Decrease of E-Cadherin Expression in Canine Cutaneous Histiocytoma Appears to be Related to its Spontaneous Regression

ISABEL PIRES[1], FELISBINA LUISA QUEIROGA[1], ANABELA ALVES[1], FILIPE SILVA[2] and CARLOS LOPES[3]

[1]CECAV and [2]Veterinary Teaching Hospital, Department of Veterinary Sciences, University of Trás-os-Montes and Alto Douro, 5000-911, Vila Real; [3]Institute of Biomedical Sciences Abel Salazar (ICBAS), Largo Prof. Abel Salazar, 4099-003 Porto, Portugal

Abstract. *Background: Canine cutaneous histiocytoma (CCH) is an epidermotropic tumour of Langerhans cells, most frequent in young dogs, which undergoes spontaneous regression. Materials and Methods: E-cadherin immuno-expression was analysed in ninety-three CCH, categorized according to Cockerell and Slauson (1976) criteria into four histological groups, representing different stages of tumour regression. Results: All tumours expressed membranous E-cadherin both in keratinocytes, and in tumoural cells and no differences were noted among the histological groups analysed. However, the intensity of the E-cadherin immunolabeling decreased in the presence of lymphoid infiltration and varied significantly among the groups considered ($p<0.0001$). Conclusion: This study strongly suggests a down-regulation of E-cadherin expression in CCH pathogenesis and progression. The loss of E-cadherin expression might represent an activation/ maturation process of the tumoural cells constituting a switch for CCH regression.*

Canine histiocytic proliferative disorders include lesions such as canine cutaneous histiocytoma (CCH), a common and usually solitary, benign neoplasm that appears as a rapidly growing, alopecic, erythematous, dome-shaped nodule, often with ulceration (1-4). In a five-year retrospective study, performed in the Laboratory of Histopathology, University of Trás-os-Montes and Alto Douro, CCH represented 29.4% of all dog skin and soft tissue mesenchymal tumours (5). The disease affects mostly young dogs, between 6 months and 3 years of age; the incidence falls strikingly in older animals (1-4, 6).

Correspondence to: Felisbina Luisa Queiroga, Department of Veterinary Sciences. University of Trás-os-Montes and Alto Douro, 5000-911 Vila Real, Portugal. Tel: +351 917826982, Fax: +351 259350480, e-mail: fqueirog@utad.pt

Key Words: Canine cutaneous histiocytoma, E-cadherin, immuno-histochemistry, tumour regression.

Immunophenotype and ultrastructural studies have confirmed that CCH is a proliferation of intraepidermal dendritic antigen-presenting cells, also called Langerhans cells, that express CD1a, CD1b, CD1c, major histocompatibility complex (MHC) class II and CD11c (7-10).

Although the rapid growth and high mitotic index suggest malignancy, CCH is a benign tumour in all aspects: it does not metastasise and spontaneous regression (within a few weeks or months) is the natural course of the disease (11). This regression seems to be associated with an initial infiltration of $CD4^+$ T-cells, followed by an increased expression of T-helper subset 1 (Th1) cytokines and recruitment of antitumour effector cells (12) and appears to be related to a change of CCH cell phenotype, with an increased membranous expression of MHC class II antigen molecules (13).

E-cadherin is a transmembranous glycoprotein, a member of a family of calcium-dependent homophilic cell–cell adhesion molecules that bind to cytoskeleton proteins through catenins (14, 15). Down-regulation of E-cadherin expression often results in tissue disorder, disturbed cellular differentiation, increased invasiveness of tumour cells and ultimately malignancy in animal and human epithelial tumours (16-20).

Immunoexpression of E-cadherin in CCH was described very recently (2008) by Baines (21) and Pires (22). Nevertheless, its implication in histiocytoma regression has not yet been clarified.

The purpose of this study was to evaluate E-cadherin expression in different stages of tumour regression, based on the lymphoid inflammatory infiltrate degree, in order to clarify if there is a link between E-cadherin expression and CCH regression.

Materials and Methods

Tissue processing and tumour classification. Ninety-three cases of CCH and ten normal canine skin samples, obtained from the UTAD Histopathology Laboratory archives were included in this study. Each sample was re-examined by two independent pathologists (IP and AA) in order to confirm the diagnosis, according to the World

Table I. *Classification of CCH into four histological groups according to the degree and distribution of the lymphocytic infiltration (adapted from (24)*.

