

Paraneoplastic syndrome in veterinary medicine

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Abstract

The aim of this review is to give general information about the paraneoplastic syndrome. Paraneoplastic syndrome has become widespread in veterinary medicine today. Paraneoplastic syndromes occur after many cancer diseases. Clinical findings of paraneoplastic syndrome include hypoglycemia, cachexia, anemia, hypercalcemia, polycythemia, disseminated intravascular coagulopathy, thrombocytopenia or thrombocytosis, increased globulin level, eosinophilia, myasthenia gravis, gastric ulceration, alopecia, neutrophilia-induced leukocytosis, osteopathy, glomerulonephritis, and fever. The effects of paraneoplastic syndrome in veterinary medicine are very high. We think that more scientific studies should be done on this subject. The effect of tumoral diseases, which are still very common today, has increased even more. It is very important to examine the shaped effects in more detail and to take preventive veterinary measures. Keywords: Paraneoplastic syndrome, tumor, veterinary medicine

1. Introduction

Indirect effects that occur with the effect of biological mediators such as some hormones, growth factors and cytokines both produced and released by tumors are called paraneoplastic syndrome (PNS). Paraneoplastic syndrome is a symptom of a tumoral disease, and it is very important in early diagnosis, evaluation of the effectiveness of treatment, and information about the prognosis of the patient. When symptoms of this syndrome are observed, it should be considered that the patient may have a tumoral disease. The clinical findings of this syndrome will regress with the treatment, but it may reappear in metastasis cases.^{1,2}

2. Common Clinical findings in paraneoplastic syndrome in veterinary

In veterinary medicine, hypoglycemia, cachexia, anemia, hypercalcemia, polycythemia, disseminated intravascular coagulopathy (DIC), thrombocytopenia or thrombocytosis, increased globulin level, eosinophilia, myasthenia gravis, gastric ulceration, alopecia, leukocytosis due to neurtophilia, osteopathy, glomerulonephritis, fever, periphery pemphigus vulgaris, ectopic adrenocorticotropic hormone production, increased estrogen level, feminization are among the clinical findings of paraneoplastic syndrome.³

3. The importance of paraneoplastic syndrome in veterinary medicine

Hypercalcemia is defined as a blood calcium level >18 mg/dL and may be a sign of a tumoral disease for animals, especially in pet medicine.⁴ Studies have shown that 2/3 of animal with hypercalcemia and 1/3 of cats have a tumoral disease.⁵ The mechanism of hypercalcemia seen in tumoral diseases is explained as follows. Parathyroid hormone-related peptide (PTHrP) produced by the tumor cell increases the reabsorption of renal calcium together with osteoclastic activity, leading to an increase in blood calcium levels. In addition, inflammatory mediators interleukin-1 β (IL-1 β), transforming growth factor- β (TGF- β) cause this situation. Hypercalcemia is seen in dogs, especially in lymphoma, thymoma and osteosarcoma.1,2,5

Hypoglycemia is defined as a decrease in blood glucose level below <45 mg/dL. There are many causes of hypoglycemia. In addition, it is involved in neoplasia.⁶ These are seen especially in tumoral cases such as insulinoma, intestinal tumors, lymphoma, lymphosarcoma, hepatic carcinoma, hemangiosarcoma and melanoma.⁷ The main reason is related to insulin produced by the tumor cell, insulin-like growth factors (IGF-1 and 2), and somatomedins.8 The tumoral cell both causes dysfunction in insulin receptors and uses glucose in excess, leading to hypoglycemia.¹

While intrapancreatic tumors produce excessive amounts of insulin, they cause hypoglycemia; On the other hand, extrapancreatic tumors cause hypoglycemia by using glucose in excess, causing disruptions in the gluconeogenesis mechanism, and with the effect of the insulin-like growth factor it produces.9,10

Ectopic production of adrenocorticotropic hormone has been observed in primary lung tumors, especially in animals. In patients with Sertoli cell tumor, an increase in estrogen level, however, caused non-pruritic symmetrical alopecia, hyperplasia of the prostate and sagging of the preputium, hyperpigmentation of the skin, enlargement of the breast tissue, and high estrogen level suppressed the bone marrow and led to pancytopenia.²

Anemia is a paraneoplastic syndrome that varies from mild to severe and is frequently seen in pet medicine.¹ Anemia types seen in tumoral diseases are classified as chronic disease anemia, immune hemolytic anemia, hemorrhagic anemia, anemia due to the use of chemotherapeutic agents, anemia due to bone marrow

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depression. Anemia of chronic disease is normocytic-normochromic in character and the main reason is the decrease in the life span of erythrocytes due to the deterioration of iron metabolism. Hemorrhagic anemia is seen especially in hemangiosarcoma, tumors of gastrointestinal origin and skin tumors, especially as a result of bleeding in the skin, gastrointestinal and thoracoabdominal spaces.⁶

Anemia occurs as a result of decreased erythrocyte production in conditions such as lymphoma, leukemia, myeloma and histiocytic sarcoma, which occur as a result of metastasis of tumors to the bone marrow. Cytokines (IL-6) released by tumoral cells cause anemia by causing depression in the bone marrow. Immune hemolytic anemia occurs as a result of the interaction of antibodies produced against tumor antigens and erythrocytes.¹¹

