

Characteristics of C-reactive Protein (CRP), α_1 -acid Glycoprotein (AAG) and Serum Amyloid A (SAA) in Dogs and Cats with Malignant Cancer

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ABSTRACT

The changes in serum concentrations of C-reactive protein (CRP), α_1 -acid glycoprotein (AAG,) and serum amyloid A (SAA), in dogs and cats with cancer were investigated. On initial examination, serum concentrations of CRP and AAG showed elevated levels in dogs with cancer. On the other hand, serum concentrations of SAA in cats with cancer were below the detection limit, and AAG was only elevated in one cat tested. CRP and AAG increased after operation to remove cancer in dogs, while SAA and AAG increased after operation in cats. However, CRP and AAG again increased at several months after operation in dogs, and this was thought to be due to metastasis, incomplete removal of cancer or presence of infection. However, this phenomenon was not observed in cats. Thus, CRP and AAG may be useful as adjunct markers of malignant

cancer in dogs, but not in cats. Tumor antigens in dogs and cats could not be measured using reagents for humans.

INTRODUCTION

Acute-phase proteins are elevated in humans and other animals in response to infectious disease, surgical treatment, or trauma.¹⁻¹⁰ C-reactive protein (CRP) is a typical acute-phase protein in dogs.^{4,5,9,10} As CRP levels change during the course of inflammatory diseases,^{4,5,9-11} it is a useful inflammatory marker in dogs. On the other hand, α_1 -acid glycoprotein (AAG) is used as an inflammatory marker in cats.⁵

In humans, serum amyloid A protein (SAA) is often used as an inflammation marker, as it has better sensitivity and dynamic range than CRP.¹² Although SAA has not been used in animals due to difficulties in measuring serum concentrations,¹³ it was recently reported that antibody against human SAA could be used to measure serum concentrations of feline SAA by turbidimet-

ric immunoassay (TIA).¹³ As a result, SAA could be used as an inflammatory marker in cats, and serum concentrations were found to increase after surgery.^{13,14}

In this way, the utility of these acute-phase proteins was investigated in dogs and cats having various diseases. However, there has been little research into clarifying whether these acute-phase proteins are useful in the diagnosis of cancer in dogs and cats. The aim of this study was to examine the changes in levels of CRP, AAG, and SAA in dogs and cats with cancer.

MATERIALS AND METHODS

Sera

Sera were collected from 27 dogs and 9 cats diagnosed with and treated for cancer at Azabu University Veterinary Teaching Hospital. Blood was collected on initial examination and after operation. Sera were stored in -80°C until measurement.

All experiments were approved by the Institutional Review Board of Azabu Uni-

versity and were conducted in accordance with the Institute's Animal Experimentation Guidelines (Japanese Association for Laboratory Animal Science, JALAS, 1987).

Measurement Mfor Acute-Phase Proteins

CRP in dogs was measured by TIA using goat anti-dog CRP antibody, as described by Yamamoto et al.^{9,10} AAG in dogs and cats was measured by single radial immunodiffusion using commercial kits (Ecos Institute Co, Ltd., Miyagi, Japan). SAA was measured by TIA using LZ Eiken SAA (Eiken Chemical Co, Ltd, Tokyo, Japan), as Hansen reported that LZ Eiken SAA could be used to measure feline SAA levels.¹⁴

Measurement methods for tumor antigens

Carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3), and squamous cell carcinoma antigen (SCC) were measured by chemiluminescent immunoassay. Tissue polypeptide antigen (TPA) was measured by radioimmunoassay. Cytokeratin 19 fragment (CYFRA) was measured by electrochemiluminescent immunoassay. All

tumor antigens were measured using reagents for humans according to standard methods.

RESULTS

Initial serum concentrations of CRP and AAG in dogs diagnosed with cancer are shown in Figure 1, while SAA and AAG levels in cats diagnosed with cancer are shown in Figure 1

Serum concentrations of CRP and AAG ranged from 37.8 to 186.8 µg/ml, and from 57.8 to 1773.4 µg/ml, respectively. On the other hand, all serum concentrations of SAA in cats were below the detection limit. Serum concentrations of AAG in cats ranged from 294.0 to 1267.7 µg/ml.

