Case 7

Bone marrow and blood involvement in a dog with mammary gland carcinoma

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Cytological description and differential morphologic diagnoses of large atypical round cells in blood:
The large atypical round cells in blood were isolated or in little sheets, with a moderate nuclear to cytoplasmic ratio, an ovoid nucleus with finely stippled chromatin pattern and numerous prominent nucleoli. Their cytoplasm was highly basophilic, with borders characterized by villous projections (Figures 1 and 2). The differential diagnosis of these cells includes megakaryocytic lineage cells, histiocytic/dendritic cells or non-hematopoietic cells.

Further complementary tests:
A cytology sample obtained from the mammary mass was air dried and stained with May-Grunwald Giemsa stain (Figure 3). Cytologic evaluation of fine needle aspirate specimens revealed a highly cellular and inflammatory sample, focally necrotic, with a population of large atypical round cells organized in thick tridimensional epithelial clumps. The nucleo-cytoplasmic ratio was moderate with an ovoid and hyperchromatic nucleus containing numerous prominent nucleoli and a highly basophilic cytoplasm. There was marked anisocaryosis and anisocytosis (Figure 3). Those cells were cytomorphologically similar to those found in the blood smear (Figure 5).
Bone marrow cytology revealed a marked hemorrhagic background and a moderate cellular specimen. A few isolated large atypical round cells (or clumps), with the same cytomorphological characteristics as in the mammary specimen, were found (Figures 4 and 5).
Immunocytochemistry on buffy coat, bone marrow and mammary specimens revealed the same positivity of the large atypical round cells described above for intracellular cytokeratins, AE1/AE3 and KL-1. (Figure 6)

Diagnosis and outcome:
This is consistent with a diagnosis of aggressive mammary carcinoma with secondary disseminated intravascular coagulation and disseminated tumour cells in bone marrow and circulating tumour cells in blood.
Due to the deterioration of the dog's clinical and biological status, euthanasia was decided. In accordance with the owner's decision, no necropsy was performed.

Discussion:

To our knowledge, this is the first documented case of disseminated and circulating tumour cells of mammary gland carcinoma in a dog. Circulating neoplastic cells have been reported in dogs in a case of extragenital transmissible tumor[1], disseminated histiocytic sarcoma[2] and dendritic cell leukaemia[3]. In the present case, evaluation of the buffy coat smear seemed to be a useful tool for identifying the circulating tumor cells and for performing immunocytochemistry. In humans, the detection and biological relevance of disseminated and circulating tumour cells in cancer patients, particularly those with breast cancer, have been largely investigated in order to detect metastatic relapse caused by minimal residual disease (presence of tumour cells that are not detectable by the current routine diagnostic procedures) after treatment. Such cells seem to represent a poor prognostic factor for patient outcome and response to therapy [4,5,6].

Disseminated intravascular coagulation (DIC) has been proved to be involved in solid tumours in humans and dogs, including mammary gland carcinoma [7,8]. The exact mechanism by which DIC occurs in solid tumour is not fully understood. It has been demonstrated in humans and animals that solid tumour cells have the ability to express different procoagulant molecules (including Tissue Factor and cancer procoagulant [9]) and to express fibrinolytic proteins. Furthermore, the role of pro-inflammatory cytokines (IL6 and TNFα for example) has been demonstrated to also contribute to the occurrence of DIC in cancer patients[10]. In addition, the role of the balance in the expression profiles of COX-derived prostanoids, prostacyclin (PGI2) and thromboxane (TXA2) may be of critical importance in the development and progression of cancer, in part by promoting an increase in thrombosis [11]. In dogs, the frequency and intensity of coagulation parameter abnormalities appear to be correlated with tumour progression as well as with tumour stage and metastasis for aPTT, fibrinogen, fibrin monomers and antithrombin III. However, clinical evidence of an increased bleeding tendency has not been frequently encountered[7]. DIC has been reported to occur in 12.2% of the dogs with malignant solid tumors including ones with mammary gland carcinoma[12]. A recent study of the evaluation of thromboelastography in dogs with various neoplasms, demonstrated a significative incidence of the hypercoagulable state in canine malignant cancer. Interestingly in this study, only dogs with metastatic disease were observed to have an overall hypocoagulable state [13].

