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Spontaneous Intestinal Melanoma in Dogs

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Abstract. *Primary melanoma of the gastrointestinal tract is a rare, highly malignant neoplasm that is associated with an unfavorable long-term prognosis. Animal studies are needed to further characterize this tumor and to develop new and more effective protocols. A spontaneous canine intestinal melanoma is described which, because of its local aggressive behavior and advanced stage, was not treatable with conventional strategies, thus being a potential candidate for investigational trials.*

While the gastrointestinal (GI) tract is a frequent site of human metastases of melanoma (1, 2), primary melanomas arising at that site are infrequently described. Of interest, GI melanoma metastases, representing approximately one-third of all metastases in this tract (3), are prevalently reported in the small bowel and colon, while primary melanomas are reported in the esophagus and rectum (3, 4).

The cornerstone for the treatment of primary malignant melanoma of the GI tract is aggressive surgical management. Nevertheless, the prognosis is dismal: after resection the 5-year survival rate ranges from 0% to 4% for the esophageal location (median survival 5-7 months) (4) and 0% for the ano-rectal location (median survival 24 months) (5). Responses to chemotherapy, radiation therapy and biotherapy are very poor (6).

Animal studies on melanoma arising in the GI tract are limited to a few investigations on orthotopic murine models (7). However, the mouse model has some limitations: the tumors are human cell lines orthotopically implanted, the mice have an altered immune system and the GI and hematological side-effects of therapy cannot be thoroughly evaluated (8). Canine oral melanoma has been considered a good model for the study of novel therapies to be used in humans due to its aggressive behavior and its tendency to spread (usually to the lungs) (9). While local control can be achieved with surgery or radiation therapy, its response to chemotherapy is low and short-lived (10). Furthermore, recent reports have underlined the value of oral melanoma to test novel immunotherapy protocols, in particular modified vaccines to treat primary and metastatic malignancies (11, 12).

In this study, two cases of canine investinal melanoma are described, indicating a remarkable potential for the investigation of novel therapeutics.

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Materials and Methods

Two male Rottweiler dogs (9 and 11 years), with primary spontaneous intestinal neoplasia, were referred for evaluation. Staging included complete blood cell count, biochemical profile, urinalysis, thoracic radiography (three projections), abdominal ultrasonography and surgical biopsy. The excised biopsy specimens of the tumors were fixed in 10% buffered-formalin and paraffin embedded. Sections of 5 μ were stained with hematoxylin-eosin, hematoxylin-van Gieson and PAS-hematoxylin.

Results

The two dogs presented with signs of hematochezia and constipation (one dog had signs of disuria and stranguria). Laboratory analyses were within the physiological range, except for mild anemia and neutrophilia. Chest radiographs were within the normal limits (not shown), but ultrasonography evidenced a colonic mass (5 cm in diameter) in dog no. 1 and two masses, one located at the colon and the other at the limit between the colon and rectum (4.5 cm and 5.5 cm, respectively) in dog no. 2 (Figures 1 and 2). Exploratory laparotomy evidenced a diffuse full thickness colonic mass with peritoneal

