

Holistic management of renal nephroblastoma in a juvenile dog with severe cachexia: A case report

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Summary

This report presents a case of a 2-month-old female German Shepherd dog with renal nephroblastoma and strong cachexia. The tumour was surgically removed and graded as a stage I with favourable histopathology, but due to its large size, adjuvant chemotherapy, including doxorubicin and vincristine, was recommended. Before, during and after chemotherapy, the body weight was gradually rebuilt with an appropriately balanced diet containing proper amounts of protein, fat and numerous supplements necessary for growth and development. Eighteen months after diagnosis, the dog was in good condition and had no metastases. In conclusion, this case study shows that close cooperation between oncologists and nutritionists is crucial for successful oncological therapy, especially in a cachectic patient.

Keywords: veterinary oncology, chemotherapy, oncology nutrition, holistic therapy, Wilms' tumour

Renal nephroblastoma (Wilms' tumour) is the most common renal tumour found in childhood. Localized and metastatic forms of this disease can be successfully treated (8, 27). The tumour originates from a retained residual blastema that has not disappeared by a particular point in pregnancy (27). Renal nephroblastoma is uncommon in dogs, but reported cases include juvenile and adult dogs, which are treated by nephrectomy with or without adjuvant chemotherapy and have a high metastatic rate (50%) and various survival times (5). Although renal nephroblastoma is most often diagnosed in young dogs (1), case reports of adult animals predominate in the literature (1, 5, 16, 19, 25).

Cancer cachexia is the most common paraneoplastic syndrome in dogs, decreasing their quality of life and response to treatment and shortening their survival time (21). Cachexia is very rarely observed in dogs with nephroblastoma and has only been observed in one case reported to date (16). Therefore, a description of nutritional treatment for this condition is lacking.

This report presents a case of renal nephroblastoma in a puppy that was successfully treated by nephrectomy and adjuvant chemotherapy with additional holistic dietary management.

Case report

Initial presentation. A two-month-old female German Shepherd dog presented to the veterinary clinic with bloody diarrhoea and a poor body condition compared to that of her littermates: the dog was cachectic and weighed only 3.8 kg. Physical examination revealed a body condition score (BCS) of 2/9 and a large palpable and nonpainful mass occupying the entire right side of the abdominal cavity, causing a distinct enlargement of the abdominal contour. A focused assessment with sonography for trauma (FAST) examination of the abdominal cavity revealed an irregular solid tumour (diameter: 120 mm) of the right kidney, compressing the urinary bladder and intestines. The tumour was homogeneously hyperechoic with several hypoechoic/anechoic areas resembling deformed pseudopapillae or recesses of the renal pelvis (Fig. 1). The contralateral kidney (length:

17 mm) and urinary tract were unremarkable. The blood test showed anaemia (RBC 4.28 T/l, Hb 5.6 mmol/l), hyperkalaemia (6.04 mmol/l), hypoproteinaemia (40 g/l) and significantly increased symmetric dimethylarginine (SDMA 2.05 μ mol/l); other parameters were within reference ranges. Urinalysis showed proteinuria (288 mmol/l) and microhaematuria. Based on the results of the clinical examination, primary renal neoplasia was suspected, and an appropriate surgical procedure was performed. It was assumed that the diarrhoea could have resulted from intestinal compression secondary to a large renal tumour. Nevertheless, amoxicillin with clavulanic acid (Synergol, ScanVet, Gniezno, Poland), meloxicam (Metacam, Boehringer Ingelheim Vetmedica GmbH, Rhein, Germany) and papaverine (Papaverinum hydrochloricum, Polfa, Warsaw, Poland) were given.

Surgical procedure. The dog underwent surgery under general anaesthesia with medetomidine (Cepetor, ScanVet, Gniezno, Poland), propofol (Propofol Pfizer 10 mg/ml, Pfizer, Kent, UK) and isoflurane (Aerrane 100%, Baxter, Warsaw, Poland). A laparotomy (upper-to-lower midline incision) revealed that the tumour was located within the retroperitoneal space, completely distorting the renal parenchyma, but apparently not exceeding the renal capsule. After the peritoneal incision, the right kidney, containing the tumour (weight: 530 g; Fig. 2), was excised together with the right ureter just at the ureterovesical junction. Due to the right ovary's proximity to the tumour mass and numerous vascular connections, the surgery was extended to include ovariohysterectomy. Neither additional tumours nor enlarged lymph nodes were detected during the surgery.



