

Utility of Serum Thymidine Kinase Activity Measurements for Cases of Bovine Leukosis with Difficult Clinical Diagnoses

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(Received 30 December 2012/Accepted 11 April 2013/Published online in J-STAGE 26 April 2013)

ABSTRACT. This study evaluated the clinical usefulness of serum thymidine kinase (TK) activity for diagnosing bovine leukosis cases for which clinical diagnosis was difficult ('BL with difficult diagnosis'). Median TK activity values in 24 'BL with difficult diagnosis' and 36 cattle for which BL was clinically confirmed by cytology findings of enlarged superficial lymph nodes ('clinically confirmed BL') were 36.8 and 39.4 U/l, respectively (no significant difference). The percentage with positive TK activity (>5.4 U/l) was also similar in both groups (83.3% for 'BL with difficult diagnosis' and 97.2% for 'clinically confirmed BL'). TK activity was significantly higher in cows with 'BL with difficult diagnosis' compared to those with other tumors (N=13) and those with inflammatory diseases (N=14). Maximum TK activity in cows with other tumors and inflammatory diseases was not high (<10 U/l). Median TK activities in cows with other tumors and those with inflammatory diseases were 1.8 and 1.4 IU/l, respectively. Positive TK activity was found in a significantly higher percentage of cows with 'BL with difficult diagnosis' (83.3%) relative to the percentages of cows with other tumors (15.3%) and inflammatory diseases (21.4%). Thus, TK activity is an appropriate marker for detecting BL onset in cows with 'BL with difficult diagnosis' as well as 'clinically confirmed BL' group. While the specificity of TK activity required for BL diagnosis is not clear, simultaneous evaluation of serum lactate dehydrogenase activity may assist in the differential diagnoses of other tumors and inflammatory diseases from BL.

KEY WORDS: atypical bovine leukosis, diagnosis, thymidine kinase.

doi: 10.1292/jvms.12-0572; *J. Vet. Med. Sci.* 75(9): 1167–1172, 2013

Bovine leukosis (BL) is one of the most common neoplastic diseases of cattle. Cattle with BL often present with loss of condition, an abrupt drop in milk production, enlarged superficial lymph nodes and exophthalmos, and are partial to complete anorexia, particularly with regard to grain or concentrates [1]. Once clinical signs appear, there is no cure for the disease [10]. Clinical findings, including superficial lymph node swelling, lymphocytosis and detection of neoplastic lymphocytes in peripheral blood, are sufficient for suspicion of BL [10]. A definitive diagnosis is usually obtained by cytology of aspirates from tumors or tumorous nodes; however, the sensitivity and specificity of fine-needle aspiration (FNA) of enlarged peripheral lymph nodes are not always reliable [15]. Definitive diagnosis of BL is difficult in cattle without lymphadenopathy, even with evidence of lymphocytosis and atypical lymphocytes in the peripheral blood [12].

Serum thymidine kinase (TK) activity has been evaluated as a serum marker for human and canine hematopoietic tumors [4, 5, 8, 9, 14] and is potentially a marker for BL with higher sensitivity than FNA [11]. In our previous study, 19 of

20 cows (95.0%) with BL showed serum TK activities above the cut-off point (>5.4 IU/l) [10]. However, the clinical usefulness of measuring TK activity in cattle as a diagnostic marker of BL for which clinical diagnosis is difficult has yet to be evaluated. There are also few data available for the specificity of TK activity in BL diagnosis. Thus, the present study evaluated the clinical usefulness of measuring serum TK activity for BL cases for which clinical diagnosis is difficult.

MATERIALS AND METHODS

Samples: Sera from 87 cows, including 60 with BL and 27 with other diseases, were used in this study. Among these, definitive diagnoses were made for 47 of the cows with BL and all 27 cows with other diseases by post-mortem examination and histopathological findings at the Obihiro University of Agriculture and Veterinary Medicine from April 2007 to November 2012. Diagnoses in 13 other cows with BL were clinically confirmed by FNA cytology of enlarged superficial lymph nodes. In most cases, routine blood and blood chemical examinations were performed and included complete blood counts and measurement of lactate dehydrogenase (LDH) activity. Peripheral lymphocyte numbers were evaluated by Bendixen's key criteria [3]. Antibodies against bovine leukemia virus (BLV) were detected by agar-gel immunodiffusion (Kitasato Institute Research Center for

