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Probable periosteal osteosarcoma in a rabbit

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The word sarcoma comes from the Greek and means "fleshy excrescence". It describes a group of malignant tumors in which a primitive mesenchymal cell can evolve in several directions and, thus, into different types of sarcomas.

Although sarcomas are well-recognized and classified tumors, their etiology is not well-known. Possible factors in their development include modifications of the genetic material (e.g. irradiation), chronic irritation of the tissue (trauma), or the introduction of a foreign body into the system (e.g.: via vaccination, injection of

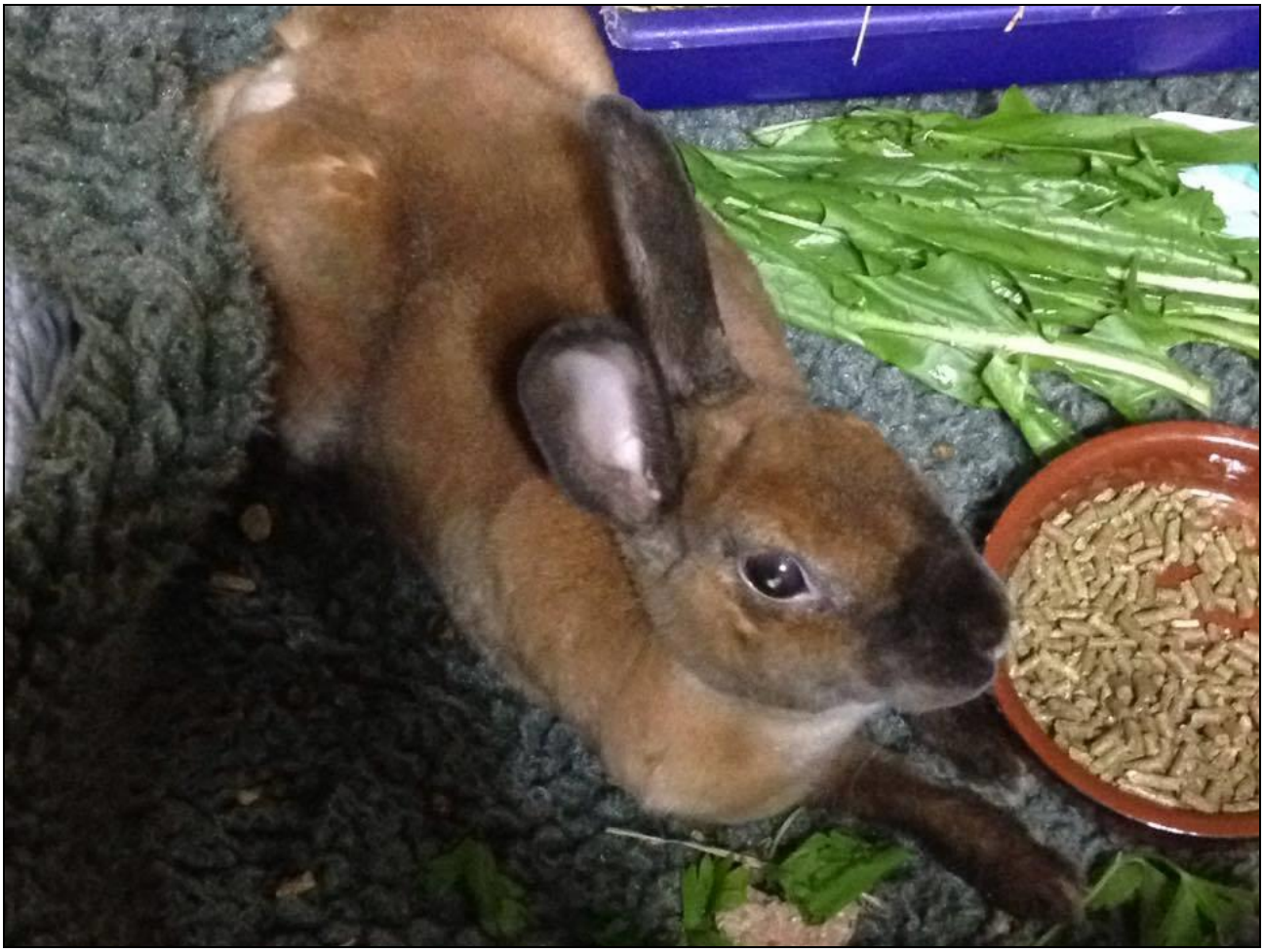

Figure 1: Hope, a Rex rabbit estimated to be 1 year old. She developed numerous calcified masses suggesting osteosarcoma and an eye problem. (Picture courtesy of Jessica Cucka)

drugs or a parasite bite).

