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Pathology

HEMATOLOGIC AND BLOOD CHEMISTRY CHANGES IN TOE TUMORS AFFECTING ARABIAN CAMELS (CAMELUS DROMEDARIUS)

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ABSTRACT Changes in blood constituents of camels affected by toe tumors have been investigated at Al-Tiba Veterinary Hospital in the UAE. In total, 150 camels with toe tumors and 150 healthy controls were investigated. Blood samples from healthy and diseased camels were collected for hematology and biochemical analysis using standard techniques. Significantly higher values of packed cell volume, hemoglobin, mean corpuscular hemoglobin, red blood cells, white blood cell count, neutrophils, monocytes, eosinophils, and basophils were observed in toe tumor camels compared to healthy controls. There were significant lower values of lymphocytes in camels affected by toe tumors compared to healthy controls. Moreover, significantly lower values of glucose, albumin, total protein, and iron were observed in camels with toe tumor compared to healthy controls. Significant higher values of blood urea, Creatinine, creatinine kinase, lactic acid dehydrogenase, alanine aminotransferase, alkaline phosphatase, and copper were observed in camels with toe tumor compared to healthy controls. In conclusion, hematological and biochemical database for toe tumors has been established. Neutrophilia, lymphocytopenia, hypoglycemia, and increased levels of creatinine kinase and alkaline phosphatase can be valuable assays in following–up camels with squamous cell carcinoma and monitoring their response to treatment.

KEYWORDS : Arabian camel, toe tumor, squamous cell carcinoma, Hematology, Biochemistry.

Introduction

The dromedary camel (*Camelus dromedarius*) is a multipurpose hard animal and well adapted anatomically as well as physiologically to the harsh arid and semi-arid environments [36, 40]. Dromedary camels rearing in the UAE are mainly for milk and meat production as well as for racing and beauty purposes [36]. Blood is the echo of health status and an important index for several metabolic processes that reflects the status of functioning organs in the body as well as animal production [29].

The camel is believed to be relatively resistant to physiological and nutritional stresses and to common diseases observed in other domestic animals living in the harsh desert environment [29]. Because of the urbanization and intensive husbandry practices, the incidence of both infectious and non-infectious diseases in camels is at increase. However, as more studies were conducted, camels were found to be susceptible to a large number of pathogenic agents which are major constrains in improvement of camel health. Camels may contract many diseases, some of which are still unknown. Siddiqui and Tellfah [35, 36] have been reported that toe tumor is the most common tumor in camel in the UAE. The higher incidence has been recorded in the medial toes of the fore limbs [36]. Constant irritation that results in ulcerative wound in the sole and overgrown of toe nails are considered possible causes [36]. In the literature there is no information on toe tumor of camels worldwide. In this study we investigate the effect of toe tumor on whole blood hematological and some biochemical parameters in camels.

Materials and Methods

Experimental animals and study zone

The current study was conducted at Al-Tiba Veterinary Hospital in Abu Dhabi Emirate, the United Arab Emirates during the period of 2012-2015. This study utilized the data of 150 cases of healthy and diseased camels (*Camelus dromedarius*). Al-Tibia's weather (Latitude D.D. 24.0278°- 24.6367° N, Longitude D.M. 54.0152°- 55.1738º E) is sunny most of the year. Healthy controls were of similar sex, age class and herd of the concurrent diseased camels for comparison. The camels were allowed to graze freely for a limited period in the desert, but were also supplemented with concentrated feed. The data of inspection for camels and farm identification were recorded. This included housing and management, concurrent diseases, body weight, age, sex, season, duration of tumor, previous tumor history, food intake and medication history of camels. All animal work has been approved by the Institutional Ethics Committee at Abu Dhabi Food Control Authority (ADFCA), No.2, 8-10-2012.