Group	Degree of lymphocytic infiltration	Distribution of lymphocytic infiltration	n
I	None to minimal	Diffuse at the periphery	15
II	Moderate	Nodular infiltrates at the periphery	15
III	Marked	Nodular infiltrates central and peripheral	42
IV	Greater than tumour cell population	Nodular and diffuse along tumour	21

Health Organization International Histological Classification of Tumours of Domestic Animals criteria (23). Histiocytomas were also grouped according to the degree and pattern of intratumoural lymphocytic infiltrate into four groups, as described elsewhere (24), representing diverse stages of tumour regression (Table I).

Immunohistochemistry. For immunohistochemical studies, 3-μm sections were cut from each specimen and mounted on silane-coated slides. The detection of E-cadherin was carried out by the streptavidin-biotin-peroxidase complex method, with a commercial detection system (Ultra Vision Detection System; Lab Vision Corporation, Fremont, USA) following the manufacturer's instructions. Antigen retrieval was carried out by micro-wave treatment in a 0.05% detergent solution (Extran; Merck, Frankfurt, Germany) at pH 6, with microwave irradiation (750 W) for 3×5 minutes. A monoclonal mouse anti-E-cadherin antibody (4A2C7; Zymed Laboratory, San Francisco, USA) which in previous studies had shown reactivity with canine species (22, 25) was used as primary antibody. The incubation was performed overnight, at a dilution of 1:150 in phosphate-buffered saline (PBS) solution. Immunoreaction was visualized by incubation with 13,3-diaminobenzidinetetrahydrochloride (DAB) at 0.05% with 0.01% H_2O_2 as the final substrate for 5 minutes. After a final washing in distilled water, the sections were counterstained with haematoxylin, dehydrated, cleared and mounted. The primary antibody was replaced with PBS for negative controls and positive controls consisted of sections from normal canine skin and from skin adjacent to neoplastic tissue.

Quantification of immunolabelling. Positivity was indicated by the presence of distinct brown labelling. Immunoreactivity was evaluated blind by two pathologists using a semiquantitative method, according to the percentage of immunoreactive cells scored as: 0, negative; 1, <25% positive cells; 2, 25-50% positive cells; 3, >50% positive cells, with a membranous (cell–cell boundaries) pattern of cellular distribution. The cytoplasmatic labelling was also reported. The intensity of reaction was also recorded as negative (–), weak (+), moderate (++) or strong (+++), as compared with the internal control (the epidermis).

Statistical analysis. Associations between histological groups and E-cadherin expression were investigated using the χ^2 test, with the SPSS system (version 12.0; SPSS Inc., Chicago, USA). A value of $p<0.05$ was considered significant.

Results

E-cadherin expression in normal skin. In all cases (n=10), the immunoreactivity for E-cadherin was membranous, diffuse and strong in cell–cell unions in the keratinocytes and in epithelial cells of the adnexal structures.

E-cadherin expression in the skin adjacent to the tumour. The immunoreactivity for E-cadherin in apparently normal skin adjacent to the tumour was evaluated in all the lesions (n=93). The immunolabelling pattern was similar to that described for the normal skin.

Semiquantitative evaluation (score) of E-cadherin expression in CCH. All the lesions analysed expressed E-cadherin in the tumour cell membrane. The majority of the cases (n=85; 91.4%) expressed E-cadherin in more than 50% of the tumoural cells (Figure 1). The percentage of E-cadherin-positive cells was similar among the different histological groups ($p=0.16$; Table II).

Intensity of E-cadherin expression in CCH. All the lesions expressed E-cadherin in the tumour cells at a lower intensity than in the keratinocytes. The intensity of reaction was not uniform in the tumoural cells, with a decrease of immunoexpression in the areas of the lymphocytic infiltrate. The intensity of reaction was significantly different among the different histological groups considered ($p<0.0001$).

In group I and group II, the cells of the epidermal surface and the cells of the centre of the lesion showed a moderate (++) reactivity to E-cadherin. However, the intensity decreased with depth, being weak or even absent in the bottom periphery of the tumour, except in one case in which the peripheral inflammatory infiltrate was very scarce.

In tumours of group III, where the lymphocytic infiltrate was more intense and diffuse, the intensity of reaction was predominantly weak (+), both in cells of the surface and the bottom of tumours.

In group IV, the tumour cells showed a weak intensity of reaction, except in one case that presented moderate intensity (Table II). In four cases, besides the membranous reaction, a weak and diffuse cytoplasmatic positivity was observed.

Discussion

The regression phenomena, so typical of this disease, makes CCH an attractive system for analysis of Langerhans cell histiocytosis behaviour and it could be regarded as an unique model to understand the pathogeny of the enigmatic disease of human Langerhans cell histiocytosis (7, 26).