Sarcoma tumors are locally aggressive and invasive. Their metastatic rate is usually low; they can, however, metastasize via the blood circulation. Once sarcoma cells have invaded the blood, they will be disseminated to remote tissues in order to colonize other organs.

Rabbits can be affected by different types of sarcoma. They are found in bones and various tissues. Metastasis can develop in the lungs as well as in tissues and organs of the chest and abdomen. The presence of the tumors can lead to pain, lameness and respiratory distress.

Osteosarcoma is a type of sarcoma derived from or containing bone cells (Figures 1, 2). It is rare in rabbits. The disease develops mainly in bones of the appendicular skeleton (front and hind limbs, shoulder and hip girdles) and, to a lesser extent, in bones of the axial skeleton (bones of the head and trunk). It is an aggressive type of sarcoma that starts spreading from the neoplastic bone to other locations in the body in very early stages of the disease. Metastases are observed in bones, various organs (e.g. the lungs), the skin, and in

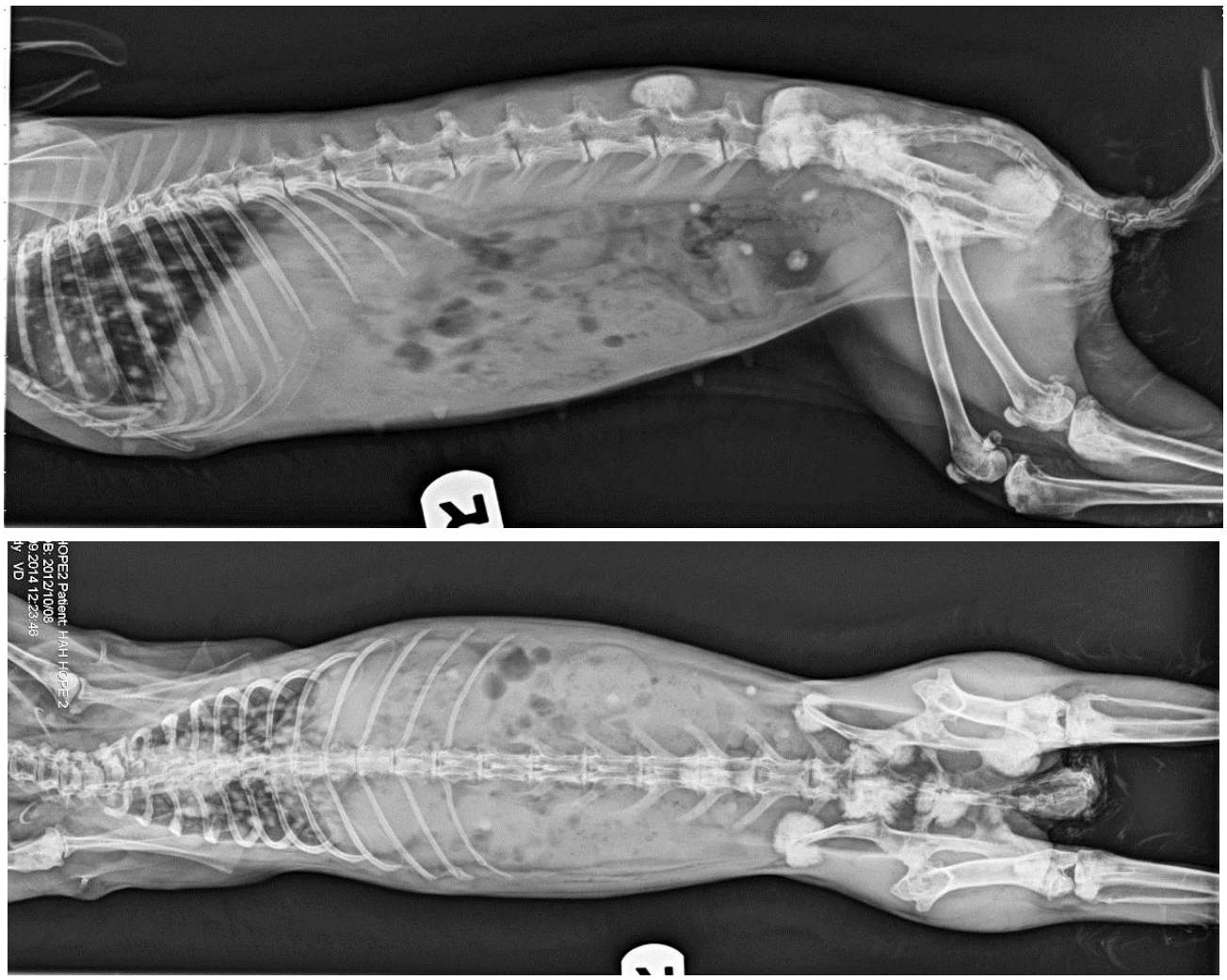

Figure 2: « Never seen anything like this» is the remarks of veterinarians upon seeing these radiographs of Hope: masses on the pelvis, on the spine and metastasis in the abdomen, the chest and the lungs. A biopsy suggests periosteal osteosarcoma. (Radiographs courtesy of Linda Thibault)

tissues throughout the body. In rabbits osteosarcoma tumors are also been observed on the mandibular jaw bone.

Osteosarcomas do not form a homogenous group of tumor. The matrix of the tumor and histological findings differ. The pattern observed on radiographies varies also, showing bone lysis or bone production. Osteosarcomas have, therefore, been classified in several subtypes.

Osteosarcoma types

Central or medullary osteosarcoma

Central or medullary osteosarcomas are the most frequently observed bone sarcomas. The tumor results from malignant osteoblasts that start to produce osteoid tissue and immature bone. The malignancy and aggressiveness of the tumor depends on its subtype. Lytic osteosarcoma develops fast and is very destructive. Most other subtypes present a mixed pattern between lysis and bone growth, and grow lowly.

Periosteal osteosarcoma