Table 1 shows the concentrations of CRP and AAG in dogs that underwent operation for cancer excision and possible to

Figure 1. Serum concentrations of CRP, AAG and SAA in dogs and cats diagnosed with cancer on initial examination.

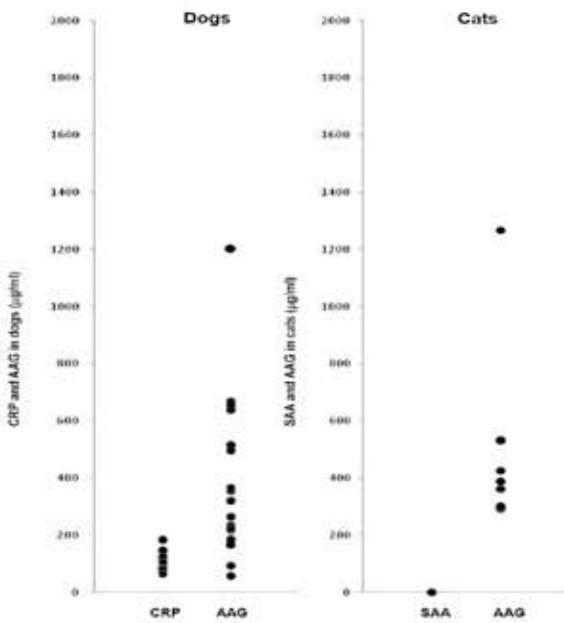


Table 1. Changes in serum concentrations of CRP and AAG in dogs with malignant cancer.

No.	Diagnosis	Days or Months after Operation	CRP	AAG
1	Infiltrating trichoepithelioma	pre-operation	116.1	680.3
		1 day after operation	155.8	882.7
		2 day after operation	117.7	784.7
		15 day after operation	121.4	571.0
2	Benign mammary gland tumors	pre-operation	112.9	265.4
		1 day after operation	216.3	416.8
		2 day after operation	142.2	622.2
		15 day after operation	160.6	430.7
3	Squamous cell carcinoma	pre-operation	73.9	658.4
		1 day after operation	146.8	851.0
		15 day after operation	94.3	647.0
		14 day after operation	135.5	813.6
		21 day after operation	80.9	966.5
		3 months after operation	325.1	3435.22
4	Anal sac adenocarcinoma	pre-operation	116.6	322.2
		1 day after operation	175.0	633.0
		8 day after operation	249.1	344.3
		3 month after operation	592.3	291.9
5	Benign mammary gland tumors	pre-operation	98.0	1773.4
		1 day after operation	182.9	1845.3
		15 day after operation	119.8	1168.8
		15 day after operation	249.5	1035.8
6	Sweat gland carcinoma	pre-operation	81.5	1203.0
		1 day after operation	337.4	1659.8
		2 day after operation	403.7	3314.3
		8 day after operation	237.3	2466.4
		14 day after operation	204.2	1265.6
7	Transitional cell carcinoma	pre-operation	62.2	223.7
		1 day after operation	24.2	619.7
		2 day after operation	189.1	885.9
		15 day after operation	122.6	294.1
		2 months after operation	314.5	135.5
8	Squamous cell carcinoma	pre-operation	128.6	697.3
		1 day after operation	152.4	927.9
		2 day after operation	150.1	1223.3
		8 day after operation	107.1	947.5
		15 day after operation	17.7	921.5
		36 day after operation	396.3	857.7

Table 2. Changes in serum concentrations of SAA and AAG in dogs and cats with malignant cancer.