Hemato-biochemical parameters

Blood samples from each healthy and toe tumor camels were collected with and without anticoagulant for hematological and biochemical estimations. The hematological parameters included haemoglobin (HGB), packed cell volume (PCV), total erythrocytes count (RBCs), total leucocytes count (WBCs), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), neutrophil count (NEUT), lymphocyte count (LYMPH), monocytes count (MONO), eosinophil

count (EOSINO) and basophil count (BASO) were measured. Serum biochemical analysis included total protein (TP), albumin (ALB), creatinine (CREAT), glucose (GLU), creatine kinase (CK), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), iron, potassium, sodium, phosphorus, calcium, chloride and copper were estimated. Hematology analysis was performed on Coulter (Cell-dyn 3700, Abbott Laboratories, IL, USA and Sysmex XT-2000, iV, Japan) while serum chemistry was done in biochemical analyzer (Cone lab 60, Thermo Electron Corporation, Finland and Roche Cobas C501, Germany).

Statistic method

Statistical analysis is done using IBM SPSS Statistics version 20. Data are presented in mean ± S.E. Statistically significant differences ($p<0.05$) were calculated between toe-tumor group and healthy control group by students t test.

Results

In the present study, 150 camel (*Camelus dromedarius*) showing clinical signs of toe tumor were included and confirmed by gross and microscopic histopathologic examinations; 114 (76%) cases were diagnosed as squamous cell carcinoma (SCC) and 32 (21%) cases were fibroma while 4 (3%) cases were spiny keratoderma. Another 150 healthy camels were also included as control group.

Hematological analysis

The total WBC was significantly increased ($P<0.0001$) in camels that had toe tumor (Table. 1). The total WBC count was significantly higher in camels affected by SCC than healthy control ($P<0.0001$) (Fig. 1). The total WBC count was significantly higher in camels affected by Fibroma and spiny keratoderma than healthy control ($P<0.0001$) (Fig. 1). There was no significant difference in WBC count between SCC and Fibroma and spiny keratoderma (Fig. 1).

The absolute neutrophil count was significantly higher ($P<0.0001$) in camels affected by toe tumors compared to healthy controls (Fig. 1). It was further observed that neutrophils were significantly higher ($P<0.0001$) in camels having SCC as compared to healthy controls. In addition, neutrophils were significantly higher ($P<0.0001$) in camels having SCC than Fibroma and spiny keratoderma (Fig.1). It is evident (Table 1.) that toe tumor camels had significant lower lymphocyte count ($P<0.01$) when compared with healthy controls (Fig.1). It was further observed that lymphocytes were significantly lower ($P<0.0001$) in camels having SCC as compared to fibroma, spiny keratoderma and healthy controls (Fig.1).

However, monocytes showed significant higher count ($P<0.0001$) in camels with toe tumor when compared with healthy controls (Fig.1). It was further observed that monocytes were significantly higher ($P<0.0001$) in camels having SCC as compared to healthy controls (Fig.1). There was no significant difference in monocytes between camels having SCC, Fibroma and spiny keratoderma (Fig.1). Eosinophils also showed significant higher count ($P<0.0001$) in camels with toe tumor when compared with healthy controls (Fig.1). It was further observed that eosinophils were significantly higher ($P<0.0001$) in camels having SCC as compared to healthy controls (Fig.1). There was no significant difference in eosinophil count between camels having SCC, fibroma and spiny keratoderma (Fig.1). Moreover, basophils showed significant higher count ($P<0.0001$) in camels with toe tumor when compared with healthy controls (Fig.1). It was further observed that basophils were significantly higher ($P<0.0001$) in camels having SCC as compared to healthy controls (Fig.1). There was no significant difference in basophil count between camels having SCC, Fibroma and spiny keratoderma (Fig.1). There was significant higher level ($P<0.001$) of PCV and HGB and RBC ($P<0.05$) in toe tumor camels as compared with healthy controls (Table 1) (Fig.1). There were also significant higher MCH and MCV values in camels with toe tumor ($P<0.001$) when compared with healthy controls (Fig.1).

Blood chemistry analysis

There were significant decrease ($P < 0.0001$) in the levels of glucose (Fig. 2), ALB (Fig. 3) and TP (Fig. 3) in toe tumor camels when compared with the healthy controls (Table 2). It was further observed that glucose levels were significantly lower in camels having SCC than healthy controls ($P<0.0001$) and camels having fibroma and spiny keratoderma ($P<0.0002$) (Fig.2). In addition, ALB and TP levels were significantly lower in camels with SCC ($P<0.0001$) than normal health controls (Fig. 3). There was no significant difference in ALB and TP between camels having SCC and fibroma and spiny keratoderma (Fig. 3).

