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What can we learn from cancer of unknown primary in canine oncology?

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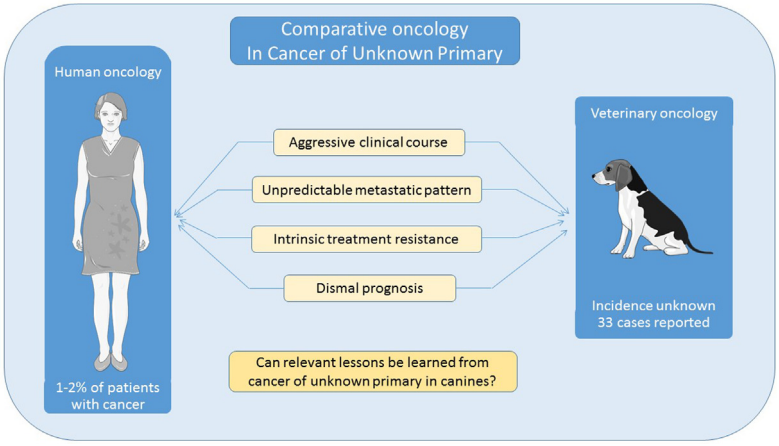
GRAPHICAL ABSTRACT



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ABSTRACT

Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumors that lack an identifiable primary site despite an extensive diagnostic work-up. It is a well-recognized entity that is characterized by early dissemination, aggressive clinical course, unpredictable metastatic pattern, intrinsic treatment resistance, and a dismal prognosis. Despite the molecular diagnostic workup and personalized therapy, the expected improvements in the diagnosis and treatment of CUP have not been achieved. Comparative oncology has a promising role in the exchange of knowledge and practices between humans and canines. Therefore, we intended to review the literature reporting on CUP in dogs in order to identify some interesting parallels and unique results that could be transposed to in-human research.

Introduction

Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumors that lacks a primary culprit after a standardized diagnostic workup [1]. The diagnostic advances in rigorous immunohistochemistry stainings and sophisticated imaging studies have decreased the prevalence of patients with CUP from 3 to 5% in the early 1990s to 1–2% currently [2]. The process that gives rise to CUP, characterized by early metastatic spread, regression of the primary site, and aggressive course of the disease, has not beel fully elucidated [3–5]. Three hypotheses have been suggested to understand the mechanisms underlying the

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carcinogenesis of CUP. The first hypothesis considers that CUP undergoes a type 2 progression thus malignant lesion formation without prior nascent primary tumor and not a type 1 progression from a premalignant to a malignant lesion. The second hypothesis is that CUP arises early in the development of a malignancy following a parallel progression model and does not develop according to a stepwise progression according to a linear progression model. Last, CUP at be attributed to the migration of deregulated, premalignant, or cancerous stem cells away from their natural tissues and to form tumors in other locations [5].

The correct diagnosis of CUP strongly relies on the clinical presentation and optimal diagnostic workup [3,6,7]. The clinical reality describes a subset of cancer patients without an identifiable primary and unique natural history characterized by a short history of symptoms and signs, early dissemination, aggressive behavior, and unpredictable metastatic patterns [4]. Traditionally, CUP patients are categorized into two prognostic subsets according to their clinicopathologic criteria [2,4]. A minority of patients with CUP (15–20%) presents a constellation of criteria that is highly suggestive of a specific site of origin, is treated accordingly and has a good prognosis whereas the majority (80–85%) is treated with empirical chemotherapy and usually presents a dismal prognosis [1,4].

Despite the molecular diagnostic workup and personalized therapy, the expected improvements in the diagnosis and treatment of CUP have not been achieved [3,5,8,9]. Comparative oncology has a promising role in the exchange of knowledge and practices between humans and animals. Canine models have a particular advantage over other animal models [10,11]. They have many genes similarities with humans, five to seven-fold accelerated aging compared to humans, respond to treatments similarly as humans do, and health care levels second only to humans [11]. This paper aims to review the clinicopathologic presentations, treatment trends, and prognosis of veterinary cases with CUP in order to identify some interesting parallels and unique results that could be transposed to in-human research.

Materials and methods

The Medline database (via PubMed) and Google Scholar were searched by using the relevant keywords for a combined search using the following phrases (cancer of unknown primary) OR (CUP) AND (dogs), (cancer of unknown primary) OR (CUP) AND (companion animals), (cancer of unknown primary) OR (CUP) AND (domestic animals). The resulting publications identified with this search strategy on July 19th, 2019 were examined by two reviewers (AK and ER) for their title and abstract. No language or time limitations were applied. The reference sections of the publications of interest were examined to identify other potentially relevant publications. Eligible publications/cases were selected if the veterinary patient presents a histological confirmed metastatic tumor without an identified primary after an adequate work-up at the time of diagnosis. The following details were retrieved: clinical presentation, physical examination, blood analysis, histopathology, imaging, treatment, and outcome.

