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METASTATIC CANCER OF UNKNOWN PRIMARY IN 21 DOGS

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Abstract

The aim of this retrospective study was to describe clinical features, treatment and outcome of 21 dogs with metastatic cancer of unknown primary (MCUP), a biopsy-proven malignancy being diagnosed at a metastatic stage, in which the anatomical origin of the primary tumor cannot be detected. All dogs underwent total-body CT. Signalment, type and duration of clinical signs, metastasis site, pathology results, treatment and outcome were recorded. Carcinoma was the most common diagnosis (57,1%), followed by sarcoma, melanoma and mast cell tumor. The median number of disease sites per dog was 2, with bones, lymph nodes, lungs, and spleen being the most frequent metastatic locations. The median survival for all dogs was 30 days. Overall, a primary site was not identified in 20 (95,2%) dogs. MCUP encompasses a variety of different pathologic entities and harbors a poor prognosis.

Metastatic carcinoma of unknown primary (MCUP) is the seventh most frequently occurring cancer and the fourth commonest cause of cancer-related death in people.[1] It refers to a biopsy-proven malignancy in which the anatomical origin of the primary tumor cannot be detected after a thorough patient history, careful physical examination, and extensive work-up including laboratory testing, chest radiographs, endoscopy, abdominal ultrasound and/or computed tomography (CT) of the head, chest, abdomen and pelvis and, in selected cases, mammography.[2] Serum tumor markers are commonly of no help, since non-specific elevations occur in the majority of MCUP patients.[3,4] In people only 20% of primary sites are identified by extensive diagnostic work-up before the patients die.[5] In approximately 70% of patients, the primary site cannot be identified even at necropsy.[4,6] Typically, MCUP progresses and spreads rapidly, with signs related to the metastatic site. Due to the lack of consensus on diagnostic guidelines and optimal treatment, patients with MCUP have a poor prognosis, with a median survival time of 6-12 months, thereby rendering this disease a dilemma for oncologists.[4] Standard management is based on empiric chemotherapy, including several taxane/platinum regimens; nevertheless as the tumor recurs or progresses after first-line chemotherapy, effective second-line treatments are not available.[3,7,8]

To the authors' knowledge, there are no studies in veterinary medicine addressing MCUP. In dogs, conventional techniques for evaluating primary tumor sites include laboratory testing, radiographs, ultrasound, endoscopy, CT scan and/or magnetic resonance imaging (MRI), depending on tumor site. Serum tumor markers being clinically useful in cancer diagnosis are not available in veterinary medicine.[9]

Advanced diagnostic procedures in pathology, such as immunohistochemistry (IHC), may enable diagnosis of the origin of primary tumors by biopsy of the metastasis in selected cases. Some markers have been used in dogs to classify tumors according to their site of origin and distinguish metastatic carcinomas, including thyroid transcription factor-1 (TTF-1) and

uroplakin III.[10,11] Nevertheless, as IHC is not 100% specific and its interpretation may be challenging, it is important to use markers for guidance in conjunction with the clinical presentation and imaging studies.

The aim of this retrospective study was to describe clinical characteristics, treatment, and outcome of dogs with MCUP.

MATERIALS AND METHODS

Criteria for selection of cases

Medical records of all contributing institutions were retrospectively searched to identify dogs with a presumed diagnosis of MCUP. Determining whether the primary site is unknown or whether it will be possible to detect it with further evaluation is difficult. In the present study, members of the Italian Society of Veterinary Oncology (SIONCOV) were asked to look through their records to identify MCUP cases. Once a possible case was identified, the histological sample of the metastatic site was retrieved and reviewed in concert by skilled pathologists with oncologic expertise (GB, SF, LR).

For the purposes of this study, dogs were considered to have MCUP if the following diagnostic procedures did not reveal a primary tumor site: a detailed medical history; complete physical examination; complete blood cell count and biochemistry; urinalysis; histopathological review of biopsy material, and total body (TB) CT. Pathologic evaluation included light microscopic evaluation in all cases. Poorly differentiated tumors had additional immunohistochemical staining.

Dogs with tumors having the capability of arising at multiple sites simultaneously, such as lymphoma or histiocytic sarcoma, were excluded from the study. In particular, to rule out

these tumors, additional immunohistochemical staining, including CD20, CD79, CD3 and CD18, were performed whenever indicated.

Procedures

Data obtained from the medical records of dogs enrolled in this retrospective study included signalment (i.e., age, sex, body weight, and breed), type and duration of clinical signs, results of imaging, site of metastasis, pathology results, treatment, response to therapy, outcome and necropsy data (if performed). Responses to treatment were defined according to the World Health Organization criteria and were required to last for at least 28 days.