No.	Diagnosis	Days or Months after Operation	SAA	AAG
1	Malignant mammary gland tumors	pre-operation	0	534.9
		1 day after operation	121.1	1713.2
		2 days after operation	43.2	2536.0
		1 week after operation	0	1047.1
		14 days after operation	0	925.9
2	Malignant mammary gland tumors	pre-operation	0	294.0
		1 day after operation	125.1	1175.2
		2 days	116.3	1356.0
		1 week after operation	0	836.3
		Operation at second times	0	537.8
		1 day after operation	69.7	975.8
		2 days after operation	76.6	1142.9
		15 days after operation	0	1069.4
		2 months after operation	0	418.1
3	Lung adenoma	pre-operation	0	362.1
		1 day after operation	41.9	724.2
		2 day operation	131.3	2134.0
		14 days after operation	0	1306.7
		15 days after operation	0	839.1
4	Fibrosarcoma	pre-operation	0	363.1
		1 day after operation	14.1	803.4
		2 days after operation	28.4	2703.2
		8 days after operation	0	1380.1
		36 days after operation	0	248.4
5	Hepatocellular carcinoma	pre-operation	0	1267.7
		1 day after operation	79.1	828.5
		2 days after operation	160.6	2060.0
		8 days after operation	20.4	1397.3

be followed. Both CRP and AAG showed high concentrations before operation, and these levels increased after operation, before decreasing gradually. Table 2 shows the concentrations of SAA and AAG in cats that underwent operation for cancer excision and possible to be followed. The concentrations of SAA were below the detection limit, while AAG was normal before operation. However, both SAA and AAG increased

after operation and decreased gradually. All tumor antigens measured in dogs and cats were below the detection limit.

DISCUSSION

The utility and characteristics of the acute-phase proteins CRP, AAG and SAA in dogs and cats were investigated in this study.

The serum concentrations of CRP and AAG in healthy beagle dogs are reported to be 8.3

and 322 µg/ml,¹⁶ respectively. Serum concentrations of CRP in all of the present dogs were higher than this level on initial examination, while 56% of dogs had higher AAG levels. CRP is more sensitive to inflammatory stimulation than AAG.¹ Thus, CRP in dogs with cancer is expected to be higher when compared to the levels seen in healthy beagle dogs. These results indicate that CRP and AAG are elevated in dogs with cancer.

These acute-phase proteins increased further after operation to remove cancer and decreased gradually thereafter, similarly to a previous report.^{9,10} However, CRP and AAG increased again at several months after operation. This was thought to be due to metastasis, incomplete removal of cancer or presence of infection.

In cats, AAG was also slightly elevated on initial examination in the present study. Feline AAG is reported to be higher in the presence of various tumors.¹³ Kajiwara et al reported that SAA was slightly elevated in cats with tumors when compared with other diseases.¹⁸ On the other hand, SAA is reported to be a useful marker in human cancer.^{19,20} However, SAA was not elevated on initial examination in the present study.

SAA peaked at about 1 day after operation for cancer excision. This is in agreement with other reports.²¹ AAG also increased after operation. AAG reportedly increases after inflammatory stimulation and peaks at 2 days after stimulation,²² and in the present study, peak concentrations were observed at 2 days after operation, before decreasing gradually. The changes in AAG in the present study were in agreement with that report.²² In addition, SAA and AAG showed no increases in the months following operation. As SAA and AAG increase in response to tissue damage rather than the presence of cancer, they are considered to be of limited use in the diagnosis of cancer in cats.

CEA, CA15-3, SCC, TPA and CYFRA in dogs and cats showed no increases. This is likely to be due to the lack of common antigenicity between humans and dogs or cats with regard to these tumor markers. Mea-

surement methods for these markers using reagents for humans were thus considered to be inapplicable to dogs and cats.

These results suggest that CRP and AAG are elevated in dogs with cancer, but SAA and AAG do not increase in cats. Specific diseases are impossible to diagnose based on increases in serum concentrations of CRP or AAG alone; however, CRP and AAG may be useful markers to support a diagnosis of cancer in dogs. On the other hand, SAA and AAG are not useful for diagnosis of cancer in cats.

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