This type of osteosarcoma tumor is relatively rare in mammals. It arises from the membrane that covers the outer surface of bones – the periosteum, except at the joints of long bones. Undifferentiated mesenchymal cells located in the membrane start to multiply. As the size of the tumor increases, it extends into the surrounding soft tissues, and, in time, invades the bone itself, into the cortex and the medulla.

The tumors present differentiation features that are intermediate between those of malignant central osteosarcoma and those of periosteal osteosarcoma. In dogs, two types of tumors have been observed:

- Periosteal tumors, which are highly malignant from the tumor's inception. Growth is fast. These highly aggressive periosteal osteosarcoma tumors present similar histological features than central osteosarcoma. It is suspected that these tumors are central osteosarcoma that originate from the metaphyseal *spongiosa* area of long bones and present an eccentric growth.
- Periosteal tumors with a low malignant behavior that develop on the metaphyseal part of long bones, unlike man where they tend to develop on the diaphyseal region of long bones. They contain a dense matrix composed of bone tissue. No complications are observed such as metastases.

Parosteal osteosarcoma

This type of osteosarcoma arises from the outer surface of the cortex of bones. In man, it represents less than 2% of osteosarcoma tumors and it affects mainly younger persons. These tumors typically develop near the metaphysis of the tibia and the proximal end of humerus. In animals, other locations have been reported, such as vertebra. The matrix is dense; it is composed of well-differentiated malignant osseous, fibrous and sometimes cartilaginous stromal elements.

Little information is available about parosteal osteosarcoma in animals. Unlike man, parosteal osteosarcomas have been observed in various regions of the body. In dogs, tumors have been observed on the fore- and hind limbs, but also in the head and on one cervical vertebra. Cats developed parosteal osteosarcoma tumors on the front and hind limbs, on the ribs, on the ramus of the mandible and on the pelvis. In horses, tumors have been reported on a cervical vertebra, the maxilla and the metacarpus.