There was also significant increase in the values of BUN, CK, LDH, ALT and ALP in toe tumor camels when compared with the healthy controls (Table 2). In addition, BUN, CK, LDH, ALT and ALP levels were significantly higher in camels with SCC ($P<0.0001$) than normal healthy controls (Fig. 3). There was no significant difference in BUN, CK, LDH and ALT between camels having SCC and Fibroma and spiny keratoderma. There was significant higher level of ALP ($P<0.0001$) in camels having SCC than Fibroma and spiny keratoderma as well as healthy controls (Fig.3). However, no significant differences ($P>0.1$) were observed between healthy and diseased camels in serum AST and GGT (Table 2).

Serum iron level was significantly lower ($P < 0.05$) in toe tumor camels when compared with healthy controls (Table 3). Whereas, significant higher levels of serum copper ($P < 0.0001$) were found in toe tumor camels as compared with normal healthy controls (Table 3). There was a significant higher level of CU in camels having SCC than health controls (Table 3) (Fig. 3). Significant higher levels of Na, Cl and K were noticed in toe tumor camels as compared to healthy controls (Table 3). No significant ($P>0.1$) differences were observed between healthy and diseased camels in serum calcium and phosphorous.

Discussion

Malignant cutaneous neoplasms have been described in dromedary camel and llama [4, 24, 36,37]. According to our field experience, toe tumors are the most common cutaneous tumors observed in dromedary camels. In the literature, there is no previous data on the hematological and serum biochemical values of toe tumor in camels. In the present study, three histologic types of toe tumors were documented in camels, namely, squamous cell carcinoma (76%), fibroma (21%) and spiny keratoderma (3%). Hematological and chemical analysis of blood are valuable diagnostic tools that can help in the differentiation between healthy and affected animals [31]. In general, the hematological and biochemical values can serve as a baseline information for comparison between physiological and disease processes [3, 30]. The blood picture is a mirror image of the health status of animals and may offer an opportunity to investigate the presence of different metabolites and other biologic constituents in animals, providing a vital role in the assessment of physiological, nutritional and pathological status of animals [14]. In this study, we have shown a significant increase in the levels of leukocytes particularly neutrophil polymorphs in camels affected with toe tumor, which might be due to host's response to tissue damage secondary to inflammation or invasion by squamous cell carcinoma [9,10]. Other factors such as excitement, fright, pain, exercise and anxiety are also known to cause leukocytosis and neutrophilia [38]. Leukocyte migration is a key event in the inflammatory response to tumors. Moreover, neutrophil polymorphs counts are significantly higher in SCC than fibroma and spiny keratoma suggesting an important role of SCC on neutrophil polymorph count. Squamous cell carcinoma releases specific chemokines that control migration of neutrophil polymorphs and functions of these cells after their arrival at the tumor site [27]. Neutrophilia in SCC, although non-specific, can also be in response to infection, inflammation or tissue necrosis. Production and release of neutrophils from the bone marrow are expected to be increased to compensate for the increased demand [2, 5]. We also observe significant lower lymphocyte counts in camels affected by toe tumors than healthy controls. Interestingly, lymphocytes counts are significantly lower in SCC than fibroma and spiny keratoma suggesting that SCC plays an important role on Lymphopoiesis. The cause of lymphocytopenia in SCC has not been fully elucidated. It has been proposed that lymphocytopenia might be due to SCC-induced T-cell apoptosis by Fas/FasL pathway. In addition, overexpression of tumor antigens will lead to tenacious polyclonal activation of lymphocytes which leads to their apoptosis [15, 21, 22]. Lymphocytopenia, which develops in SCC in the present study, might also be related to the immune suppression caused by SCC. Anosa et al. [6] reported intense antigenic stimulations will increase the demands for lymphocytes to be transformed into plasma cells which can also contribute to lymphocytopenia. An elevated neutrophil to lymphocyte ratio has been shown to be an independent prognostic factor for

