm nodule within the splenic parenchyma with expanding growth deforming the splenic capsule. The mass was densely cellular and composed of sheets of large, polygonal to spindle-shaped, cohesive, cells within a thin collagen stroma. The cytoplasm was pale eosinophilic, with a granular appearance and the nucleus was round to ovoid with clumped chromatin. The cells exhibited mild atypia and 2 mitosis per 2.37mm² were observed. Focal necrosis, focal haemorrhage with hemosiderophages and a moderate multifocal lymphocytic infiltrate were also observed (Figure 4).

The histological diagnosis revealed a neoplasm composed of granulated cells exhibiting both epithelioid and spindle cell morphology, consistent with either a gastrointestinal stromal tumor (GIST), a granular cell tumor or an atypical mast cell tumor.

To further characterize the tumor, additional histochemistry and immunohistochemistry were performed (Table 1, Figure 5). Neoplastic cells were negative for toluidine blue, c-kit and S-100, but positive for PAS (with few cells being diastase-resistant), vimentin and neuron specific enolase (NSE).

Final diagnosis was suggestive of a granular cell tumor, however, the possibility of an atypical mast cell tumor could not be entirely ruled out due to overlapping cytological features.

Based on the histological criteria established by Fanburg-Smith et al. (1998) to predict malignancy and prognosis in human granular cell tumours, the present case can be considered a malignant variant for meeting three of the proposed criteria: spindle cell morphology, pleomorphism and cell necrosis.[1]

Figure 4. Histopathology of the splenic mass, H&E stain.
A, B: Relatively well demarcated tumor (T) composed of sheets and trabecules of polygonal to fusiform cells with an eosinophilic granular abundant cytoplasm and oval nuclei with finely stippled chromatin.