Results

Clinical presentation

Our review of the literature identified 33 dogs diagnosed with CUP (Table 1). The median age at diagnosis in CUP is 10 years (range 4–15 years) with a female: male ratio of 1.3 [12–15]. The majority has symptomatic tumors including which manifested in lameness (n = 11) [12,13], depression/weakness (n = 10) [12,13], pain (n = 9) [12–15], dyspnea (n = 8) [12,14], lethargy (n = 4) [12–14], anorexia (n = 3) [13], weight loss (n-= 2) [13], stiff gait (n = 2) [13], tenesmus (n = 1) [13], polyuria/polydipsia (n = 1) [12], and progressive tetraparesis (n = 1) [15].

Diagnostic work-up

The minimal basic work-up reported include physical examination (including head and neck, rectal, pelvic and breast examination), basic blood and biochemical analyses, as well as chest and abdominal radiography (Table 1). The diagnosis of CUP was confirmed by pathologic evaluation which can be categorized into a majority of undifferentiated carcinomas followed by sarcomas, squamous cell carcinomas, and mast cell tumor. Patients had commonly two metastatic sites or more at diagnosis (Table 1). The immunohistochemistry algorithm and staining were not always detailed. Undifferentiated carcinomas (n = 9) were pan-cytokeratin positive and vimentin negative (n = 6); pan-cytokeratin negative, vimentin positive and CD18 negative (n = 3), and pan-cytokeratin positive, vimentin negative and TTF1 negative (n = 1) [12]. The delay between symptomatic manifestation and diagnosis was approximately 2–3 weeks [12,13].

Treatment and prognosis

The majority of patients with CUP did not receive anti-cancerous therapy with 4 being euthanized shortly after diagnosis. Treatments vary between systemic or metronomic chemotherapy, surgery, palliative radiation therapy with or without surgery. Nine reported cases were treated with palliative care (n = 3; one case with pericardial effusion treated cephalexin, prednisone, colchicine plus microprostol before being euthanized), chemotherapy (n = 5 among which 2 were treated with metronomic regimens), targeted therapy (one case treated with toceranib), radiotherapy (n = 1) and surgery (n = 2). The prognosis was dismal as the median survival was limited to 4 weeks (range 0.4–72 weeks) (Table 1).

Discussion

Cancer of unknown primary is often neglected in veterinary oncology which limits the understanding of this entity overall and in animals particularly [12]. In human oncology, the diagnosis of CUP is not straightforward and is often a diagnosis of exclusion with primaries being identified in 75% of cases at autopsy [16]. The published literature in veterinary oncology focusing on CUP is very sparse. The majority of the reported veterinary cases with CUP are dogs whereas few cases included cattles and mules [18]. This review identified 33 dogs with a histologically confirmed CUP diagnosis. The minimal basic workup included physical examination, basic blood, and biochemical analyses, chest and abdominal radiography. Interestingly, the reported cases did not report any evaluation of tumor markers or the use of sophisticated imaging. The most commonly identified histologies include undifferentiated carcinomas followed by squamous cell carcinomas, sarcomas, and melanomas. Unfortunately, the immunohistochemical patterns cannot be comprehensively analyzed as most cases did not detail the stains that were performed (Table 1). Moreover, a limited panel of immunohistochemical stainings was commonly used mainly because of financial concerns and the lack of site-specific markers [12].

Among humans, the failure to identify the culprit tumors often delays treatment decisions. Oncologists and patients do not fare well with the diagnosis which puts into question the accuracy of the diagnostic approach. Subsequently, further testing is performed whereas quick treatment decisions are required instead of spending the remaining lifetime, which lies in the range of one year, performing diagnostic tests [17]. The median survival of cani-

Table 1
Summary of the clinical, pathological and treatment of the dogs with cancer of unknown primary.