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Table 1. TK activities and profiles of cattle with bovine leukosis which were not clinically diagnosed, but confirmed by necropsy. None of the cows showed lymphadenopathy

No.	Breed	Sex	Age (Months)	Hematological findings			TK (IU/l)	LDH (IU/l)	BLV Ab	Type
				WBC (μ l)	Total Lymphocytes (μ l)	Atypical Lymphocytes (μ l)				
1	HF	F	64	9,100	6,916	0	0.5	3,550 **	+	Enzootic
2	HF	F	125	7,500	3,450	0	2.5	30,000 **	+	Enzootic
3	HF	F	67	20,300	6,496	0	5.4	3,490 **	+	Enzootic
4	HF	F	61	8,200	4,510	0	17.0 *	764	+	Enzootic
5	HF	F	23	5,600	1,512	0	30.0 *	2,400 **	+	Enzootic
6	JB	F	87	NT	NT	NT	30.0 *	1,370	+	Enzootic
7	JB	F	52	NT	NT	NT	32.0 *	2,165 **	+	Enzootic
8	HF	F	65	14,600	7,884	4,088	39.0 *	2,310 **	+	Enzootic
9	JB	F	60	NT	NT	NT	45.0 *	3,590 **	+	Enzootic
10	HF	F	94	12,900	6,579	0	51.0 *	1,410	+	Enzootic
11	HF	F	72	13,400	8,576	4,422	52.5 *	3,060 **	+	Enzootic
12	HF	F	74	6,400	4,480	0	55.0 *	898	+	Enzootic
13	HF	F	85	13,900	8,618	4,865	71.0 *	4,545 **	+	Enzootic
14	HF	F	83	15,300	10,863	6,426	74.7 *	3,050 **	+	Enzootic
15	JB	F	92	NT	NT	NT	110.0 *	2,805 **	+	Enzootic
16	F1	CM	25	10,200	6,936	2,244	120.0 *	2,570 **	+	Enzootic
17	JB	F	50	NT	NT	NT	210.0 *	5,875 **	+	Enzootic
18	HF	F	8	5,900	4,425	0	2.7	1,140	-	Calf
19	HF	F	11	12,100	4718	0	26.0 *	2,480 **	-	Thymus
20	HF	F	67	17,100	2,736	0	8.2 *	4,891 **	-	Unknown
21	HF	F	34	11,600	8,120	30	32.0 *	1,490 **	-	Unknown
22	HF	F	37	5,500	4,290	0	34.6 *	3,380 **	-	Unknown
23	JB	F	92	NT	NT	NT	92.0 *	2,515 **	NT	Unknown
24	JB	F	60	NT	NT	NT	120.0 *	2,915 **	NT	Unknown
Median			64.5	11,600	6,496	0	36.8 *	2,688 **		

BLV Ab: Bovine leukemia virus antibody, HF: Holstein-Friesian, JB: Japanese Black, F1: hybrid of HF and JB, F: female, CM: castrated male, NT: not tested, *: TK activity more than cut-off point (>5.4 IU/l), **: LDH activity more than reference value ($>1,445$ IU/l).

Biologicals, Kitamoto, Japan).

The 60 cows with BL were divided into 2 groups. 'BL with difficult diagnosis' (N=24) and 'clinically confirmed BL' (N=36) (Tables 1 and 2). None of the cows in the 'BL with difficult diagnosis' group showed enlarged superficial lymph nodes. As such, a definitive diagnosis of BL was impossible when these cows were alive, despite the fact that some of the cows showed lymphocytosis and evidence of atypical lymphocytes in the peripheral blood (Table 1). Definitive diagnoses for all 24 cows in the 'BL with difficult diagnosis' group were made by post-mortem examination and histopathological findings. Among these, we found enzootic type (N=17), calf type (N=1), thymus type (N=1) and an unknown type (N=5) of BL. In contrast, all 'clinically confirmed BL' cows showed superficial lymph node swelling and/or lymphocytosis. Neoplastic lymphocytes in peripheral blood or FNA samples were detected in all cows of this group. Among these 36 cows with BL, we found enzootic type (N=27), calf type (N=2), skin type (N=2), thymus type (N=3) and an unknown type (N=2) of BL.