Fig. 2. The right kidney immediately after nephrectomy. The contour of the kidney is irregular, but the renal capsule remains intact

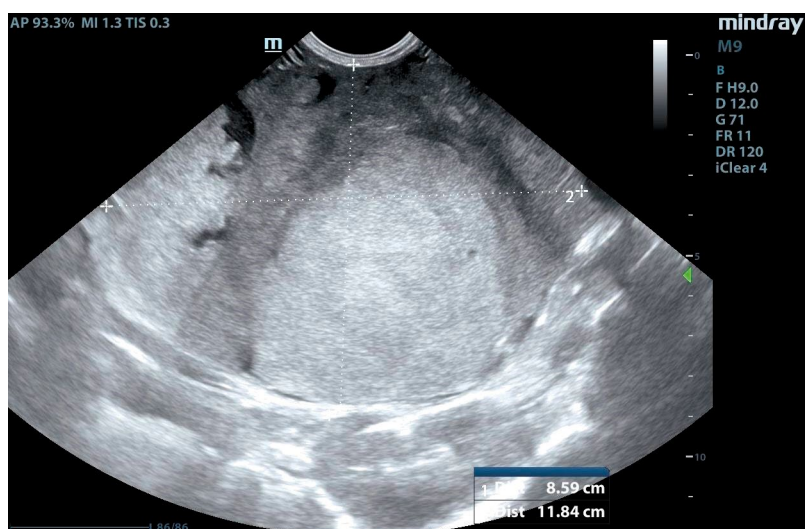


Fig. 1. Ultrasound of the right kidney, deformed by a large tumour

The peritoneal cavity was rinsed with sterile physiological saline, and the abdominal wall was sutured in a standard manner. The postoperative outcome was unremarkable. The diarrhoea resolved during postoperative hospitalization. Microhaematuria and proteinuria resolved within one and three weeks after surgery, respectively. The level of SDMA decreased within two weeks after surgery, but remained above the reference range (1.28 μ mol/l).

Histopathology. Tumour samples were immediately fixed in 10% buffered formalin, routinely processed, embedded in paraffin wax, cut and stained with Mayer's haematoxylin and eosin. Histopathological examination revealed a poorly circumscribed neoplasm, infiltrating and effacing the renal cortex and medulla, composed of undifferentiated blastemal cells with areas of epithelial and stromal differentiation (Fig. 3). Small round to oval blastemal cells with scant cytoplasm, round nuclei with finely dispersed chromatin and inconspicuous nucleoli showed high mitotic activity, with up to 12 mitotic figures per HPF (high-power field, 400 $\times$). Areas of epithelial differentiation were composed of pseudorosettes, pseudotubules and occasionally papillae and primitive glomeruli. The stromal element consisted of densely packed, oval to spindle-shaped cells with small myxoid areas. Necrotic areas had neutrophil infiltration

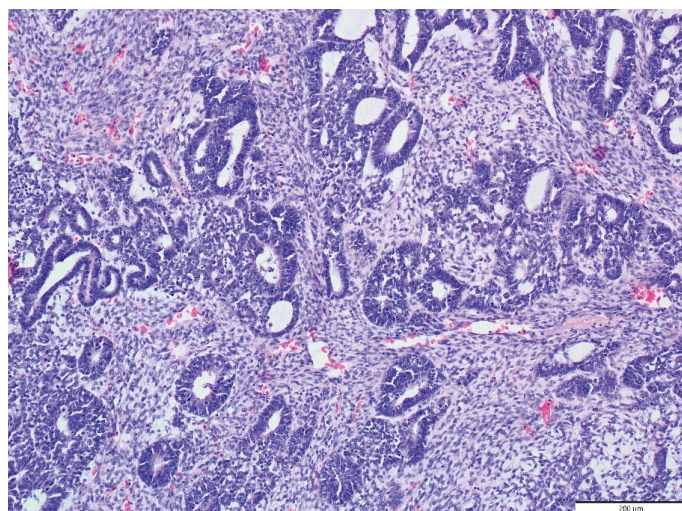


Fig. 3. Undifferentiated blastemal cells show areas of epithelial and stromal differentiation (HE, magnification. 10 $\times$)

within the tumour parenchyma. Tumour cells infiltrated the renal sinus without distinct vascular invasion. Based on typical histopathologic features, the tumour was classified as a nephroblastoma. The tumour was designated as stage I, with no evidence of anaplasia (favourable histopathology). Due to the tumour's size and significant blastemal cell content (with a high mitotic count), adjuvant chemotherapy was recommended.