The present case demonstrates that haematogenous metastasis exists in canine mammary carcinoma by providing evidence of tumour cells escape from the primary tumour mass into the bloodstream and bone marrow. The disseminated intravascular coagulation could be associated with the haematogenous metastasis since the development and progression of cancer depends partly on the cancer-related thrombosis. The buffy coat smear could be a relevant complementary test to detect circulating tumour cells when DIC of unknown origin occurs in dogs.

References

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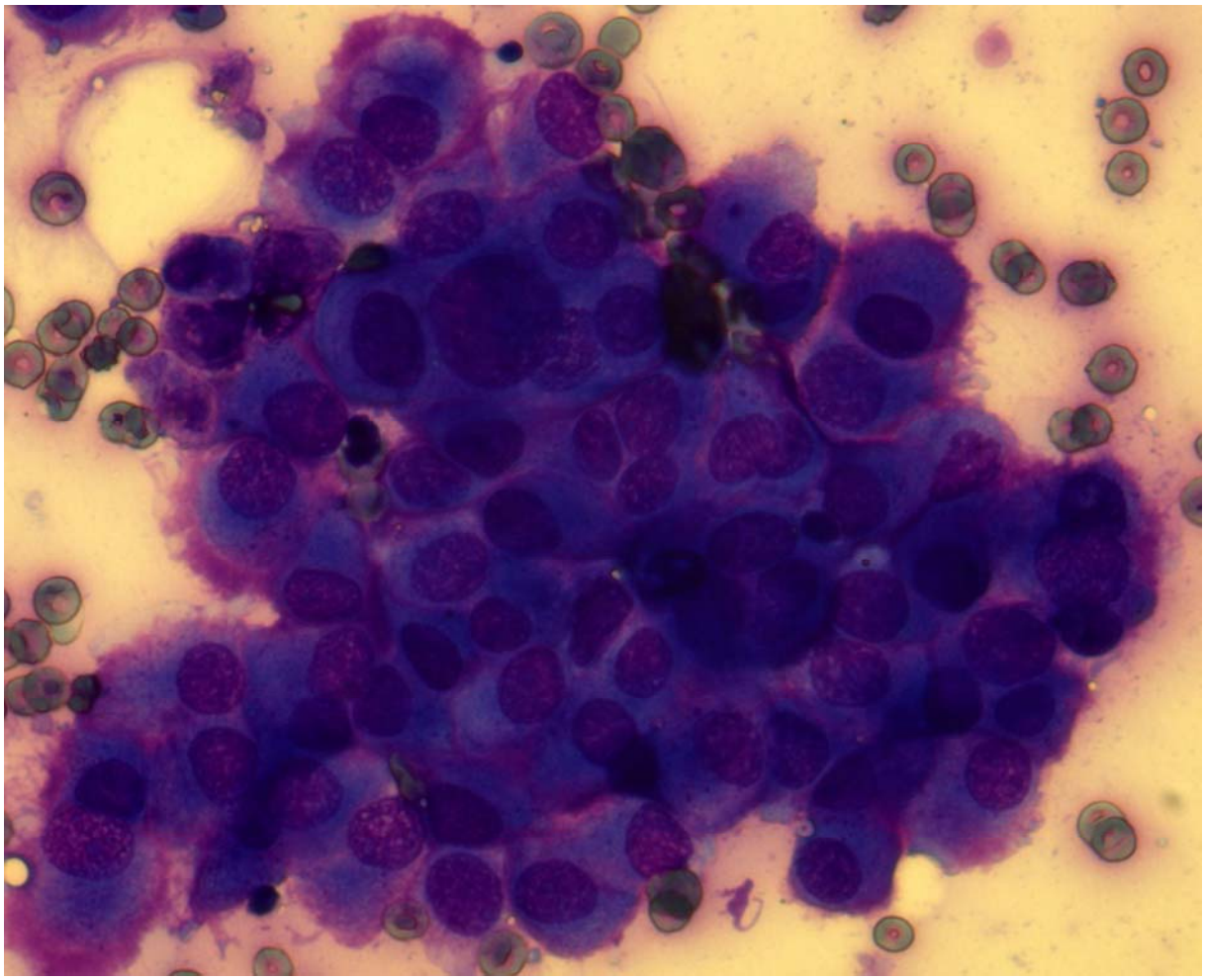