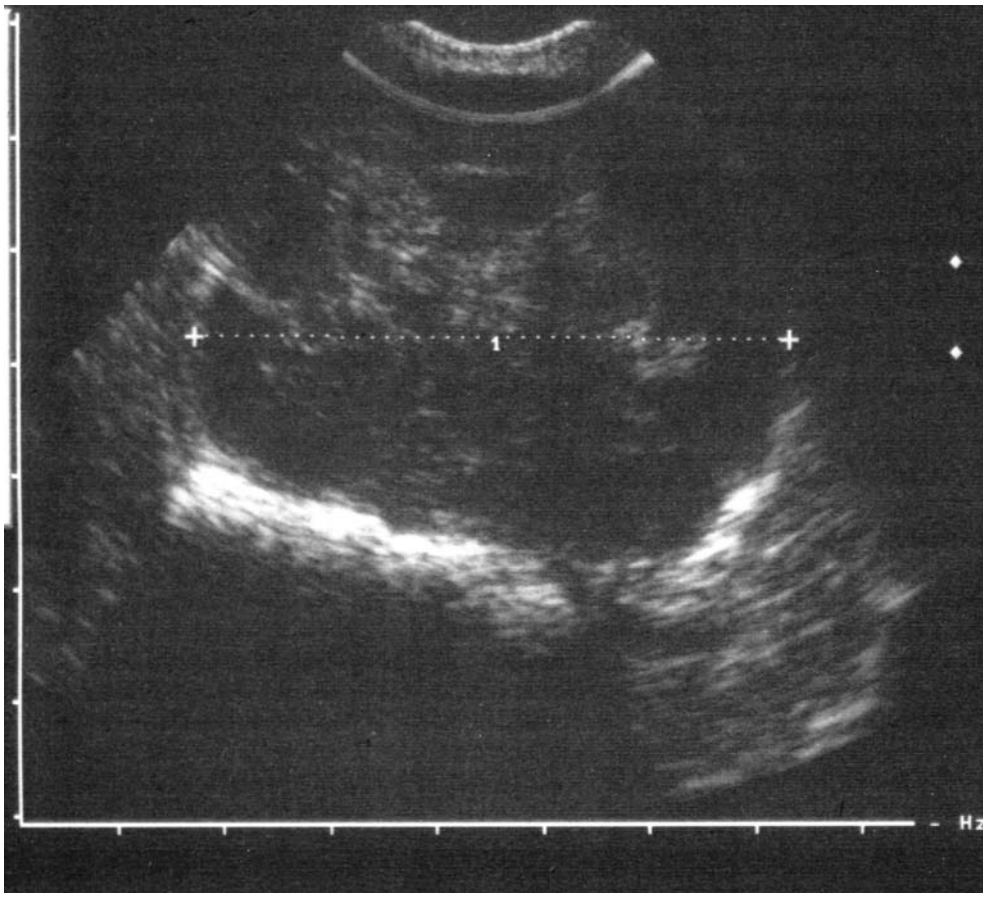

Figure 1. *Ultrasonographic appearance of a large solitary melanocytic mass in the distal colon of a dog.*

adherences in dog no. 1 and two large masses involving the distal colon and proximal rectum in dog no. 2. Due to the extension of the disease, surgical excision could not be performed; therefore multiple samples were collected for histopathological analysis. Light microscopic examination revealed a neoplasia constituted by atypical pigmented melanocytes growing singly or in irregularly-sized nests, with a host response consisting of lymphocytes infiltrating amidst the neoplastic melanocytes (Figure 3). The histopathological appearance of the lesion was interpreted as a malignant nodular melanoma.

The first suspicion was that the dogs were experiencing unusual metastasis from a primary tumor located elsewhere, considering that melanoma has a high incidence in dark-skinned dogs such as Poodles, black Labradors, Schnautzers, Dobermans, New Foundlands and German Shepherds. However, careful examination of the oral mucosa, mucocutaneous cavities, nail bed (including foot radiographs) and foot pads failed to identify melanocytic cancer in these districts, strongly indicating primary melanomas of the GI tract.

Treatment options for such an advanced disease were limited to chemotherapy with platinum compounds, but the owners, after inquiring into the possibility of inclusion of their companion animals in ongoing compassionate trials (13), elected for euthanasia on emotional and financial grounds.

Discussion

Primary GI melanoma of humans is rarely described in the literature, and is preferentially identified in the distal esophagus or in the rectum (1-4). These tumors are twice as common in men as in women and usually affect individuals who are in the sixth or seventh decade of life. Although it has been postulated that it is impossible for melanoma to arise in these organs, it has been shown, in autopsy series, that 4% to 8% of individuals have melanoblasts in the esophageal mucosa and melanocytes have been identified in the rectal mucosa by immunohistochemical staining (14). Due to the absence of benign melanocytes in the normal gastric and intestinal mucosa, some reports of primary