The 27 cows with other diseases were also divided into two groups; Thirteen with other tumors and 14 with inflammatory diseases (Table 3). The group with other tumors

included 4 brain tumors, 2 liver tumors, 1 lung tumor, 1 osteosarcoma, 1 leiomyosarcoma, 1 lipoma, 1 granulose cell tumor, 1 papilloma and 1 yolk sac tumor. All cows with inflammatory diseases showed lymphadenopathy or palpable masses in the pelvic cavity, and BL was suspected as part of the differential diagnosis. Post-mortem examination and histopathological findings for cows in this group revealed 6 cases of abscess in the pelvic cavity, 3 of mastitis, 2 of pneumonia, 1 of pericarditis and 1 of polyarthritis with amyloidosis.

TK activity assay: TK activity assays were performed on serum samples using a commercial radioenzyme TK-assay kit and 125 I-iododeoxyuridine tracer (Kishimoto Clinical Laboratory, Inc., Obihiro, Japan). TK activity was expressed as units per liter (U/l). The reportable range of the assay was 0.5 to 1,000 U/l. TK activities of 20 cattle among 60 with BL have been already reported in a previous report [11].

Statistics: Mann-Whitney U tests were used to compare TK activity levels of 'BL with difficult diagnosis' cases with that of other groups. Chi square analysis was also used to compare the positive rates of each group. A P-value of less than 0.05 was considered statistically significant.

Table 2. TK activities and profiles of cattle with bovine leukosis. Clinical confirmation was made through cytology findings of fine needle aspiration for enlarged lymph nodes or the high degree of lymphocytosis with neoplastic lymphocytes in the peripheral blood

No.	Breed	Sex	Age (Months)	Hematological findings			TK (IU/l)	LDH (IU/l)	BLV Ab	Type
				WBC (/μl)	Total Lymphocytes (/μl)	Atypical Lymphocytes (/μl)				
25	HF	F	71	8,000	2,640	0	5.4	2,135 **	+	Enzootic
26	F1	F	20	216,000	203,040	200,880	5.5 *	2,660 **	+	Enzootic
27	HF	F	66	16,200	8,910	3,402	7.2 *	NT	+	Enzootic
28	HF	F	88	21,600	15,768	1,296	11.0 *	1,219	+	Enzootic
29	HF	F	61	33,200	28,220	21,580	14.0 *	1,143	+	Enzootic
30	HF	F	71	10,900	4,905	1,635	16.5 *	1,130	+	Enzootic
31	HF	F	65	26,500	12,985	1,060	19.0 *	1,430	+	Enzootic
32	HF	F	122	27,200	17,680	3,264	22.0 *	1,650 **	+	Enzootic
33	HF	F	42	34,800	32,016	31,320	22.0 *	6,750 **	+	Enzootic
34	HF	F	30	33,200	21,248	1,660	23.1 *	1,465 **	+	Enzootic
35	JB	F	36	450,200	441,196	247,610	32.9 *	5,260 **	+	Enzootic
36	HF	F	115	11,100	4,662	0	33.8 *	3,340 **	+	Enzootic
37	HF	F	64	11,500	8,625	2,760	37.0 *	3,160 **	+	Enzootic
38	HF	F	74	60,700	55,237	33,385	38.7 *	3,280 **	+	Enzootic
39	HF	M	18	230,900	221,664	219,355	40.0 *	4,740 **	+	Enzootic
40	HF	F	129	20,800	11,440	5,200	41.0 *	4,700 **	+	Enzootic
41	HF	F	44	10,600	3,286	0	44.0 *	3,210 **	+	Enzootic
42	HF	F	83	6,700	2,948	0	45.6 *	2,690 **	+	Enzootic
43	HF	F	132	NT	NT	NT	52.8 *	5,800 **	+	Enzootic
44	HF	F	101	12,700	4,826	0	69.0 *	2,110 **	+	Enzootic
45	JB	F	36	312,900	306,642	303,513	97.0 *	4,360 **	+	Enzootic
46	HF	F	73	44,100	39,690	38,808	99.1 *	6,410 **	+	Enzootic
47	HF	F	72	70,500	69,090	69,090	115.6 *	9,630 **	+	Enzootic
48	HF	F	78	14,600	5,694	1,752	240.0 *	3,650 **	+	Enzootic
49	HF	F	89	269,700	261,609	248,124	1,000.0 *	5,910 **	+	Enzootic
50	HF	F	50	107,000	105,930	101,650	1,000.0 *	2,380 **	+	Enzootic
51	HF	F	85	17,500	12,950	2,100	1,000.0 *	2,510 **	+	Enzootic
52	HF	F	12	10,400	5,512	0	6.8 *	1,700 **	-	Calf
53	HF	F	4	29,700	26,136	5,940	270.0 *	3,770 **	-	Calf
54	HF	F	31	27,200	22,304	13,328	77.3 *	6,450 **	-	Skin
55	HF	F	41	10,600	3,710	0	100.3 *	12,500 **	-	Skin
56	HF	F	22	8,300	6,308	0	19.3 *	3,000 **	-	Thymus
57	HF	F	17	8,200	4,346	0	28.0 *	2,550 **	-	Thymus
58	HF	F	8	14,600	11,534	11,388	132.6 *	2,740 **	-	Thymus
59	HF	F	36	12,400	11,780	8,928	38.0 *	3,200 **	-	Unknown
60	HF	F	71	24,900	12,450	8,217	83.0 *	9,700 **	-	Unknown
Median			64.5	21,600	12,950	3,402	39.4 *	3,200 **		