On radiographies, tumors appear like a cauliflower mass or like a "sunburst" on the surface of the bone. The amorphous

consistency of the matrix presents variations in radiodensity. The tumor may be directly attached to the bone or have a small peduncle. The underlying bone and cortex do not present changes. The "string sign", which separates the tumor from the underlying cortex, has not been observed in animals and is, therefore, not considered to be of diagnostic importance, on the contrary to man.

Growth of parosteal osteosarcoma is slow, and tumors are considered low grade. In time, their behavior may become more aggressive, with invasion of the cortex and medulla of the bone. Metastases develop in the lungs after a few months.

Diagnosis

Diagnosis is based on clinical signs and imaging tools (radiography, ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT)). Radiography allows to locate of the tumors in the body, and to visualize the extent of bone destruction or the size of the tumor.

Cytological and/or histological analysis of tumor samples is necessary for the final diagnosis. The histologic analysis will help to differentiate osteosarcoma from other bone neoplasia. Occasionally, a bacterial jaw abscess accompanied by osteomyelitis of the underlying bone is misdiagnosed as

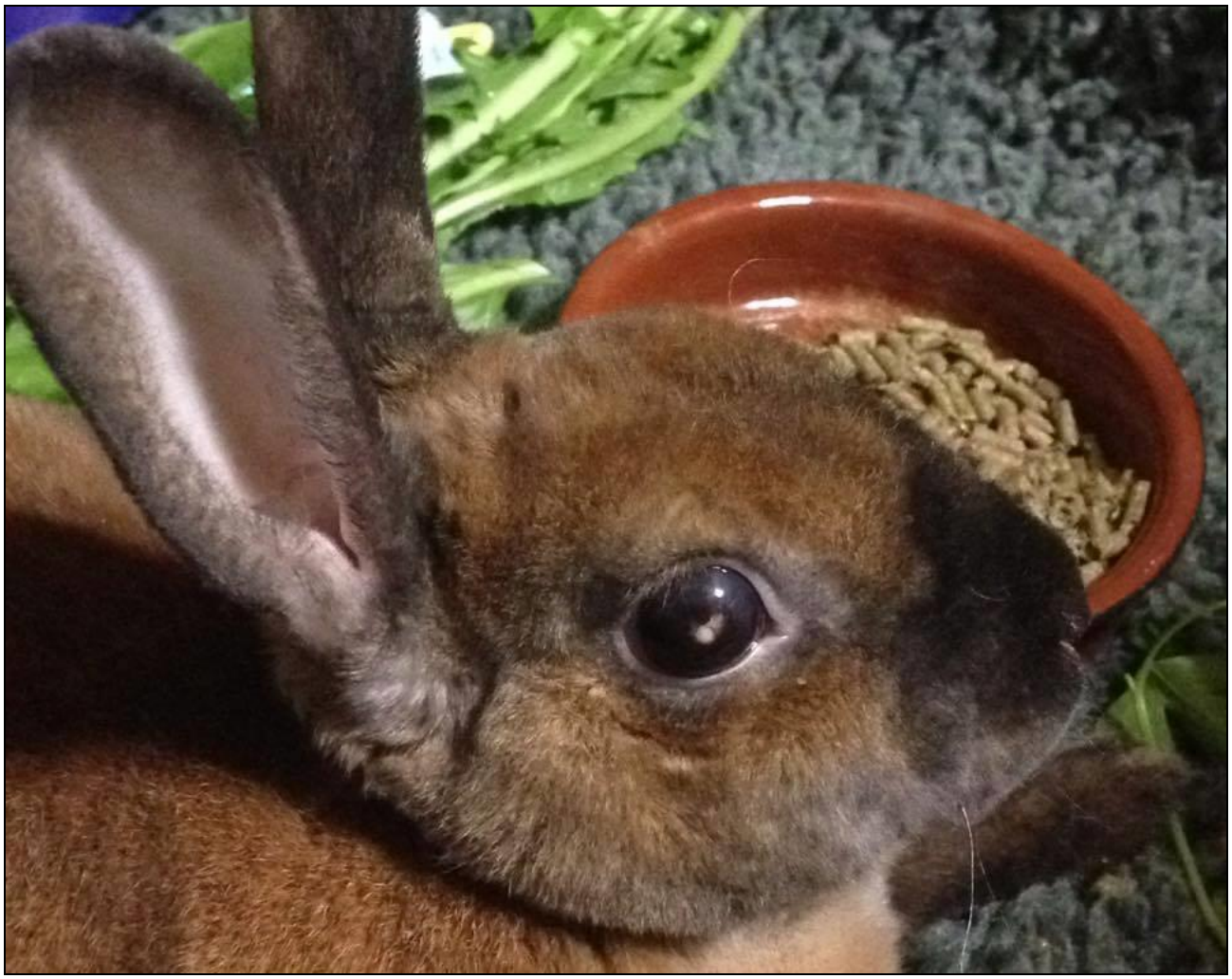

Figure 3: Hope, detail of the eye. In animal, periosteal osteosarcoma may rarely develop in the eye after a trauma. (Picture courtesy of Jessica Cucka)

osteosarcoma.

Diagnosis requires precise differentiation between infective, tumoral, and metabolic diseases of the bone. Malignant features of osteosarcoma, e.g. cellular pleomorphism and abnormal cell division activity (mitosis), should be ruled out. It is also important to differentiate osteosarcoma from an early bone callus forming around a bone fracture. It is, therefore, important that the specialized laboratory to which the sample is sent has experience in analyzing material collected from rabbit tissues.

Osteosarcoma is often accompanied by a raised level of total serum alkaline phosphatase (ALP). The increased ALP is suggestive of liver failure, but may also have a bone origin. In humans and in dogs suffering from osteosarcoma, elevation of the ALP level has been linked with a poor prognosis.

Clinical signs

Clinical signs are few, absent or not indicative of osteosarcoma: anorexia, pain, respiratory distress, and/or lameness are the sole signs. Lameness is caused by the swelling of tissues surrounding the affected bones, e.g. in the shoulder/brachium region or joints. Radiography may reveal massive destruction or production of bone tissue.

Treatment

There is no cure for osteosarcoma and prognosis is poor due to the aggressive nature of the tumors. Pain medication must be administered.