Fig.3: Mammary mass. May Grunwald Giemsa. 400X

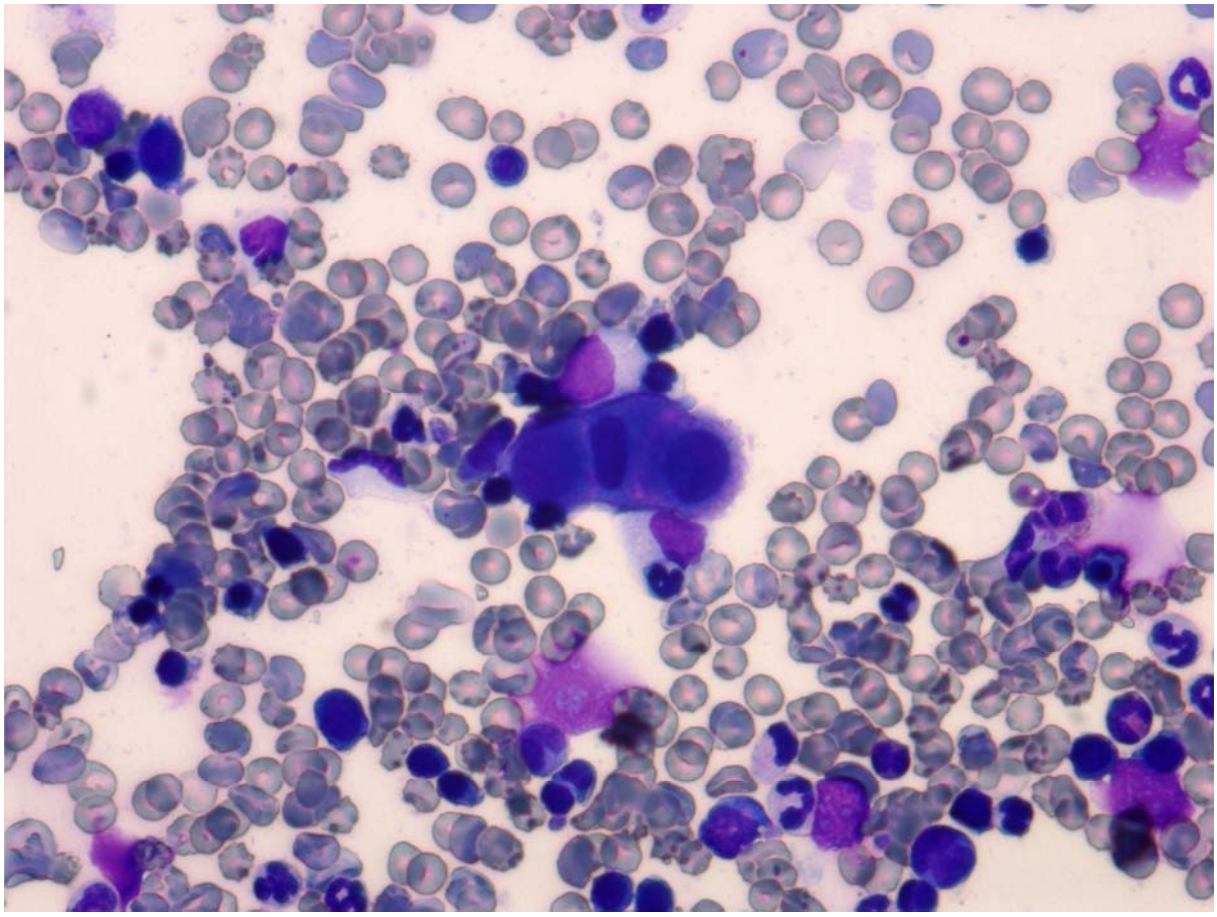

Fig.4: Bone marrow. May Grunwald Giemsa. 400X

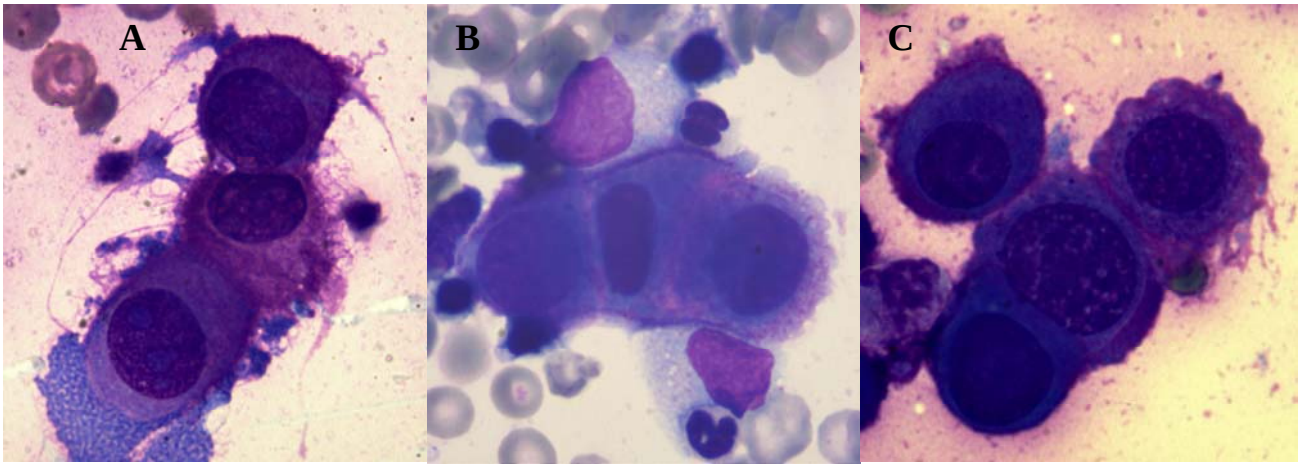

Fig. 5: Similar cytomorphological characteristics of the cells found