cancers at various different sites, suggesting that this parameter is a clinically accessible and useful biomarker for patient survival [10]. A significant monocytosis was observed in camels affected by toe tumors and might be related to long-term inflammation caused by toe tumors. A significant higher eosinophil count was also observed in camels affected by toe tumors. Eosinophil chemotactic factors can be produce by SCC leading to increased eosinophil count in peripheral blood [28]. Although RBC and HGB values are within normal range in healthy and diseased camels, there is no definite explanation for the significant higher values of RBC and HGB in toe tumor cases than healthy controls, but the possible contributing factors may be related to the enhanced production of erythropoietin by toe tumors [1, 19, 22, 23]. It is possible that hypoxic microenvironment in SCC can stabilize hypoxia inducible factor-1 α which will stimulate transcription of erythropoietin [7, 20]. It is possible that the significant increase in PCV in camels with toe tumors can be due to haemoconcentration.

The significant decrease in glucose levels in camels affected by toe tumors might be due to decreased appetite or starvation resulted from tumor stress. Tumor-bearing animals have a consistent tendency toward hypoglycemia due to insufficient gluconeogenesis or increased concentrations of insulin-like growth factor II (IGF-II) or liver dysfunction [13, 18, 19, 26]. Interestingly, inulin –like growth factor has been identified in cutaneous SCC and might be related to the associated hypoglycemia in camels affected by SCC [26]. Hypoglycemia in SCC, although non-specific, can be valuable in following –up camels with SCC and monitoring their reponse to treatment. The hypoproteinemia and hypoalbuminemia that have been observed in diseased camels could be related to the seepage of protein and albumin through exudation as a result of tissue damage caused by tumor or decrease synthesis of protein and albumin due to decreased intake of proteins. Hypoproteinemia and hypoalbuminemia can result from protein loss caused by anorexia/starvation or hemorrhage [8]. We also show significant higher serum values of CK and LDH in camels affected by toe tumors possibly due to secondary tissue necrosis and inflammation [12, 33]. CK is a useful marker for skeletal muscle or cardiac muscle damage. The increase in CK and LDH in camels with toe tumors can be due to skeletal muscle damage by tumor pressure or invasion [11]. The significant increase in BUN and creatinine levels in toe tumor camels in comparison to healthy controls may be attributed to renal dysfunction resulted from prolong inappetence and dehydration. Worldwide, limited data are available to show the association of tumors with serum level of electrolytes and trace elements [16, 40]. The decreased iron level observed in the present study is in agreement with the finding of Kazmierski et al. [25], who found serum iron concentrations and total iron-binding capacity significantly lower in dogs with lymphoma and osteosarcoma when compared to normal dogs. Extensive studies investigating the role of copper in cancer have been carried out [32]. The resulted increase copper level in the present study shows an association of copper with toe tumors in camels. This observation was in agreement with Goyal et al. [17] and Trupti et al. [39]. The exact mechanism of hypercupremia in malignancy is unclear. Neoplastic growth seems to interfere with normal processes regulating the serum level of ceruloplasmin, a copper-containing oxidase, which accounts for 96% of serum copper [39]. Copper is believed to be the switch that turns on angiogenesis in cancer by activating growth factors [39]. The serum level of copper is often elevated in animals and humans with cancer. It appears that this elevation of serum copper that occurs as a part of the body's response to the cancer, rather than its cause [39].

In conclusion, a hematological and biochemical data base for toe tumors has been established. Toe tumors and in particular SCC, which is the predominant cause of toe tumors in our study, is associated with leukocytosis, neutrophilia, lymphocytopenia, monocytosis, eosinophilia, basophilia, hypoglycemia, hypoproteinemia, hypoalbuminemia, and increased levels of CK, LDH, ALP and copper. Neutrophilia, lymphocytopenia, hypoglycemia, and increased levels of CK, and ALP can be valuable assays in following –up camels with SCC and monitoring their response to treatment.

Conflict of Interest

There is no conflict of interest.