RESULTS

Twenty-one dogs fulfilled the inclusion criteria. There were 2 Beagles, 2 German shepherd dogs, 2 Labrador retriever, 2 Corso dogs, 2 mixed breeds, and one each of Schnauzer, Cocker spaniel, Basset hound, Mongrel, Siberian husky, Boxer, American Staffordshire terrier, Weimaraner, Rhodesian Ridgeback, West Highland white terrier, and Beauceron. There were 12 males (1 of which was castrated) and 9 females (7 of which were spayed). Median age at presentation was 10 years (range, 7 to 15 years), whereas median weight was 24 kg (range, 6 to 42 kg). Patients' characteristics are listed in Table 1.

When considering clinical signs, 3 (14,3%) dogs were asymptomatic and their tumors were diagnosed incidentally. Two of them had a painless enlargement of a peripheral lymph node (mandibular: n=1, axillary: n=1), and the other dog developed multiple, painless, subcutaneous nodules. Eighteen (85,7%) dogs showed clinical signs, such as dyspnea (n=7), lameness (n=5), depression/lethargy/weakness (n=2), tenesmus (n=1), abdominal pain (n=1),

lethargy (n=1), and polyuria/polydipsia (n=1); in these dogs clinical signs had been present for a median of 14 days (range, 3 to 150 days) prior to presentation.

All enrolled dogs underwent complete history, physical examination, CBC, chemistry profile, urinalysis, and contrast-enhanced TBCT scan, showing metastatic disease without obvious primary. The CT scan images were acquired with dogs in sternal recumbancy in order to minimize lung collapse/hypostasis, which may hide small peripheral metastatic lesions. The patients were scanned before and after the intravenous administration of a non ionic contrast medium (Ioversol, Covedian, Milan, Italy) at the dose of 600-800 mgI/kg through a power injector at a speed of 3 ml/sec. Different scanners were used. These included a single-slice CT (GE, HiSpeed FX/I) in 3 dogs, and a 16-slice multidetector scanner (GE, BrightSpeed) in 18 dogs. The slice thickness was 1.25 to 3.0 mm, depending on the machine used. All images were reviewed by two board-certified radiologists (FR, MV), who were unaware of the histopathological diagnosis in the cases for which it was available. All cases included in this study had multiple nodules of similar size and vascularization, located in different organs, confirmed to be neoplastic in origin based on histopathological evaluation. An evaluation of the CT did not suggest that any of these lesions could be the primary tumor. The metastatic origin of the pulmonary lesions was supported by the finding of multiple nodules of soft tissue density and similar size, growing in the pulmonary interstitium in an expansive way and compressing the surrounding structures. CT features typically associated with primary neoplasia, like the presence of a larger single mass or a focal area of soft tissue lung infiltrate, associated with signs of local aggressiveness, were never observed in this group of patients.[12] The sites of metastasis are listed in Table 1. The median number of disease sites per dog was 2 (range, 1 to 11). Ten (47,6%) dogs had a single metastatic organ site, 3 (14,2%) had 2, 2 (9,6%) had 4, 1 (4,8%) had 3, 1 (4,8%) had 5, 1 (4,8%) had 6, 1 (4,8%) had 7, and 1

(4,8%) had 11. Bones, lymph nodes, lungs, and spleen were the most frequent metastatic locations (Table 1).

Pathologic samples were obtained by surgical excision (n=3) or core needle biopsy (n=18). All biopsy specimens were of good quality allowing for accurate histological interpretation. Twelve (57,1%) dogs were diagnosed with carcinoma (undifferentiated carcinoma: n=11; squamous cell carcinoma: n=1), 7 (33,3%) with sarcoma (undifferentiated sarcoma: n=3; fibrosarcoma: n=2; hemangiosarcoma: n=2), 1 (4,8%) with amelanotic melanoma and 1 (4,8%) with mast cell tumor. Immunohistochemical analysis to better characterize poorly differentiated tumors was performed in 17 cases. Tests performed included cytokeratin, vimentin, S-100 as standard panel, and PNL2 for amelanotic melanomas. Additional pathologic evaluation (including TTF-1, Factor VIII and CD18) was individualized on the basis of clinical and pathologic features. The pathological diagnoses of the dogs and details on immunohistochemistry are reported in Table 1.