If a limb is affected and no metastases are detected in other parts of the body, amputation is the treatment of choice. If this is impossible, aggressive surgical excision with a large margin is necessary. The rate of recurrence after removal is high, often within months. The intervals of time between recurrences appear to decrease after each surgical excision. If this is the case, or when surgical excision is not possible, palliative care and euthanasia must be considered, in order to spare suffering to the rabbit.

During surgery as much of the tumor and its extensions must be removed to prevent recurrence. The distinction between microscopic branches of the tumor and healthy tissue is, however, not easily defined, rendering complete surgical excision of the tumor difficult even when a precautionary adequate margin is removed. This surgical margin should comprise as much tissue as can be resected without compromise to the patient's health. Its width and depth are determined prior to surgery based on the tumor's location, grade, and behavior.

Other methods of treatment include radio and chemotherapy.

Radiotherapy should be avoided in certain locations in the body to prevent damage to surrounding tissues. Radiation damage includes tissue death and scarring caused by premature aging or destruction of blood vessels and by radiation-related arteriosclerosis and disruption in tissue circulation. Obstructed blood supply to the tissues leads to cell death. Radiation therapy in head and neck tumors can induce carotid stenosis or development of osteosarcoma.

The use of chemotherapy in rabbits is experimental and information is scarce. Prior to determining the advisability of chemotherapy, histological examination should be performed to determine the rate of mitosis. The sensitivity to chemotherapy is, indeed, increased when many tumor cells are dividing. Using near-toxic dosage can dramatically improve treatment results, but this must be weighed carefully against the quality of life of the rabbit. An oncologist should be consulted prior to a chemotherapy treatment. In rabbits, some attempts to

treat with chemotherapy have been made, accompanied by close monitoring to prevent or minimize intestinal dysbiosis and onset of diarrhea. Some decrease in tumor size was observed. Drugs regularly used in other animals are often accompanied by secondary effects, which are more severe in rabbits and can quickly turn fatal.

Some rabbits died during or shortly after treatment of unknown causes. Therefore it is important to do regular follow-ups, with examination of tumor size and metastasis; determination of liver, pancreas, and kidney functions; and hematopoiesis. The length of time the tumor remains in remission is more indicative of success than is survival time of the treated rabbit. When quality of life is severely decreased, or prognosis is poor, humane euthanasia should be considered.