TABLES

Table 1: Hematological values in camels with toe tumors and healthy controls

Parameters	Unit	P-value	Camel status (No.)		
			Camels found affected with toe tumor (150)		Healthy camels (150)
			SCC (124)	Other tumor type (36)	
Packet cell volume	%	P < 0.001	32.39±1.07	32.75±1.71	27.34±0.9
Hemoglobin	g/dl	P < 0.001	14.14±0.55	14.42±0.89	12.19±0.48
Red blood cell count	106µl	P < 0.05	9.55±0.39	9.11±0.63	8.61±0.35
Mean corpuscular volume	fl	P < 0.001	34.96±0.68	34.57±1.10	29.17±0.60
Mean corpuscular hemoglobin	pg	P < 0.001	14.36±0.31	15.75±0.49	13.42±0.27
White blood cells count	/µL	P < 0.0001	16546 ± 361	16322 ± 646.8	10508 ± 262.5
Neutrophils	/µL	P < 0.0001	12742 ± 282	9882 ± 472.5	4584 ± 150.5
Lymphocytes	/µL	P < 0.0001	2059 ± 77.81	3278 ± 194.8	2707 ± 117.7
Monocytes	/µL	P < 0.0001	1035 ± 35.60	926.2 ± 45.51	440.5 ± 14.36
Eosinophils	/µL	P > 0.0001	711.0 ± 46.8	662.0 ± 75.33	315.3 ± 18.62
Basophils	/µL	P > 0.0001	164.8 ± 12.25	197.9 ± 37.70	102.9 ± 3.997

Table 2: Serum biochemical values in camels with toe tumors and healthy controls

Parameters	Unit	P-value	Camel status (No.)		
			Camels with Toe tumor (150)		Healthy camels (150)
			SCC (124)	Fibroma & Spiny keratoderma (36)	
Glucose	mg/dl	P < 0.0001	60.52±13.93	75.00±8.45	98.94 ± 2.325
Blood urea nitrogen	mg/dl	P < 0.001	16.37±1.82	14.64±2.84	12.10±1.63
Creatinine	mg/dl	P < 0.05	1.38±0.10	1.52±0.16	1.48±0.09
Albumin	g/dl	P < 0.0001	2.17±0.15	2.04±0.24	3.15±0.13
Creatinine-kinase	IU/I	P < 0.001	178.1 ± 5.117	138.1 ± 4.434	92.37 ± 3.924
Gamma-glutamyle transferase	IU/I	P > 0.1	14.43±0.81	15.86 ± 1.612	15.89 ± 0.506
Lactate dehydrogenase	IU/I	P < 0.0001	617.0 ± 16.12	628.4 ± 26.21	516.1 ± 12.01
Total protein	g/dl	P < 0.0001	4.934 ± 0.036	4.933 ± 0.0895	5.949 ± 0.0537
Aspartate aminotransferase	IU/I	P > 0.1	77.53 ± 2.164	84.31 ± 4.681	81.38 ± 2.113
Alkaline phosphatase	IU/I	P < 0.0001	127.14±8.17a	77.16±11.36	64.55±8.62
Alanine aminotransferase	IU/I	P < 0.0001	11.86±0.78a	8.33±1.37b	7.58±0.89b

Table 3: Serum minerals and electrolytes values in camels with toe tumors and healthy controls

Parameters	Unit	P-value	Camel status (No.)		
			Camels with Toe tumor (150)		Healthy camels (150)
			SCC (124)	Fibroma & Spiny keratoderma (36)	
Iron	ug/dl	P < 0.05	73.17±9.98	70.33±16.06	95.56±8.73
Sodium	mmol/l	P < 0.05	151.68±2.67	149.55±4.28	145.71±2.38

Potassium	mmol/l	P < 0.001	5.86±0.36	6.15±0.54	4.51±0.30
Phosphorus	mg/dl	P > 0.1	5.68±0.50	5.80±0.81	5.27±0.44
Calcium	mg/dl	P > 0.1	9.17±0.46	10.60±0.74	9.06±0.40
Chloride	mmol/l	P < 0.001	112.91±0.92	108.92±1.46	115.05±0.81
Copper	ug%	P < 0.0001	91.52±3.82	84.53±5.11	64.13±3.58