When considering histological type and metastatic pattern detected after TBCT, 8 out of 12 (66,7%) dogs with carcinoma had a single metastatic site. All dogs with sarcoma had multiple metastatic sites, whereas both the dog with melanoma and the one with mast cell tumor also had a single metastatic site.

Eleven (52,4%) dogs received no treatment and were euthanized shortly after diagnosis. Four (19%) dogs received systemic chemotherapy (2 of which were treated with metronomic chemotherapy), 2 (9,5%) dogs were treated with firocoxib (Previcox, Merial, Milanofiori, Italy), 1 (4,8%) underwent surgery, 1 (4,8%) was treated with palliative radiation therapy and immunotherapy with the canine melanoma vaccine (Oncept, Merial, Milanofiori, Italy), 1 (4,8%) dog was treated with surgery, chemotherapy and radiation therapy, and 1 (4,8%) dog was treated with surgery and toceranib (Palladia, Pfizer, Italy).

The median survival time was 30 days for all dogs diagnosed with MCUP. Eighteen (85,7%) dogs were dead at the end of the study for cancer-related causes after a median of 12 days (range, 1 to 504 days). Seven of them underwent therapy; in five dogs the metastatic tumors did not respond to any form of treatment, thereby being classified as progressive; 1 was stable, and 1 obtained a partial remission before developing pulmonary metastases The median survival time for dogs undergoing any form of treatment was 80 days (range, 30 to 504 days). Necropsy was only performed in a single case; no primary tumor site was found.

Three dogs were still alive at data analysis closure, after 882, 101 and 80 days. Among these, one dog had a metastatic amelanotic melanoma in the mandibular lymph node with no evidence of a primary tumor based on physical examination and complete work-up, including TBCT. Seven months after radiation therapy and immunotherapy, the dog developed a melanoma in the ipsilateral footpad and was irradiated again, thereby obtaining a complete response. It was hypothesized that the footpad was the primary site, possibly having remained occult when the metastasis first appeared. The IHC staining pattern was similar between the melanoma in the footpad and the lymph node.

The second dog had a metastatic carcinoma involving peripheral, intrathoracic and abdominal lymph nodes, both adrenal glands, liver, pancreas, lungs, and muscles. At the time of writing, the dog was still receiving daily firocoxib; however, the metastatic tumor was shown to be progressive according to follow-up imaging.

The third dog had a carcinoma metastatic to the medial iliac lymph node. Due to hypercalcemia, a clinically occult anal sac carcinoma was suspected, and the dog underwent lymphadanectomy and bilateral anal sacculectomy. However, based on histopathology, both anal sacs were morphologically normal, thereby prompting the diagnosis of MCUP metastatic to the medial iliac lymph node. After surgery the hypercalcemia resolved, and at the time of

writing the dog is being treated with toceranib and is considered to be in complete remission based on clinical and imaging features.

DISCUSSIONMCUP is perceived to be a very aggressive disease carrying a poor prognosis. It refers to a biopsy-proven metastatic cancer in the absence of an identifiable primary tumor despite a complete diagnostic work-up.[1] Although the biologic characteristics of MCUP remain to be determined, some hypothesis have been postulated. The primary tumor may remain diminutive, thereby escaping clinical detection, or it may undergo spontaneous immune-mediated regression or dormancy after seeding the metastasis.[12] Alternatively, the angiogenic incompetence of the primary tumor may lead to marked apoptosis and cell turnover, resulting in a cancer that acquires a metastatic phenotype.[13] Other explanations include various theories, including stem cell and embryologic migration hypotheses.[14] Nevertheless, all these theories cannot be clinically tested and remain speculative.

MCUP is not rare in people, representing 3-5% of all malignancies diagnosed in oncology practice.[4] There are no studies in veterinary oncology focusing on MCUP, therefore its prevalence is unknown. In this case series, we described 21 dogs with MCUP for which TBCT and tumor histology were available. Only dogs undergoing TBCT were included, as conventional radiography and ultrasound may miss tumors located in the head and neck region, pelvic cavity or intracardiac structures, thereby being inadequate for diagnosing MCUP. It is unknown whether the use of more sophisticated imaging studies (such as, for instance, MRI or PET, if available) would be beneficial and appropriate in these cases. Indeed, the poor prognosis typically being associated with metastatic cancer raises issues of cost effectiveness for intensive diagnostic work-up, which may be unrevealing and of unclear