BLV Ab: Bovine leukemia virus antibody, HF: Holstein-Friesian, JB: Japanese Black, F1: hybrid of HF and JB, F: female, NT: not tested, *: TK activity more than cut-off point (>5.4 IU/l), **: LDH activity more than reference value (>1,445 IU/l).

RESULTS

Results of TK activity assay for each group are shown in Tables 1, 2 and 3 and Fig. 1. Median TK activity values for cows in the 'BL with difficult diagnosis' and 'clinically confirmed BL' groups were 36.8 and 39.4 U/l, respectively (Fig.1), with no significant difference between the two groups. Although the percentage of cows with positive TK activity (>5.4 IU/l) was higher in those with 'clinically confirmed BL' (97.2%) than in those with 'BL with difficult diagnosis' (83.3%), this difference was not significant (Table 4). Of the 24 cows with 'BL with difficult diagnosis', four (Nos. 1, 2, 3 and 18) showed TK activities lower than the

cut-off point. This was also the case for one (No. 25) of the 36 cows with 'clinically confirmed BL'. However, 4 of these 5 cows showed higher LDH activity than the reference range [7] (Tables 1 and 2).

TK activity was significantly higher in cows with 'BL with difficult diagnosis', compared to that measured in cows with other tumors and inflammatory diseases (Fig. 1). Median TK activities in cows with other tumors and inflammatory diseases were 1.8 and 1.4 IU/l, respectively (Table 3). The maximum TK activities in cows with other tumors and inflammatory diseases were 9.4 and 6.9 U/l, respectively. The percentage of cows with positive TK activity was significantly higher in cows with 'BL with difficult diagnosis'

Table 3. TK activities and profiles of cattle with neither bovine lymphosarcoma nor bovine leukemia. All diagnoses were confirmed by necropsy

(1) Tumors other than bovine leukosis										
No.	Breed	Sex	Age (Months)	Hematological findings			TK (IU/l)	LDH (IU/l)	BLV Ab	Pathological Diagnosis
				WBC (μ l)	Total Lymphocytes (μ l)	Atypical Lymphocytes (μ l)				
61	JB	F	169	6,300	2,835	NT	0.5	1,173	-	Granulosa cell tumor
62	HF	M	2	5,700	2,964	NT	0.5	2,670 **	-	Yolk sac tumor
63	HF	F	48	NT	NT	NT	0.5	1,395	-	Liver tumor
64	HF	F	59	NT	NT	NT	0.6	1,935 **	-	Lung tumor
65	HF	F	78	10,500	3,150	NT	0.6	920	-	Brain tumor
66	HF	F	7	9,600	6,240	NT	1.6	NT	-	Thiratic tumor
67	HF	F	21	11,900	9,044	NT	1.8	NT	-	Lipoma
68	HF	F	3	7,200	4,032	NT	1.9	871	-	Brain tumor
69	HF	F	38	8,700	3,393	NT	2.0	1,380	-	Brain tumor
70	HF	F	9	14,300	2,717	NT	2.6	2,440 **	-	Brain tumor
71	HF	F	135	12,200	2,074	NT	3.6	1,777 **	-	Liver tumor
72	JB	F	11	6,600	4,620	NT	5.9 *	1,180	-	Papilloma
73	HF	F	66	7,300	4,234	NT	9.4 *	1,048	-	Osteosarcoma
Median			38	8,700	3,393	-	1.8	1,380		
(2) Inflammatory diseases and abscess										
No.	Breed	Sex	Age (Months)	Hematological findings			TK (IU/l)	LDH (IU/l)	BLV Ab	Pathological Diagnosis
				WBC (μ l)	Total Lymphocytes (μ l)	Atypical Lymphocytes (μ l)				
74	HF	F	80	9,800	2,450	NT	0.6	968	-	Mastitis
75	HF	F	84	7,900	3,634	NT	0.7	1,019	-	Polyarthritis
76	HF	F	60	13,200	3,828	NT	0.7	1,036	+	Abscess
77	HF	F	95	5,600	1,792	NT	1.0	842	-	Mastitis
78	HF	F	15	17,000	4,930	NT	1.2	967	-	Pericarditis
79	HF	F	102	13,300	7,847	NT	1.2	1,430	-	Abscess
80	HF	F	38	11,700	3,159	NT	1.4	1,690 **	-	Arthritis
81	HF	F	38	10,500	2,940	NT	1.4	1,058	-	Abscess
82	HF	F	61	14,500	6,090	NT	1.5	1,173	-	Mastitis
83	HF	F	14	10,400	6,240	NT	2.0	2,400 **	-	Pneumonia
84	HF	F	48	16,700	3,841	NT	3.5	623	-	Abscess
85	HF	F	76	17,600	4,400	NT	5.5 *	1,141	-	Abscess
86	HF	F	4	12,300	9,594	NT	5.8 *	981	-	Pneumonia
87	HF	F	1	13,700	4,384	NT	6.9 *	921	-	Abscess
Median			54	12,750	4,113	-	1.4	1,028		