Figures legends

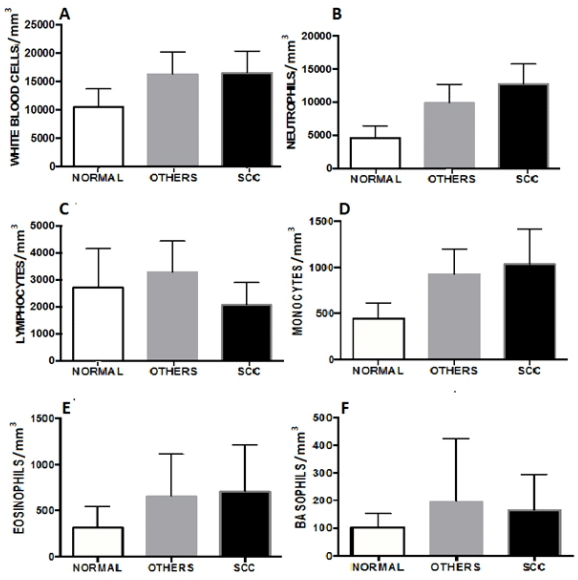

Figure 1: Absolute counts of white blood cells, neutrophil polymorphs, lymphocytes, monocytes, eosinophils, and basophils in camels affected by squamous cell carcinoma, others (fibroma and spiny keratoderma) compared with normal controls.

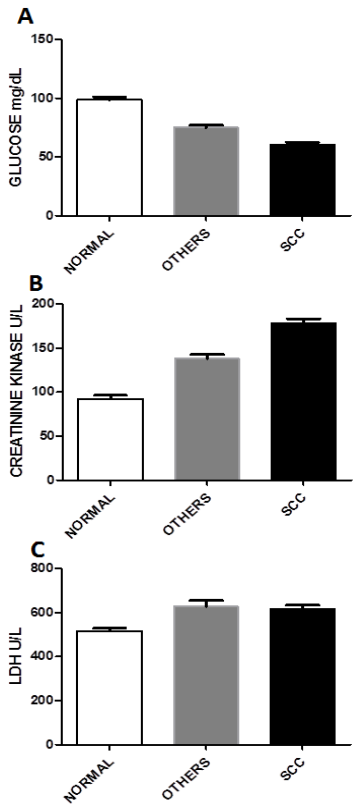

Figure 2: Comparison of serum values of glucose, lactic dehydrogenase, and creatine kinase between camels affected by squamous cell carcinoma, others (fibroma and spiny keratoderma) and normal controls.

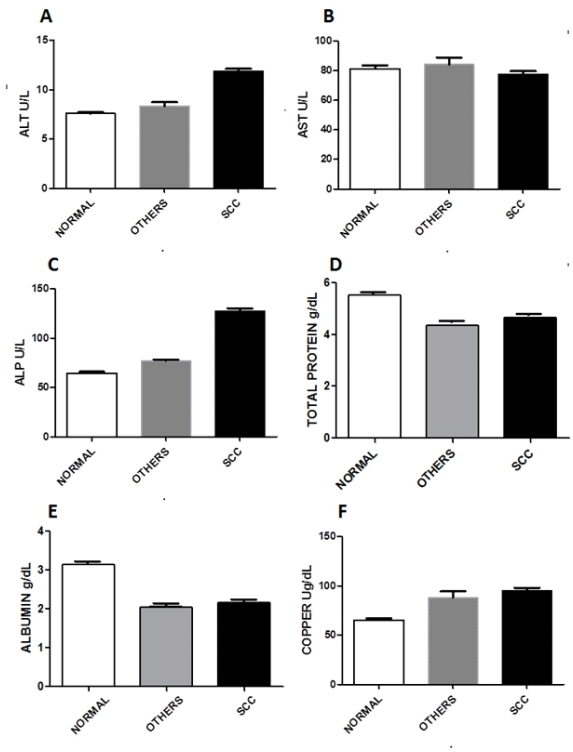

Figure 3: Comparison of serum values of alanine transaminase, aspartate transaminase, alkaline phosphates, total protein, albumin, and copper between camels affected by squamous cell carcinoma, others (fibroma and spiny keratoderma) and normal controls.

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