Changes in platelet count are among the findings seen in paraneoplastic syndrome. Thrombocytopenia occurs especially in tumoral diseases such as hemangiosarcoma, lymphoma, and melanoma. The main reason is the decrease in production despite the increase in consumption. Thrombocytosis is seen as a result of increases in some serum factors that stimulate platelet aggregation and increase their number. It is the main cause of thromboembolism. Polycythemia is a paraneoplastic syndrome that occurs especially in tumoral diseases of the kidneys. An increase in erythropoietin levels is observed in renal masses. The reason for this is the production of erythropoietin by the tumor cell in the kidney.¹²

As a result of the production of colony stimulating factors (granulocytic/macrophage-colony-stimulating factor, GM-CSFs) by the tumor cell.¹³, eosinophilia occurs as a result of the production of interleukin-5 (IL-5). This condition is usually seen in lymphoma and mast cell tumor. Excess globulin production from plasma cells or neoplastic lymphocytes is seen in neoplastic diseases such as multiple myeloma, lymphoma, lymphocytic leukemia and plasmacytoma. Disseminated intravascular coagulopathy has been reported in hemangiosarcoma and breast and lung carcinoma.^{7,14,15}

Alopecia is seen in cats with thymoma-derived exfoliative dermatitis and nodular dermatofibrosis, superficial necrolytic dermatitis originating from testicular tumors, and pancreatic and bile duct carcinomas. It is usually acute, progressive and nonpruritic. Mostly symmetrical hair loss draws attention. Lesions are seen in the neck, waist, perineal and genital areas. Feminization occurs in cases such as Sertoli cell tumor, seminoma and interstitial cell tumor in the testicles. Its main cause is estrogen secretion from the germinal epithelium and Leydig cells. In this syndrome, clinical findings such as gynecomastia, interest in men, sagging of the preputium, penile atrophy, prostatic squamous metaplasia, myelosuppression are seen in addition to skin lesions.^{2,16}

Superficial necrolytic dermatitis is seen in cases of glucoganoma in dogs, and pancreatic carcinomas and insulinomas in cats. Its main cause is hepatopathy and it is clinically characterized by erythema, crusting, exudation, ulceration and nonpruritic alopecia. Lesions spread diffusely.^{17,18}

Cachexia is one of the paraneoplastic syndrome findings seen in veterinary medicine. It is particularly common in lymphoma cases.¹ Fatigue, progressive weight loss, immunosuppression, muscle atrophy, and loss of appetite are common in tumoral diseases. The main reason for this is the metabolic problems that occur. Considering the blood picture of these patients, they have severe anemia and hypoalbuminemia.^{6,22}

With the development of tumoral disease, protein, fat, and carbohydrate metabolism in the living thing is impaired. In particular, negative nitrogen balance occurs due to protein catabolism. Under normal conditions, living cells use fatty acids in gluconeogenesis; tumor cells use amino acids. This is the main cause of protein degradation and cachexia. Impairment of lipid metabolism leads to an increase in the mobilization of fats in the body, resulting in an increase in energy need. Tumor cells use more glucose than the body needs, leading to the activation of anaerobic metabolism and an increase in lactate level. As a result of these metabolic changes, a negative energy balance emerges and the tumor cell continues to grow under these conditions.^{2,6}

The main cause of paraneoplastic gastrointestinal ulceration is some substances (histamine in mast cell tumor, gastrin in gastrinoma) released from the tumor cell. These substances attach to the receptors in the parietal cells, stimulate gastric acid secretion and cause ulceration.¹⁹

Myasthenia gravis is a finding of a paraneoplastic syndrome seen in osteosarcoma, cholangiocellular carcinoma, anal sac adenocarcinoma, especially in thymoma cases.²⁰ The main reason is the production of antibodies against nicotinic acetylcholine receptors (AChRs) by the tumor cell. In patients with myasthenia gravis, muscle weakness, dysphagia, megaesophagus, regurgitation and aspiration pneumonia are among the clinical findings.²¹

Peripheral neuropathy is frequently encountered in animals with lymphoma, multiple myeloma, carcinoma, and sarcoma. The main reason is the development of antigen-antibody reaction between the tumor and peripheral nerves. It also occurs because of the side effects of chemotherapeutic agents used in the treatment of the disease. It is characterized by a local or diffuse cachexia.¹

Glomerulonephritis and the resulting nephropathy is a finding of paraneoplastic syndrome that occurs as a result of accumulation of immune complexes of tumor origin, especially in the glomerulus. Especially with protein loss. Hypertrophic osteopathy is a paraneoplastic syndrome characterized by progressive periosteal proliferation in the diaphysis of long bones in the distal extremities. It occurs especially in tumoral masses located in the thoracic cavity. Stimulation of the vagus nerve plays a role in the pathogenesis of increased blood flow to the distal extremities. Fever is another finding of paraneoplastic syndrome that occurs with the release of pyrogenic cytokines, secondary to the immune response of the immune response of the living thing, especially against the tumor cell. The mentioned pyrogens cause fever especially by affecting the heat center in the hypothalamus.1-3

4. Conclusion and suggestions

There is a positive relationship between early diagnosis and treatment of diseases and survival rate. Paraneoplastic syndrome is a rare and life-threatening disease with different pathogenesis and clinical findings. Clinical and laboratory findings are frequently used in the diagnosis of paraneoplastic syndrome. Paraneoplastic findings provide very important clues in the early diagnosis of tumoral diseases. In this regard, there is a need to obtain more detailed information about paraneoplastic syndrome in terms of hematological and biochemical aspects by creating tumoral models with experimental animals. As a result, the effects of paraneoplastic syndrome in veterinary medicine are very high. We think that more scientific studies should be done on this subject. The effect of tumoral diseases, which are still very common today, has increased even more. As a result, it is very important to examine the shaped effects in more detail and to take preventive veterinary measures.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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