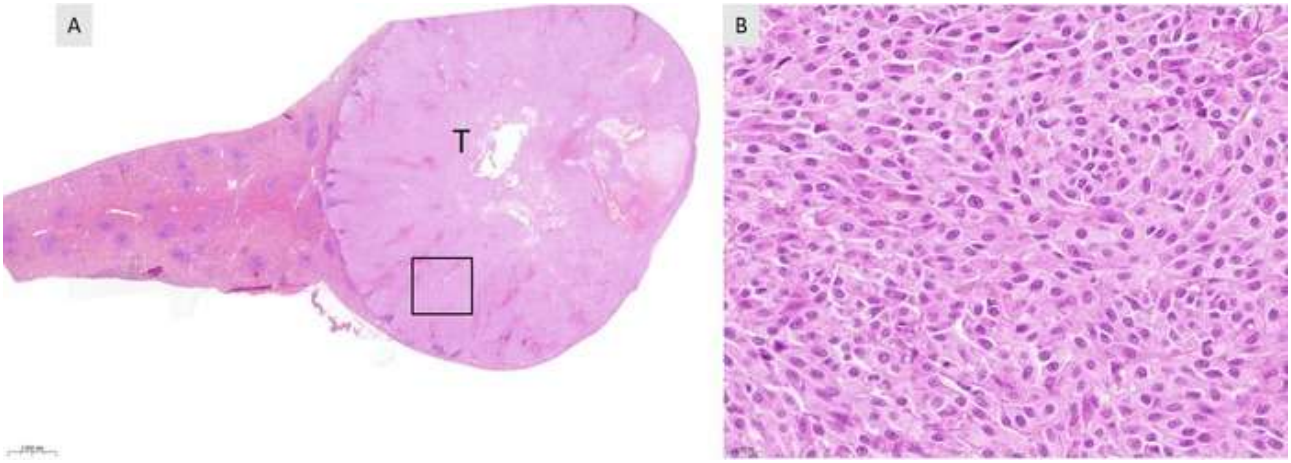
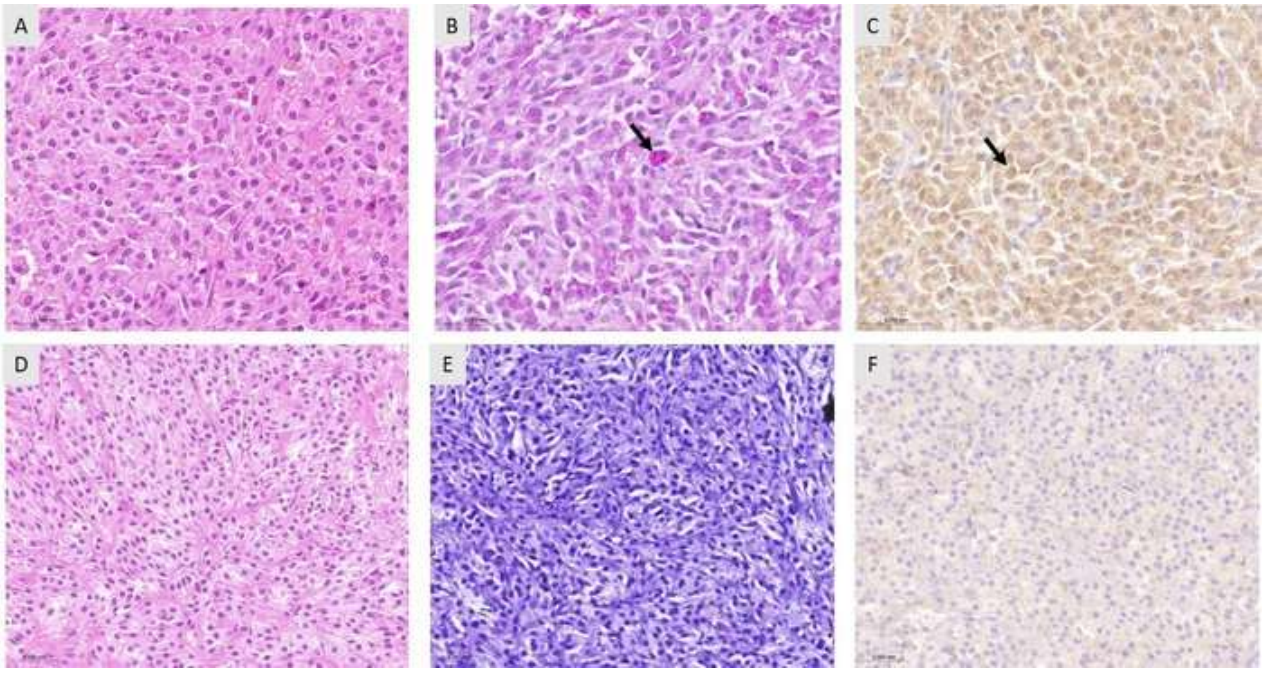


Figure 5. Histochemical and immunohistochemical stainings of the splenic mass.
A, B, C: Neoplastic cells of the same area showing PAS positive cytoplasmic reaction (B, arrow) and cytoplasmic expression of NSE antibody (C, arrow). D, E, F: Neoplastic cells of the same area negative for toluidine blue (E) and for c-kit antibody (F).



Follow-up and clinical outcome

After the last visit, the cat presented anorexia and multiple episodes of vomiting, and was presented at the emergency unit. POCUS revealed a thoracic effusion that was sampled and submitted to the laboratory for cytological evaluation. The effusion was consistent with a hemothorax, based on the bloody macroscopic appearance, a PCV equal to 19% and the presence of erythrophagocytosis images. Concurrent CBC showed a marked non-regenerative anemia (Ht 0.11L/L [0.30-0.54], Hgb 35.0g/L [94.1-161.4]) probably secondary to the hemothorax. Rare granulated cells were also observed on the peripheral blood smear.

A whole-blood compatible transfusion was performed, but the cat presented a cardio-respiratory failure the next day and reanimation was unsuccessful. A necropsy was proposed but refused by the owner.