Hope, clinical presentation

Hope is a Rex female rabbit. She was rescued by the Hopalong Hollow rescue and her age has been estimated to be 1 year old. She was brought to a local veterinarian with the complaint of lameness and gait difficulties with the hind limbs (paresis). A blood samples was taken for analysis and radiographies were made.

Interpretation of X-rays

Radiographic findings reveal the presence of numerous bone anomalies: eccentric calcified masses on the pelvis, on a lumbar vertebra and at the base of the tail. Different areas of calcification are also observed in the abdomen, the chest and the pulmonary tissues.

There are few reported cases of osteosarcoma in rabbits. Most mention that osteosarcoma can develop in the mandible, ribs, frontal bones, and tibia and metastasize via the hematogenous route to the lungs, to the abdomen and to the chest. It leads to the conclusion that this species has a much higher risk of metastasis as compared to other animals like dogs (Figure 4).

Hypothesis: the large eccentric calcified masses may be the primary tumors, with metastasis in the subcutaneous tissues and in the abdomen, the chest and the calcification observed in the pulmonary tissue.

Results of the blood exam

The biochemistry panel was normal, except for a few serum parameters:

- Glucose is elevated, 219 mg/dL (normal: 75-145). This may be the result of stress related to the visit to clinic and manipulation by veterinarians.
- Alkaline phosphatase (ALP) is elevated, 356 U/L (normal: 70-145). Other liver values are normal. This hints to a bone problem, possibly osteosarcoma.

An elevated level of alkaline phosphatase has been reported in rabbits suffering from osteosarcoma. In dogs, it is been suggested that the serum level of ALP may help to predict prognosis. Most rabbits did, however, die soon after the diagnosis or were humanely euthanized.

The complete blood count (CBC) presents anomalies too:

- Red blood cells (RBC) are slightly elevated: 6.24M/µl (normal: 4.62-5.96).
- Hematocrit (HCT) is slightly low, 35.9% (normal: 40-50%) indicates anemia. This result contradicts the elevated level of red blood cells.
- Hemoglobin (HGB) is low, 12.4 g/dL (normal: 13.3-16.7) hinting to anemia. This result contradicts the slightly elevated level of red blood cells, hinting to the presence of immature blood cells in the blood.
- Basophils, a type of reticulocyte white blood cell that plays an important role in