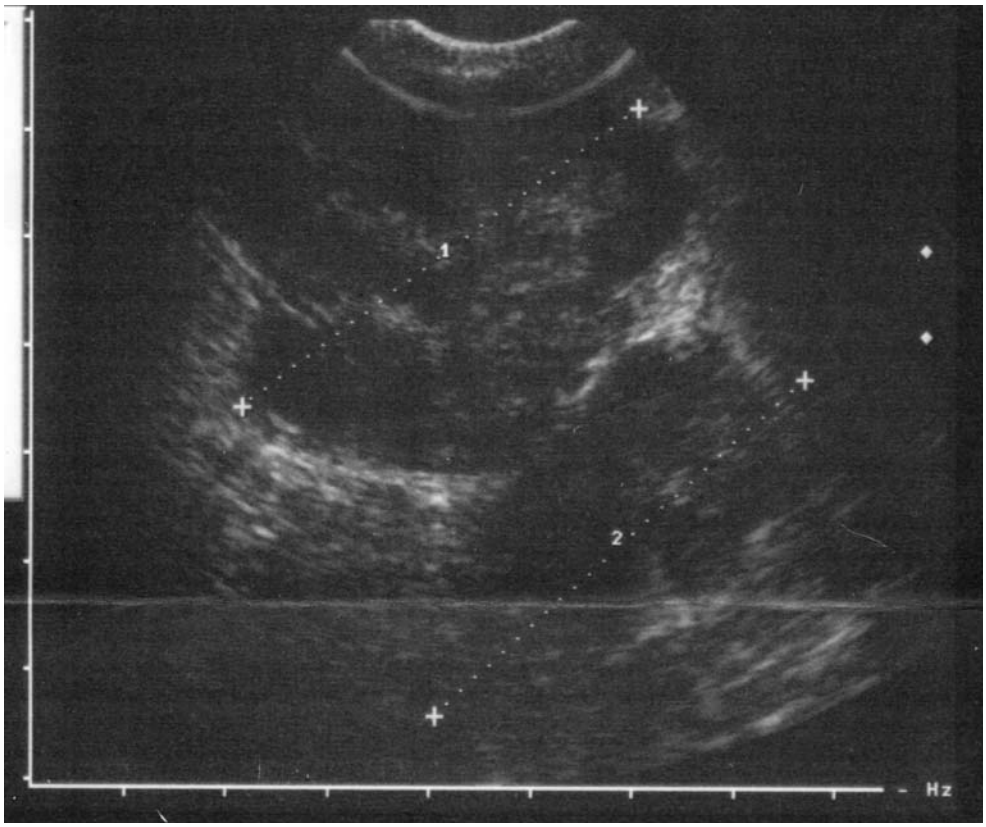

Figure 2. *Ultrasonographic appearance of two non-connected melanomas of colon and rectum, distorting normal architecture of the organs.*

gastric melanoma have been questioned (15, 16); however, several authors hypothesize that GI melanomas originate from ectopic melanocytes which emigrate to the digestive tract during embryogenesis. This is supported by the previously mentioned presence of melanocytes in the GI mucosa and by the occasionally reported melanosis or melanocytosis and atypical junctional melanocyte proliferation in the esophageal mucosa of humans (17, 18).

The dogs in our small cohort presented some interesting similarities with their human counterparts: both were male, dark-skinned (mucosal melanoma is very rare in Caucasians) and aged (equivalent to the seventh and eighth decades of humans) (19). Moreover, the symptoms at presentation were close to those of man: weight loss, abdominal pain, dyschezia, hematochezia and the stage of the tumors at the time of diagnosis was advanced. Finally, the diagnosis of primary melanoma in our dogs fits the criteria proposed by Blecker *et al.* for humans: i) lack of concurrent or previous removal of melanoma or atypical melanocytic lesion; ii) *in situ* change of the overlying or adjacent GI epithelium (20).

It is conceivable that, in lieu of the increasingly popularity of certain dog breeds especially the Rottweiler in Italy and in Europe, the incidence of intestinal melanoma will increase. The determination of many owners to seek the best treatment for their pets has led to enrolment of companion animals in clinical phase I and II trials, especially when the available treatment options are of limited efficacy.

Investigators should be aware of the possible availability of canine intestinal melanoma patients for the investigation of new surgical, chemotherapeutic and immunotherapeutic treatments.

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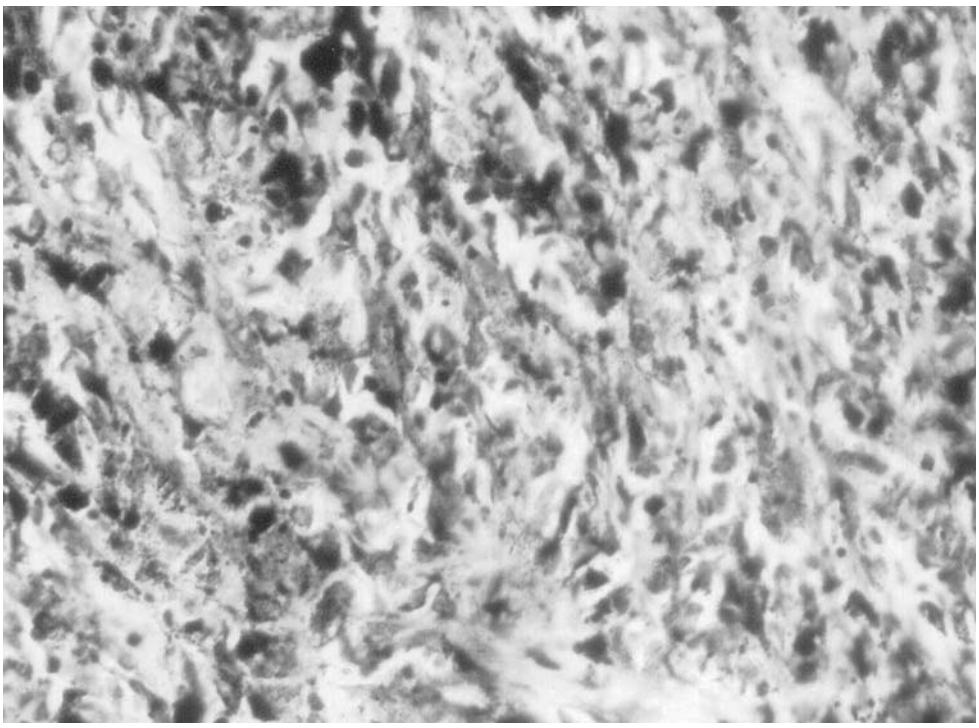

Figure 3. *Intestinal biopsy showing the features characteristic of a malignant melanoma (H&E; original magnification X50).*

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