Dietary management. As the dog's BCS was insufficient to start adjuvant chemotherapy immediately after nephrectomy, a complex dietary consultation was performed. The patient was still cachectic (weight: 3.4 kg, BCS: 2/9). The anamnesis revealed that the dog was constantly hungry, eating copious amounts of dry food recommended after initial clinical examination (Royal Canin Veterinary Diet Renal, Aimargues, France) without gaining body weight. As this kind of food was not appropriate for a growing animal (dry dog food contains only 16% protein, while the minimum, according to nutritional guidelines (2), is 22%), a switch to a specialized wet (canned) veterinary diet (Dr. Berg Pro-Niere, Runding, Germany) containing high-quality chicken or beef protein (26% protein content, 40% fat content, 0.56% phosphorus, 0.8% calcium, and a caloric value of 125 kcal/100 g), formulated for dogs with renal failure, was recommended to protect the remaining kidney. The diet was enriched with raw fruits and vegetables, which were boiled and shredded into mush. The feeding amount was regularly adjusted for the increasing weight of the dog, using the BCS and the muscle mass score (MMS) for proper assessment. Furthermore, the diet was supplemented with beneficial bacteria (*Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*), prebiotic psyllium (Azodyl; Vetoquinol, Fort Worth, USA), devil's claw (*Harpagophytum procumbens*; Lunderland – Tierfutter GmbH, Luchow, Germany), dried bovine blood (source of iron to counteract anaemia), inactive brewer's yeast (source of vitamin B complex), omega-3 fatty acids and dried chlorella. During chemotherapy, the diet was continued, with adjustments for the dog's weight and energetic demands. Dietary supplementation was enriched with red elm bark (*Ulmus rubra*) to prevent diarrhoea and vomiting (20). As the canned veterinary diet did not seem to satisfy the dog's hunger (and for financial reasons), this diet was gradually replaced with homemade meals (prepared according to a nutritionist's guidelines) based on turkey meat (with skin, without bones; 60% of the diet), offal (hearts and liver; 10% and 5% of the diet, respectively), cooked and shredded vegetables (25% of the diet) and egg yolks as a source of choline (26). The dog preferred the homemade meals over the canned veterinary diet. The homemade meals were supplemented with 3-hydroxy-3-methylbutyric acid (HMB) and calcium carbonate to support growth and enriched with dried rabbit ears for behavioural reasons. In the following weeks, the dog continuously gained weight, and no gastrointestinal disturbances were observed. After fourteen weeks, the dog reached a weight of 12 kg, and the diet was enriched with duck meat (breast with skin, without bones) and krill oil, a valuable source of phospholipids (associated with eicosapentaenoic acid and docosahexaenoic acid) and some minor bioactive components, such as astaxanthin,

sterols, tocopherols, vitamin A, flavonoids and minerals, which have anti-inflammatory and anticancer properties (28). When the chemotherapy was finished, the dog reached a weight of 17.3 kg (at 7 months of age) and a BCS of 4/9, and a properly balanced, biologically appropriate raw food (BARF) diet was introduced, based on high-quality fresh meat (human-grade meat), offal, fruits and vegetables, supplemented with calcium carbonate, sea algae (a source of iodine), brewer's yeast, fish oil and krill oil. After three months, the dog reached a weight of 24.0 kg and a BCS of 5/9. At 20 months of age, the dog reached a weight of 27.3 kg (BCS of 5/9 and excellent MMS) and showed no problems with appetite or digestion.

Chemotherapy. After three weeks of dietary management, the animal's condition significantly improved, her body weight increased to 5.5 kg, and her BCS was 3/9. The dog was vital, active and interested in her surroundings. Therefore, adjuvant chemotherapy, based on a protocol including doxorubicin hydrochloride (3 doses with 3-week intervals; Doxorubicin, Accord Healthcare Limited, North Harrow, UK) and vincristine sulfate (11 doses with one-week intervals; Vincristine Teva; Teva Pharmaceuticals Poland, Warsaw, Poland), was started (dosage and schedule are included in Tab. 1). Since the animal's weight was below 15 kg, doxorubicin was administered per body weight and not per body surface area. Additionally, vincristine was used at the lowest therapeutic dose because of the patient's age and condition. During the entire chemotherapy cycle, blood tests were performed before each infusion and revealed no abnormalities. Chemotherapy was well tolerated and no side effects were observed. Before each administration of doxorubicin, echocardiographic and electrocardiographic examinations were performed, but did not reveal any heart disorders that would disqualify the dog from receiving chemotherapy. One year after the last dose of chemotherapy, regular general check-ups every three months (including chest X-ray, abdominal cavity ultrasound examination, cardiological examination, blood and urine tests) did not reveal any abnormalities (anaemia and hypoproteinaemia resolved within 4 months after surgery). Constant monitoring was recommended (abdominal ultrasound examination every three months and chest X-rays every six months) for the next two years.