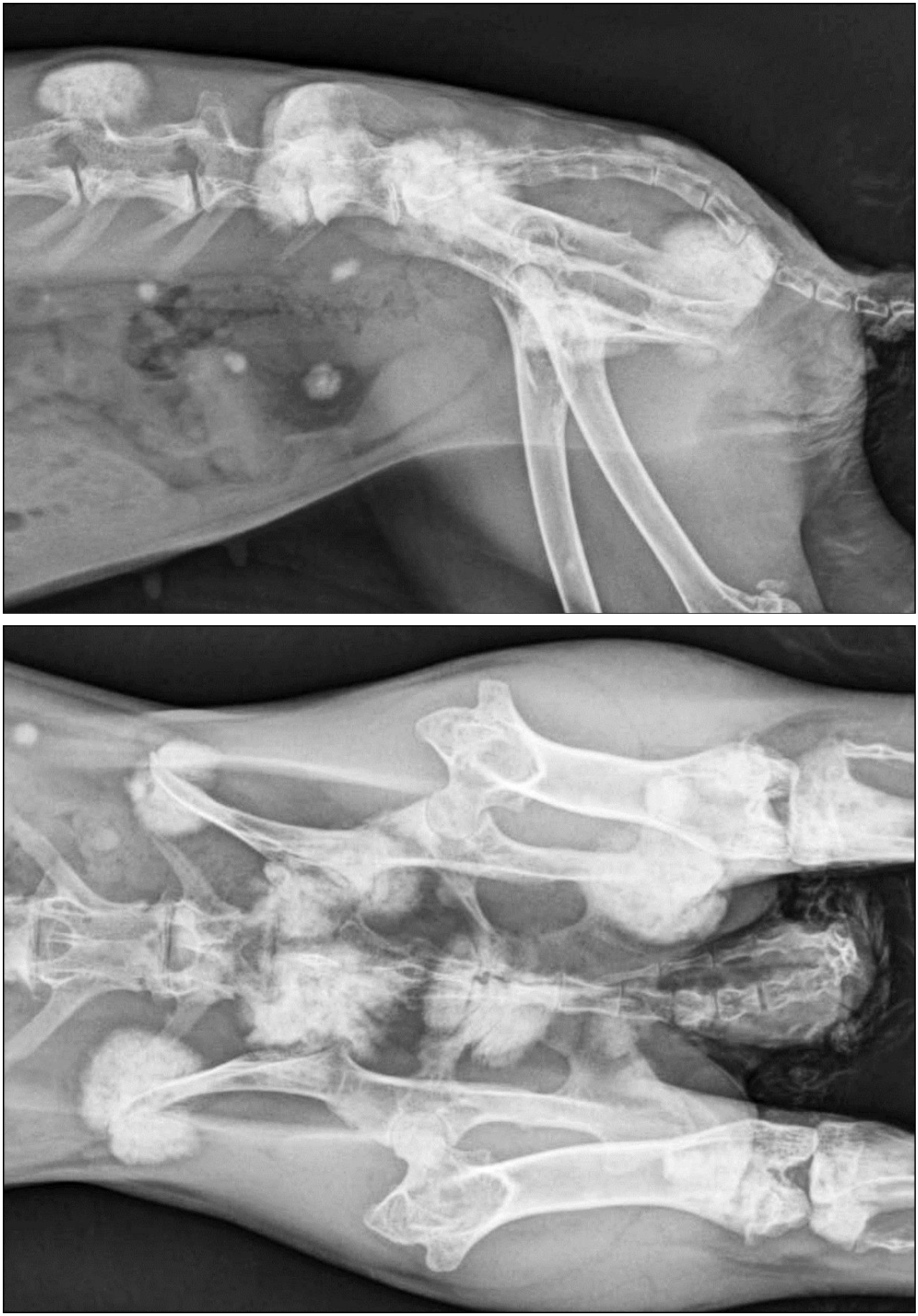

Figure 4: More detailed views of the masses with sunburst pattern on the pelvis, on the spine and metastasis in the abdomen, the chest and the lungs. A biopsy suggests periosteal osteosarcoma. (Radiographs courtesy of Linda Thibault)

the immune system is very high: 0.54 K/µl (normal range: 0.00-0.01).

Primary liver disease and nephrotic syndrome has been ruled out, as the biochemical parameters of, respectively, ALT/AST and creatinine/BUN are normal. The high levels for red blood cells and basophils do not relate to the presence of bone sarcoma; they are in contradiction with findings in animals and man suffering from osteosarcoma. Indeed, the presence of cancer-related anemia has been found in many patients with osteosarcoma.

Hypothesis: Both red blood cells and basophils develop from stem cells in the bone marrow. Are the elevated RBC and extremely high basophils level related to overactive neoplastic bone marrow tissue present in the masses (see Histological findings) ?

Or did Hope suffer from an additional bone marrow disorder (basophilic leukemia) ?

Histological findings

Samples were taken from the masses on the right wing of the pelvis and histologic evaluations were performed in order to determine the nature of the tumors. The samples were decalcified before staining.

Histologic evaluation of the mass shows the presence of mineralized bone material. These discrete and expansive lesions are composed of interlacing and mineralizing bone that is arranged randomly (ruling out intramembranous bone formed in response to stress, also called reactive bone). Bone marrow tissue is present in some larger intraventricular spaces. Others are lined with numerous pleomorphic cells. These cells are characterized by an indistinct cytoplasm and a round nucleus. Some lesions are bordered by a thin rim of fibrous connective tissue.

Result: the masses contained neoplastic cells whose appearance is consistent with spontaneous osseous sarcoma, possibly periosteal osteosarcoma.

Conclusion

Clinical, radiologic, and pathologic data support the diagnosis of spontaneous osteosarcoma – possibly periosteal osteosarcoma, with multiple metastases in the abdomen, the chest and in the lungs. Since a precise diagnosis of these tumor is difficult, further studies would be required by a pathologist specialized in bone tumors.

The health of Hope started, however, to decline rapidly after the diagnosis and she started to show respiratory problems. She has been humanely euthanized.

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