Study	Patient/gender/age	Clinical presentation	Diagnostic workup	Findings	Histology	Treatment	Outcome
Cooley and Waters 1998 [13]	Golden retriever/M/ 11 years	Left forelimb lameness	Thoracic and abdominal Radiography	Extra skeletal carcinoma deposit found at necropsy	Carcinoma, NS	NR	Median survival 4 weeks
	Labrador retriever/M/8 years	Stiff gait; Lethargy; Anorexia	Thoracic and abdominal Radiography				
	Airedale Terrier/F spayed/11 years	Left forelimb lameness; Weight loss	Thoracic and abdominal Radiography Abdominal US; Cardiac US				
	Mixed breed/F spayed/ 10 years	Left hindlimb lameness; Weight loss	Thoracic and abdominal Radiography Abdominal US				
	Beagle/F spayed/6 years	Lameness Recurrent urinary tract infection	Thoracic and abdominal Radiography				
	Mixed breed/F/12 years	Masson rib; Painful when rising	Thoracic and abdominal Radiography				
	Astralian shepherd/F/9 years	Progressive posterior paresis; Depression; Anorexia	Abdominal Radiography				
	Golden retriever/F/ 11 years	Progressive posterior paresis; Depression Weakness	Thoracic Radiography				
	Mixed breed/M/9 years	Listless Progressive hindlimb weakness	NR				
	Mixed breed/ M/4 years	Painful ambulation; Listlessness Anorexia	Thoracic and abdominal Radiography Abdominal US				
	Miniature poodle/F/ 13 years	Cervical pain; Stiff gait; Left hindlimb and left forelimb nonspecific pain	Thoracic Radiography				
Kirsh et al., 2000 [14]	Siberian husky/F spayed/ 6.5 years	Lethargy; tachypnea; painful abdomen	Physical examination; Blood tests; Cardia ultrasounds; IHC	Cardiac tamponade and weakness; elevated liver enzymes; abdominal distension and painful abdomen	Emboli of metastatic cells carcinoma in the epicardium	Pericardiocentesis; pericardiectomy after pericardial effusion recurrence; after the persistence of thoracic effusion:	
			cephalexin + prednisone + colchicine + microprostol during 12 days	Euthanasia 3 weeks post-operation			
Rossi et al., 2015 [12]	Cocker/M/8 years	Symptomatic	Physical examination; Blood tests; IHC; light microscopy; total body-CT	Multiple nodules in the spleen	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-)	Chemotherapy	Died after 7 months
	Labrador retriever/F spayed/10 years	Asymptomatic		Multiple nodules in the axillary lymph nodes	Mast cell tumor	Surgery, toceranib	Died after. 8 months
	Beagle/F spayed/9 years	Symptomatic		Multiple nodules in the medial iliac lymph node	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-)	Chemotherapy	Died after 2 months
	Corso dog/F spayed/7 years	Symptomatic		Multiple nodules in the paravertebral muscles, vertebral body (L1), rib, ileum and spleen	Undifferentiated carcinoma (pan-cytokeratin-, vimentin+, CD18-)	Palliative care	Died after 1 months
	Mixed breed/F/12 years	Symptomatic		Multiple nodules in the paravertebral muscles	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-)	Surgery; chemotherapy;	Died after 1.5 years

(*continued on next page*)

Table 1 (*continued*)