Answers to questions

1/ How would you describe the cytological samples (Figures 1 and 2)? What is the most probable diagnosis?
See interpretation/diagnosis

2/ What would you recommend to confirm the diagnosis?
Although cytology is supportive of a mast cell tumor, histopathology with additional stain (eg. toluidine blue) can help confirm the diagnosis. Immunohistochemistry is rarely needed to confirm a diagnosis of mast cell tumor, but IHC panel could be done to exclude some tumors in specific atypical cases, including c-kit and CD25.[2]

3/ Identify the granulated cells on peripheral blood smear (Figure 3) and give the differential diagnosis.
The granulated cells on peripheral blood smear were mostly consistent with mast cells.
In cats, mastocytemia is most commonly associated with visceral and cutaneous mast cell tumors but has also been reported in lymphoid neoplasia, hemangiosarcoma and chronic kidney disease.[3]

Discussion

There is a limited number of tumors composed of granulated cells reported in the literature in cats and other species, including but not limited to: mast cell tumors, some types of lymphoma (including the large granular lymphocytes lymphoma subtype), granular cell tumors, oncocytomas, rhabdomyomas, carcinoids and some other neuroendocrine tumors, “globule leukocyte tumors”, “granulated round cell tumors”, and some variants of neoplasia usually not granulated such as histiocytic neoplasia, hemangiosarcoma, meningiomas, peripheral nerve sheath tumors, trichoblastoma and mesotheliomas.[4-22]

Large granular lymphoma and mast cell tumors (MCT) are the most common neoplasia composed of granulated cells in cats, and are the only ones reported in the spleen and liver. The former was considered unlikely in our case based on the cell morphology including the size, and the large amount of cytoplasm filled with numerous small-medium sized granules at cytology.

Cytological examination led to a presumptive diagnosis of MCT, however, in our case, the cellular morphology and tissue organization observed on histopathology were not consistent with MCT, such as histochemistry and IHC. Granules were PAS positive and partly resistant to diastase as expected in MCT, but while mast cells are expected to be vimentin positive, they are not expected to be NSE positive.[23] Moreover, the absence of c-Kit expression and lack of metachromasia with toluidine blue further weakened this hypothesis —although such findings have been rarely reported in feline cases.[2,24] Notably, unlike our case, mast cell tumors that fail to stain with toluidine blue typically also lack visible granules on H&E staining.[2]

Granular cell tumor (GCT) is a histopathological diagnosis based on morphology and has been reported in human and various animal species. The most consistent finding is a solid neoplasm composed of sheets and clusters of round to polyhedral, sometimes spindle-shaped cells with abundant cytoplasm filled with PAS positive (and usually diastase resistant) granules.[4,25,26] Those tumors have been rarely reported in cats in tonsils, cerebrum, spinal dura, palate, and vulva, digit, and tongue.[26-30] GCTs are the most common primary lung tumor in horses, often associated with hypertrophic osteopathy, and have also been reported in optic disc and bronchus in this species.[25,30-39] In dogs there are several reports of GCTs in tongue, meninges, and cerebrum, and rare reports in the larynx, eyelid, pituitary gland, nerves, skin, lymph node, heart, pulmonary and visceral pleura, and mesentery.[40-58] GCTs have also been described in the brain of rats and in various locations in exotic species, but have never been reported in the spleen or liver in animals.[59,60]

The histogenesis of GCTs has not been clearly established and the term GCT probably encompasses tumors of various origin. In rats brain, GCTs are established as a distinct entity of meningeal or astrocytic origin, and in human, most GCTs are thought to originate from Schwann cells or their progenitors as most of these tumors react positively with antibodies against S-100 protein, NSE and vimentin although an epithelial or myogenic origin has been established in a minority of human GCTs.[26] In horses, GCTs are consistently positive for S-100 and vimentin, and variably positive for NSE and GFAP, which supports that neoplastic cells originate from Schwann cells.[30-39] In dogs and cats, IHC patterns are variable (Table 1), nearly all GCTs are vimentin positive, most are S-100 and/or NSE positive, some are desmin or cytokeratin positive and all are chromogranin negative.[26-30, 40-58] A neuro-ectodermal origin is suspected in most GCTs in those species based on tumor location and S-100 positivity, but various IHC patterns have been observed and could represent various histogenesis.