214 benefit in terms of improving prognosis. Therefore, the list of investigations for MCUP is
215 difficult to define, and requires continual updating.
216 In this case series, in one single dog the primary site was suspected to be found antemortem,
217 being in accordance with most studies conducted in people.[4-6] This dog had a metastatic
218 melanoma in the mandibular lymph node and 7 months later developed a melanoma in the
219 ipsilateral footpad, which was hypothesized to be the primary site. Although the mandibular
220 lymph node is not the draining lymph node for the footpad, nodal metastases may also occur
221 in a random process, with the second and third level lymph nodes being involved with
222 metastatic disease when compared with the nodes closest to the tumor. Beside the
223 identification of the neoplastic anatomical site of origin, great interest has been given to the
224 recognition of specific histological subtypes, as the chemotherapeutic regimens chosen to
225 treat MCUP cases in people depend not only on the site of primary origin, but also on the
226 cancer subtype.[14] While epithelial histotypes are more frequently diagnosed,[1,3,4] malignant
227 melanomas and sarcomas occasionally occur as apparent metastasis to lymph nodes or viscera
228 without a detectable or known primary lesion.[15-21] IHC stains are an important complement to
229 light microscopy in the investigation of MCUP. Several panels of stains are recognized as
230 important in the diagnosis of specific subtypes of cancer by predicting with greater certainty
231 the likely tissue of origin of the malignancy.[3] Several examples include GCDFP-15,
232 mammoglobulin, oestrogen and progesterone receptors,in breast cancer, TTF-1 in
233 pulmonary carcinoma, HEPAR-1 in hepatocellular carcinoma, thyroglobulin/TTF-1 in
234 thyroid carcinoma placental alkaline phosphatase/OCT-4 in germ-cell tumors, CDX-2 in
235 colorectal cancer, and synaptophysin and chromogranin in neuroendocrine tumors
236 (OIEN). Because the morphological and immunohistochemical features are often not
237 characteristic, gene expression-based analysis are an emerging tool to help in identifying the
238 primary site and, possibly, selecting targeted treatment.[22] Gene expression profiling is a new

239 frontier in veterinary oncology, and usually not routinely offered. In this retrospective series
240 of cases, we limited the pathological evaluation to morphology and, in selected cases,
241 immunohistochemistry. In agreement with the human counterpart, carcinomas were the most
242 frequently diagnosed tumors in this case series, followed by sarcoma, melanoma and mast cell
243 tumor. It must be stressed that a limited panel of IHC tests were used here, mainly due to
244 financial concern and to the lack of site-specific markers with high sensitivity and specificity,
245 thereby precluding the possibility to further characterize some of the tumors. Whether the use
246 of a large panel of antibodies is associated with clinical gain and change in management is not
247 known and cannot be recommended at the moment.

248 In human oncology, it appears that patients with MCUP have a limited life expectancy with a
249 median survival approximately of 6-12 months, and with fewer than 25% of patients
250 surviving beyond 1 year.[4] The same holds true for dogs, as a median survival time of 30 days
251 was recorded here. This data is not unexpected, as proven metastatic cancer is typically
252 associated with a poor outcome, regardless of the recognition of the tumor's primary site.

253 In human patients, several clinical and biologic variables have been demonstrated to have
254 significant impact on survival, including performance status, weight loss, histological
255 subtype, presence of liver metastases, more than two metastatic sites, elevated levels of serum
256 alkaline phosphatase and lactate dehydrogenase, thereby allowing the inclusion of patients
257 into groups requiring specific guidelines that translate into prolonged survival.[23-25] Favourable
258 subsets are usually treated with locoregional treatment or systemic platinum-based
259 chemotherapy, achieving responses and survival times that are similar to those of patients
260 with relevant known primary tumours.[14,26] Conversely, patients in unfavourable subsets are
261 treated with empirical chemotherapy based on various combination regimens, but responses
262 and survival are generally poor.[14, 26] Due to the small size of our population and the non
263 uniformity of treatment, prognostic factors were not identified in this work. More information

needs to accumulate to verify whether these data may provide useful diagnostic and therapeutic information for dogs with MCUP as well.

The purpose of this study was to describe a collection of eclectic, previously unreported cases; however, the retrospective nature of this study and the small population size represent main limitations. Many questions still need to be answered: not only MCUP is a rare disease entity, but it is also neglected, more over because of the lack of information and understanding about the disease. The uncertainty which surrounds almost all aspects of care for dogs with MCUP is most clearly seen when decisions need to be made about investigations and treatment, as shown in this series of cases. Additionally, the consistently poor prognosis is a further disadvantage when discussing options with the owners or when trying to support research. Collaborative studies are warranted to improve the knowledge and, possibly, the care of animals with MCUP.

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