Tab. 1. Chemotherapy schedule

Week	Drug	Dose
I	Doxorubicin	1 mg/kg IV
IV-X	Vincristine	0.5 mg/m ² IV
XI	Doxorubicin	1 mg/kg IV
XIII-XX	Vincristine	0.5 mg/m ² IV
XXI	Doxorubicin	1 mg/kg IV

Discussion

In human medicine, nephroblastoma is treated with nephrectomy, adjuvant chemotherapy and, in some cases, radiation therapy (15). The therapy depends mainly on the tumour stage and histopathology (favourable/unfavourable) – other factors include patient age, tu-

mour weight, histologic response to therapy and allelic status of chromosomes 1p and 16q in resected tumours. Treatment with surgery alone is recommended only for patients up to 2 years of age with a stage I tumour, favourable histology and a tumour weight (plus kidney) of up to 550 g (6). In veterinary medicine, there are no strict recommendations on adjuvant chemotherapy after nephrectomy in renal nephroblastoma, and the reported outcomes are very diverse (5). There are reports of paediatric renal nephroblastoma that were successfully treated with nephrectomy alone (12, 17), but they also rapidly metastasized (9) or were multicentric (11). In the present case, adjuvant chemotherapy was recommended despite the early stage (stage I) and favourable histology of the tumour because of the tumour's elevated weight (530 g). Furthermore, the blastemal cells showed a high mitotic count, which was previously demonstrated to signify a higher risk of malignancy (5, 9).

Although there are no veterinary treatment protocols for canine renal nephroblastoma, adjuvant chemotherapy protocols in reported cases included vincristine sulphate, doxorubicin and actinomycin D (4, 10, 16, 25), similar to protocols in human medicine (6, 13). In the present case, we decided to include doxorubicin and vincristine. We did not include actinomycin D, as it was previously shown to potentially exacerbate the toxicity of doxorubicin in dogs (14). Doxorubicin, despite its cardiotoxicity, shows a high effectiveness in treating Wilms' tumours, increasing the life expectancy of patients (13).

Cancer cachexia is associated with metabolic alterations in carbohydrate, protein and lipid metabolism, and is aggravated by accompanying anorexia. Tumours preferentially metabolize glucose by anaerobic glycolysis and use protein for energy at the expense of the host (22). In the present study, cachexia was a result of a large, energy-consuming tumour, but the food intake was normal (or even increased). Dietary management was designed not only to address the demands of the very young, rapidly growing, large-breed dog, but also to rebuild the patient's body weight and prevent renal failure. In nutrition of cancer patients, the diet should be relatively low in simple carbohydrates and contain moderate amounts of high-quality proteins and fats (21). In the present study, the dry veterinary diet with a low protein content (16%), designed for adult dogs with chronic renal failure, was insufficient to meet the nutritional requirements of the dog and was therefore replaced with a canned veterinary diet containing more proteins (26%), a relatively high amount of fat (40%) and less phosphorus, enriched with vegetables, prebiotics and supplements necessary for the proper growth and development of the puppy. Although specialized veterinary diets for dogs with renal insufficiency have a reduced protein content, the dietary protein restriction is recommended only in cases with a protein-losing glomerulopathy (3). In the present case, the diet was

supplemented with omega-3 fatty acids, which may be effective in reducing or eliminating some of the metabolic alterations associated with cancer cachexia (21). Furthermore, during chemotherapy, the diet was enriched with red elm bark, which soothes and astringes the intestinal lining and is used in gastritis, enteritis and diarrhoea (20).

In cancer patient nutrition, foods should be not only highly bioavailable and easily digested, but also highly palatable with a good smell and taste (21). In the present case, the homemade diet seemed to fulfil the dog's requirements better than the canned, specialized veterinary diet. In our opinion, professionally designed homemade diets have a better effect on an animal's health than commercially available veterinary diets, especially those formulated for kidney diseases. It was previously shown that many commercially available renal diets for dogs and cats contained more than twice the recommended amounts of phosphorus, and therefore, these diets did not meet the expectations of customers and veterinarians (7). For this reason, more emphasis should be placed on research on homemade diets versus commercial diets.

There is a growing interest in homemade pet nutrition, and raw-meat-based diets are increasingly popular among pet owners (23). These diets are regarded as a more natural and healthier alternative to commercial pet food (18). However, these diets can also pose some risks of microbial transmission and nutritional imbalances, and should therefore be formulated by a professional nutritionist (18, 24). In the present case, the professionally balanced BARF diet was introduced after full restoration of body weight and completed chemotherapy, and seemed to meet the nutritional requirements of the adolescent dog perfectly.

In conclusion, this case study shows that close cooperation between oncologists and nutritionists is crucial for successful oncological therapy, especially in a cachectic patient.

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