in the buffy coat smear (A), the bone marrow (B) and the mammary mass (C). May Grunwald Giemsa.400X

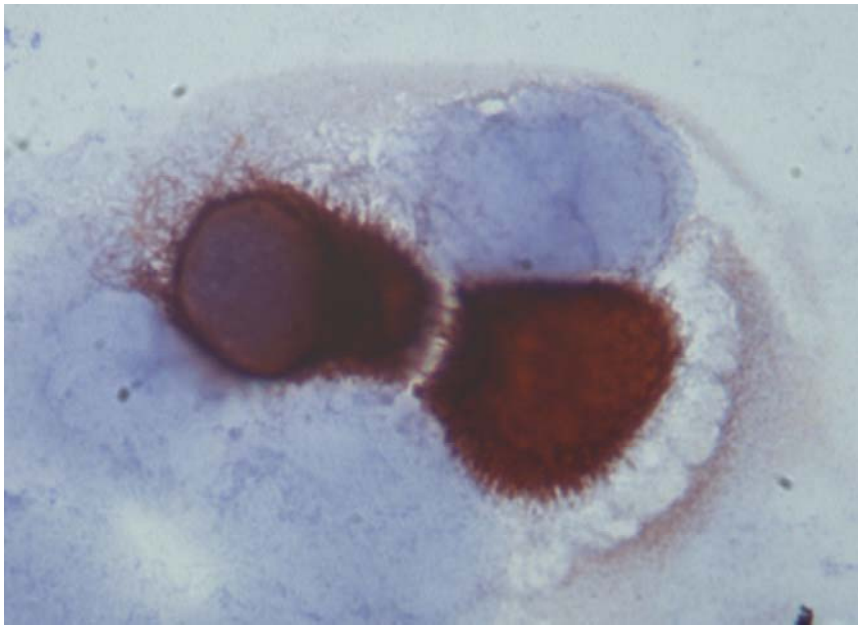

Fig.6: Immunocytochemistry on buffy coat smear. Positivity to intracellular cytokeratins AE1/AE3. 1000X