Table II. *Imunoexpression of E-cadherin in the four histological groups.*

E-cadherin	Group I	Group II	Group III	Group IV	*p*-Value
Score					
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.116
2	0 (0.0)	3 (0.0)	2 (4.8)	3 (14.3)	
3	15 (100)	12 (100)	40 (95.2)	18 (85.7)	
Intensity					
+	2 (13.3)	7 (46.7)	31 (73.8)	18 (95.2)	
++	13 (86.7)	8 (53.3)	11 (26.2)	1 (4.8)	<0.0001
+++	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

In the present study, ninety-three CCH were examined by immunohistochemistry for expression of E-cadherin. Although previous studies showed E-cadherin expression in CCH (21, 22), little is known about its role in tumour progression and regression.

All CCHs studied in this work expressed E-cadherin. However, unlike the results described by Baines *et al*. (21), in our study the immunolabelling was predominantly membranous both in tumour cells and in keratinocytes. In fact, E-cadherin is a transmembranous protein that constitutes the major adhesion molecule in *adherens* junctions and mediates the binding of Langerhans cells to keratinocytes (27-29). The membranous location of E-cadherin observed in our study is also supported by ultrastructural studies that revealed adherens junctions between the CCH tumour cells in the dermis, as we reported recently (22). This apparent contradiction between the results of Baines *et al*. (21) and ours could be related to the use of different primary antibodies that could recognize different domains of E-cadherin: cytoplasmic or extracellular, as described lately in human tumours (30, 31).

In the present study, the lesions were classified into four histological groups, representing diverse stages of tumour regression. No significant differences in the score for E-cadherin expression were found in the different groups. However, when we evaluated the E-cadherin immunolabelling intensity, the differences were significant. A decrease of E-cadherin intensity occurred with an increase of the lymphoid infiltrate. In contrast to epithelial tumours, in which a decrease or lack of E-cadherin expression is associated with invasion and metastasis (19, 32-34), in CCH this phenomena seems to be associated with tumour regression.

The work of Baines *et al*. (21) on E-cadherin expression in 37 CCHs does not report a variation in the E-cadherin intensity. To our knowledge, this is the first study where this characteristic is described. Interestingly, a similar reduction of E-cadherin occurs in normal Langerhans cells in the inflammatory response. The migration of Langerhans cells from the epidermis to the dermis and lymph nodes, induced by contact allergens and proinflammatory cytokines, is associated with a decrease of E-cadherin messenger ribonucleic acid (mRNA) and its synthesis. This decrease with consequent loss of connection between Langerhans cells and keratinocytes is one of the first events in the skin immune response leading to Langerhans cell activation, facilitating their emigration and the initiation of immune responses against antigens encountered in the epidermis (35, 36). Moreover, it has been speculated that E-cadherin-mediated signalling might suppress Langerhans cell maturation and maintain their immature state *in vivo* (37, 38). In canines, the histiocytoma tumoural cells seem to mimic normal Langerhans cells in an inflammatory environment that undergo an activation/maturation process. This maturation/activation and the interaction with lymphocytes might result in tumour regression and imply, most probably, many other pathways.

It has been proposed that during CCH regression a shift of MHC class II antigen distribution from the cytoplasm to the tumour cell surface occurs with increased infiltration of $CD3^+$ T-cells. However, this study includes only tumours of groups I and II, the tumours in an early regression process (13).

Canine cutaneous histiocytoma has similarities with some forms of human Langerhans cell histiocytosis. Nevertheless, Langerhans cells histiocytosis has distinct clinical behaviours in dogs and humans. In dogs, regression is the natural course of the process. In humans, the clinical picture of Langerhans cell histiocytosis is greatly variable: a limited number of lesions undergo regression (39-42) and other lesions can disseminate and be potentially fatal (43-45). E-cadherin expression in human Langerhans cell histiocytosis is limited to localized forms. Dissemination of this disease and poor outcome may be related to the loss of functions mediated by E-cadherin (46). However, Kapur *et al*. (47) found a lack of E-cadherin expression both in cutaneous and disseminated forms of human Langerhans cells histiocytosis, which reflects the need to continue studies on this subject.