BLV Ab: Bovine leukemia virus antibody, HF: Holstein-Friesian, JB: Japanese Black, F: female, NT: not tested, *: TK activity more than cut-off point (>5.4 IU/l), **: LDH activity more than reference value (>1,445 IU/l).

(83.3%) compared to cows with other tumors (15.3%) and inflammatory diseases (21.4%). Of the cows with positive TK activity, two cows (Nos. 72 and 73) with other tumors included a cow with papilloma and another with osteosarcoma. Three cows with inflammatory diseases included two with pelvic cavity abscesses (Nos. 85 and 87) and one with pneumonia (No. 86) (Table 4). LDH activity was lower than the reference value of 1,445 IU/l [7] for all five of these cows.

DISCUSSION

TK converts thymidine to thymidine monophosphate in rapidly proliferating cells and serves as part of a DNA synthesis salvage pathway. TK is activated during the G1/S

phase of the cell cycle, and its activity correlates with tumor cell proliferation [2]. Serum TK concentrations increase in patients with several types of hematopoietic tumors [4, 5, 8, 9]. Serum TK activity is useful for detecting, grading and monitoring tumors in lymphoma and leukemia patients, may also be helpful in diagnosing and monitoring canine lymphoma and leukemia [13] and is also a possible marker of bovine leukosis [11]. However, BLV infection with no onset of BL would not induce TK activities [11]. The present study evaluated the clinical usefulness of serum TK activity for diagnosis of 'BL with difficult diagnosis' by comparing TK activity in cows with 'BL with difficult diagnosis' to that in cows with clinically confirmed BL, those with lymphadenopathy, or those with other diseases.