Study	Patient/gender/age	Clinical presentation	Diagnostic workup	Findings	Histology	Treatment	Outcome
						radiation therapy	
	Basset hound/F/8 years	Symptomatic		Multiple nodules in the heart, mucles, subcutis and kidneys	Fibrosarcoma	No treatment	Euthanasia at diagnosis
	Beagle/F spayed/ 11 years	Symptomatic		Multiple nodules in the lungs, liver, adrenal gland, spleen, omeuntum, ileum, vertebral body T3	Fibrosarcoma	No treatment	Euthanasia at diagnosis
	German Shepherd/M/8 years	Symptomatic		Multiple nodules in the pleurae	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-, TTF1-)	No treatment	Euthanasia at diagnosis
	German Shepherd/M/8 years	Symptomatic		Multiple nodules in the pericardium	Squamous cell carcinoma	No treatment	Died after 5 days
	West Highland White Terrier/F spayed/ 13 years.	Symptomatic		Multiple nodules in the peripheral, intrathoracic and abdominal lymph nodes (axillary, sternal, mediastinal. Mesenteric, medial iliac, lombo-aortic), adrenal glands, liver, pancreas, lungs and muscles.	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-)	Palliative care	Died after 3 months
	Rhodesian ridgeback/F spayed/10 years	Asymptomatic		Multiple nodules in the subcutaneous tissue and lungs.	Undifferentiated carcinoma (pan-cytokeratin-, CD18-, vimentin +)	Metronomic chemotherapy	Died after 2.5 months
	Corso dog/M/10 years	Symptomatic		Multiple nodules in the vertebral body (T2, L1, L2, L5), spleen and liver.	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-)	No treatment	Died after 2 weeks
	Siberian husky/M/8 years	Symptomatic		Multiple nodules in the lungs, spleen and liver	Hemangiosarcoma (vimentin+, Factor VIII +)	No treatment	Died after 1.5 months
	Labrador retriever/M/ 15 years	Symptomatic		Multiple nodules in vertebral body (L2, L5), spleen and liver	Undifferentiated carcinoma (pan-cytokeratin-, CD18-, vimentin +)	No treatment	Died after 5 days
	Boxer/M/11 years	Symptomatic		Multiple nodules in the base of the heart, liver and retroperitoneal space.	Hemangiosarcoma (vimentin+, Factor VIII +)	No treatment	Died after 4 days
	Mixed breed/M/ 14 years	Symptomatic		Multiple nodules in the lungs.	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-, TTF1-)	No treatment	Died after 10 days
	American Staffordshire terrier/M/10 years	Symptomatic		Multiple nodules in the lungs.	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-, TTF1-)	Metronomic chemotherapy	Died after 1 month
	Beauceron/M/10 years	Symptomatic		Multiple nodules in the lungs and spleen.	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-, TTF1-)	No treatment	Died after 3 days
	Weimaraner/F/ 11 years	Symptomatic		Multiple nodules in the lungs and tracheobronchial lymph nodes.	Undifferentiated carcinoma (pan-cytokeratin+, vimentin-, TTF1-)	No treatment	Died after 7 days
Miyazaki et al., 2016 [15]	Chihuahua/F/12 years.	Cervical pain and progressive tetraparesis	Physical examination; Blood tests; MRI; Cervival Radiography Abdominal US CT-Scan; IHC	Mass in the dorsal atlantoaxial region	Squamous cell carcinoma	No treatment	Death 32 days post-palliative surgery.
Kang et al., 2019 [19]	Shih Tzu/M castrated/ 9 years	Cough; tachypnea; muffled heart sounds; decreased appetite and depression.	Physical examination; blood tests; thoracic radiography; electrocardiography; pericardial effusion analysis; multi-detector computed tomography and IHC	Pericardial effusion; no mass lesions was found at the heart base, aorta and right atrium; hemorrhagic cytology of the pericardial effusion. Metastatic carcinoma involving epicardium, sternal lymph nodes and multiple lung nodes.	Carcinoma pan-cytokeratin+, vimentin-	Conservative treatment with steroids and diuretics	Died after 457 days

F: female; IHC: immunohistochemistry; M: male; NR: not reported; NS: not specified.

nes with CUP is approximately 4 weeks which limits an extensive diagnostic testing. The prevalence of euthanasia at diagnosis and the non-uniformity of treatment approaches limit solid conclusions and extrapolations to CUP in humans (Table 1).

Comparative oncology on this topic is mainly limited by the relatively low numbers of reported cases which can be attributed to the rare occurrence of CUP in canines or the underreporting publication bias. The reported literature shows that dogs are commonly quickly euthanized at diagnosis which is a further disadvantage when trying to support research on the topic. A descriptive database and clinical trial registry would overcome these limitations and would help dog owners and veterinarians to start trials for pets suffering from CUP while taking into consideration animal welfare. Moreover, as CUP in canines mimics the human pathological conditions, genetic studies similarly to those reported by the Comparative Oncology and Genomics Consortium (CCOGC; www.ccogc.net) Inc., should provide quality data that address the gaps in understanding the CUP carcinogenesis and preclinical studies such as those conducted by the Comparative Oncology Program (COP; https://ccr.cancer.gov/comparative-oncology-program) may help in identifying the promising drugs before entering the traditional phase I in-human trials.

Conclusion

As comparative oncology helps in studying disease patterns, inheritance, and genetic history, the purpose of this paper was to evaluate whether relevant lessons can be learned from CUP research in animals, particularly canines, and the possibility of transferring this research to in-human studies. The review of the published data on veterinary cases identified many similarities between humans and animals with CUP in regards to the diagnostic approach and prognosis. The standard workup for veterinary patients with CUP includes a physical examination, basic blood tests, pathology and immunohistochemical analysis, chest and abdominal imaging. The prognosis is dismal and the median survival is four weeks with several cases being euthanized at diagnosis. In view of the similarities between the characteristics of CUP between humans and canines, the value of comparative oncology can be recognized in the field of CUP research.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

None.

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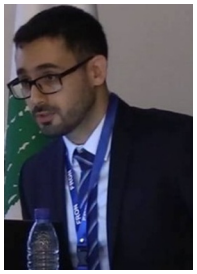

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