Despite the progress in investigation, the aetiology and pathogenesis of CCH remain unknown. However, our results lead us to speculate that a dysregulation of the E-cadherin or even the E-cadherin–β-catenin cascade could be a step in the pathogenesis of CCH, similar to what was proposed in human Langerhans cell histiocytosis. A careful regulation of this cascade is essential in normal Langerhans cell activation (48) and abnormalities in the E-cadherin–β-catenin cascade are a major cause of epithelial neoplastic proliferation (49-52). Nevertheless, further studies involving β-catenin are needed to clarify this possible implication. Additionally, heterotypic adhesive interactions between epithelial cells and intraepithelial lymphocytes *in vitro* are mediated by E-cadherin and its interaction with αEβ7 intraepithelial lymphocyte integrin. This interaction could have a functional relevance for the control of skin local immune response (46, 53) and perhaps in Langerhans cell pathology.

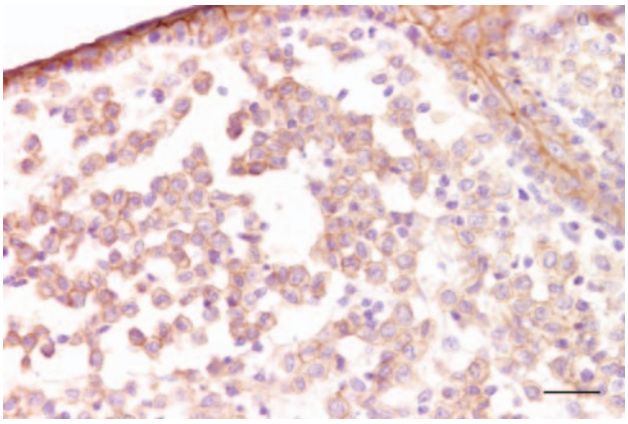

Figure 1. *Predominant membranous moderate immunoreactivity for E-cadherin in a group I canine cutaneous histiocytoma. Bar=30 μm.*

Since E-cadherin expression in dendritic cells is limited to the Langerhans cells, the presence of this molecule in CCH tumoural cells might be one indication of a Langerhans cell ontogeny, as suggested by others (7, 54). The expression of this molecule should be considered as a useful diagnostic tool for formalin-fixed tumours.

Furthermore, E-cadherin expression and the existence of adherens junctions between CCH tumoural cells might also suggest a high degree of differentiation and might support the benign behaviour of this tumour.

In conclusion, all the CCHs studied here immunoexpressed E-cadherin and this molecule could be related to tumour regression. This study strongly suggests that pathological Langerhans cells in CCH appear in an immature state in early lesions and undergo a maturation process characterized by a down-regulation of E-cadherin. In the regression lesions, these cells differentiate towards a mature phenotype and might themselves interact with lymphocytes. CCH appears as a dynamic lesion that changes its phenotype and determines its own regression.

Acknowledgements

We thank Mrs Lígia Bento for expert technical assistance.