We first compared TK activity in cows with 'BL with dif-

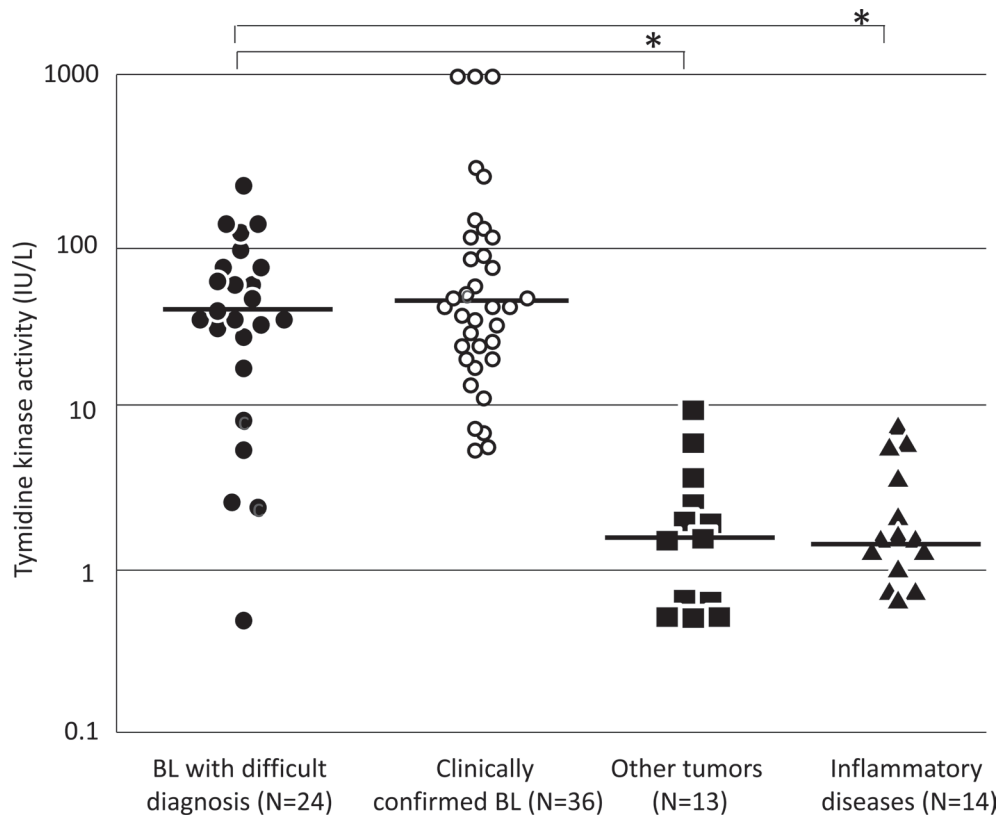


Fig. 1. Serum thymidine kinase activities of clinical cases of bovine leukosis for which diagnosis was difficult (black circles), bovine leukosis which was clinically diagnosed according to cytology findings of enlarged lymph nodes (white circles), other tumors (squares) and inflammatory diseases (triangles). Asterisks indicate significance ($P < 0.001$; Mann-Whitney U-test) when compared to cows with bovine leukosis that was difficult to diagnose.

Table 4. Positive ratio of TK activity in bovine leukosis (BL) cows with difficulties of clinical diagnosis and clinically confirmed, cows with other tumors and inflammatory diseases

Group	N	Positive (>5.4 IU/l)	Positive ratio (%)
BL cows with difficulties of clinical diagnosis	24	20	83.3
BL cows with clinically confirmed	36	35	97.2
Other tumors	13	2	15.3*
Inflammatory diseases	14	3	21.4*

* :Significant difference compared to BL cows with difficulties of clinical diagnosis.

difficult diagnosis' to that in cows with 'clinically confirmed BL' and found no significant differences in activities or positive rates between the 2 groups. These results suggest that TK activity is a sufficient marker to detect BL, even when typical clinical signs of superficial lymph node enlargement as well as typical forms are not clear. TK activity can be used

as a marker for BL in suspected BL cases without apparent clinical evidence, such as lymphadenopathy, lymphocytosis and/or increased neoplastic lymphocytes in peripheral blood.

We then evaluated the specificity of TK activity and found that TK values in cows with 'BL with difficult diagnosis' were significantly higher than in those with other tumors and inflammatory diseases. The percentage of cows that showed positive TK activity was also significantly higher in cows with 'BL with difficult diagnosis' compared to the other two groups. These results suggest that TK activity can be a useful BL marker when BL is suspected. However, 15.3% of cows with other tumors and 21.4% of those with inflammatory diseases also showed TK activity levels above the cut-off point. TK activity can be induced by the herpes virus infection [6], and elevated serum TK activity was reported for human patients with acute viral hepatitis [13]. With the exception of BLV, viral infections were not evaluated in the present study, but it is certainly possible that a herpes virus infection (e.g., infectious bovine rhinotracheitis) affected the serum TK activity in our cattle. Future studies should evaluate the effects of viral infection on serum TK activity in cattle.

In the present study, 4 of the 5 cows with BL who had

lower TK values showed higher LDH activity. In contrast, all 5 non-BL cows with higher TK activity had LDH activity lower than the reference value. Although specificity of TK activity required for diagnosis of BL is not currently clear, simultaneous evaluation of serum lactate dehydrogenase activity may help with differential diagnoses of other tumors and inflammatory diseases due to BL. Future studies regarding the specificity and cut-off points of TK activity are needed.

ACKNOWLEDGMENTS. We thank the veterinarians of the Tokachi Agricultural Mutual Aid Association for sampling. This work was supported in part by the Ito Foundation and Research Grant under President's Discretion in Obihiro University.

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