Table 1: Immunohistochemical profile of the splenic mass compared to reported feline GCT and the expected immunohistochemistry of feline MCT.
NA = Not assessed, + = positive reaction, - = negative reaction, +/- = inconsistent positive reaction
** = based on studies in dogs*

Location	Spleen (current case)	Spinal dura[29]	Brain[28]	Tonsil[27]	Tongue, Vulva, Digit[30]	Palate[26]	MCT[2, 23, 61-64]
Toluidine Blue	-	NA	NA	NA	NA	NA	+
c-kit	-	NA	NA	NA	NA	NA	+
PAS	+	+	+	+/-	+	+	+
PAS + diastase	+/-	+	+	NA	+	+	NA
Vimentin	+	+	+	NA	+	-	+
NSE	+	+	-	-	-	-	NA
S100	-	+	+/-	-	-	-	Variable* (mostly -)
Desmin	NA	+	NA	NA	-	-	-*
Electron microscopy	NA	NA	NA	Numerous laminated, round to oval, vesicular structures; smaller electron-dense amorphous granules	NA	0.1-0.7µm single membrane-bound granules of heterogenous electron density (some multivesicular)	Granules moderately electron dense (either homogenous or containing amorphous, very electron-dense areas of various sizes)

Electron microscopy has also been used as a diagnostic tool for GCTs, particularly for better characterising the granules, which are suspected to be lysosomes and phagolysosomes in GCTs and are mitochondria in oncocytomas and rhabdomyomas.[65] The expression of autophagy markers (LC3B, ubiquitin, p62, NBR1) in some equine pulmonary GCTs and lingual and intracranial canine GCTs also support this hypothesis.[37,52,66]

The primary significance of this case lies in its distinctive features. To date, GCTs have not been reported in the spleen or liver of cats or other animal species, and only rarely in human.[67-69] Moreover, in this case, cytological findings, when considered alongside the clinical and epidemiological context, initially supported a diagnosis of MCT. The presence of presumptive erythrophagocytosis —previously described in feline MCTs but not in GCTs of any species— and mastocytemia, a finding more commonly associated with visceral MCTs in cats, further reinforced this preliminary diagnosis.[3,70]
However, the origin of the circulating granulated cells remains uncertain, particularly due to the cytological similarity between neoplastic GCT cells in this case and mast cells. Although the presence of circulating neoplastic GCT cells could not be definitively excluded, such a phenomenon has not been reported in any species to date. Toluidine blue staining of a blood smear could have aided in distinguishing between circulating neoplastic cells and mastocytemia. However, as no granulated cells were identified on examination of two buffy coat smears stained with May-Grünwald-Giemsa (MGG), toluidine blue staining was not pursued.

Cytological descriptions of GCTs in dogs and horses have identified variably sized, round to polygonal, non-cohesive but occasionally clustered cells, characterized by small eccentric nuclei and abundant granular eosinophilic cytoplasm.[41,47,49,55-57,71] This description aligns with the cytological appearance observed in the present case but could also correspond to MCT. However, GCT granules are typically finer than those seen in MCTs and those observed in this case. While some reports describe larger or variably sized granules, MCT has never been suggested as a differential diagnosis in GCTs, including in a dog with an intestinal GCT that had a prior auricular grade II MCT resected eight months earlier.[38,51] Histopathological evaluation was consistent with GCT, though definitive confirmation remains challenging due to the high variability of IHC profiles in cats and other species. Notably, the absence of S-100 expression was unexpected in light of the broader IHC findings. However, NSE-positive and S-100-negative profiles have been documented in canine GCTs.[26] Importantly, both histochemical and IHC results were not consistent with typical features of MCT, thereby making a diagnosis of mast cell tumor highly unlikely. Although electron microscopy would have provided additional support for a GCT diagnosis, it was not performed in this case.

In conclusion, this case represents the first reported presumptive malignant granular cell tumor involving the spleen and liver in a cat, although electron microscopy would be valuable to confirm the diagnosis

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