References

1 Coomer AR and Liptak JM: Canine histiocytic diseases. Compend Contin Educ Vet *30*: 202-204, 2008.
2 Fulmer AK and Mauldin GE: Canine histiocytic neoplasia: an overview. Can Vet J *48*: 1041-1043, 2007.
3 Kelly DF: Canine cutaneous histiocytoma. A light and electron microscopic study. Pathol Vet *7*: 12-27, 1970.
4 Dobson JM, Samuel S, Milstein H, Rogers K and Wood JL: Canine neoplasia in the UK: estimates of incidence rates from a population of insured dogs. J Small Anim Pract *43*: 240-246, 2002.
5 Pires MA, Travassos FS and Pires I: Neoplasias em canídeos. Um estudo retrospectivo de 6 anos. RPCV *98*: 111-118, 2003.
6 Scott DW, Miller WH and Griffin CE: Neoplastic and non-neoplastic tumors. *In*: Muller & Kirk's Small Animal Dermatology. 6th edition. Philadelphia, W.B. Saunders Company, pp. 1346-1355, 2001.
7 Moore PF, Schrenzel MD, Affolter VK, Olivry T and Naydan D: Canine cutaneous histiocytoma is an epidermotropic Langerhans cell histiocytosis that expresses CD1 and specific beta 2-integrin molecules. Am J Pathol *148*: 1699-1708, 1996.
8 Affolter VK and Moore PF: Canine cutaneous and systemic histiocytosis: reactive histiocytosis of dermal dendritic cells. Am J Dermatopathol *22*: 40-48, 2000.
9 Affolter VK and Moore PF: Localized and disseminated histiocytic sarcoma of dendritic cell origin in dogs. Vet Pathol *39*: 74-83, 2002.
10 Marchal T, Dezutter-Dambuyant C, Fournel C, Magnol JP and Schmitt D: Immunophenotypic and ultrastructural evidence of the Langerhans cell origin of the canine cutaneous histiocytoma. Acta Anat (Basel) *153*: 189-202, 1995.
11 Guvenc T, Haligur M, Orman MN and Haziroglu R: Mitosis and apoptosis in canine cutaneous histiocytoma and transmissible venereal tumour. Acta Vet Hung *50*: 315-321, 2002.
12 Kaim U, Moritz A, Failing K and Baumgartner W: The regression of a canine Langerhans cell tumour is associated with increased expression of IL-2, TNF-alpha, IFN-gamma and iNOS mRNA. Immunology *118*: 472-482, 2006.
13 Kipar A, Baumgartner W, Kremmer E, Frese K and Weiss E: Expression of major histocompatibility complex class II antigen in neoplastic cells of canine cutaneous histiocytoma. Vet Immunol Immunopathol *62*: 1-13, 1998.
14 Harrington KJ and Syrigos KN: The role of E-cadherin–catenin complex: more than an intercellular glue? Ann Surg Oncol *7*: 783-788, 2000.
15 Suzuki SC and Takeichi M: Cadherins in neuronal morphogenesis and function. Dev Growth Differ *50*: S119-130, 2008.
16 Takeichi M: Cadherin cell adhesion receptors as a morphogenetic regulator. Science *251*: 1451-1455, 1991.
17 Gooding JM, Yap KL and Ikura M: The cadherin–catenin complex as a focal point of cell adhesion and signalling: new insights from three-dimensional structures. Bioessays *26*: 497-511, 2004.
18 Behrens J, Mareel MM, Van Roy FM and Birchmeier W: Dissecting tumor cell invasion: epithelial cells acquire invasive properties after the loss of uvomorulin-mediated cell–cell adhesion. J Cell Biol *108*: 2435-2447, 1989.
19 De Matos AJ, Lopes CC, Faustino AM, Carvalheira JG, Rutteman GR and Gartner F: E-cadherin, beta-catenin, invasion and lymph node metastases in canine malignant mammary tumours. APMIS *115*: 327-334, 2007.
20 Zhong LP, Li J, Zhang CP, Zhu HG, Sun J, Zhang ZY: Expression of E-cadherin in cervical lymph nodes from primary oral squamous cell carcinoma patients. Arch Oral Biol *52*: 740-747, 2007.
21 Baines SJ, McInnes EF and McConnell I: E-cadherin expression in canine cutaneous histiocytomas. Vet Rec *162*: 509-513, 2008.
22 Pires I, Alves A, Rodrigues P, Queiroga FL and Lopes CS: E-cadherin expression in canine cutaneous histiocytoma. Vet Rec *163*: 59-60, 2008.
23 Hendrick MJ, Mahaffey EA, Moore FM, Vos JH and Walder EJ: Tumors of Vascular Tissue. Histological Classification of Mesenchymal Tumors of Skin and Soft Tissues of Domestic Animal. Washington: AFIP, pp. 22-24, 2008.

24 Cockerell GL and Slauson DO: Patterns of lymphoid infiltrate in the canine cutaneous histiocytoma. J Comp Pathol *89*: 193-203, 1979.
25 Gama A, Paredes J, Gartner F, Alves A and Schmitt F: Expression of E-cadherin, P-cadherin and beta-catenin in canine malignant mammary tumours in relation to clinicopathological parameters, proliferation and survival. Vet J *177*: 45-53, 2008.
26 Marchal T, Saint-Andre I, Magnol JP, Dezutter-Dambuyant C and Schmitt D: Dendritic cells in dogs and cats: models of study in human pathology. Pathol Biol (Paris) *43*: 910-920, 1995 (in French).
27 Tang A, Amagai M, Granger LG, Stanley JR and Udey MC: Adhesion of epidermal Langerhans cells to keratinocytes mediated by E-cadherin. Nature *361*: 82-85, 1993.
28 Jakob T, Brown MJ and Udey MC: Characterization of E-cadherin-containing junctions involving skin-derived dendritic cells. J Invest Dermatol J *112*: 102-108, 1999.
29 Blauvelt A, Katz SI and Udey MC: Human Langerhans cells express E-cadherin. J Invest Dermatol *104*: 293-296, 1995.
30 Chetty R, Serra S and Asa SL: Loss of membrane localization and aberrant nuclear E-cadherin expression correlates with invasion in pancreatic endocrine tumors. Am J Surg Pathol *32*: 413-419, 2008.
31 Chetty R and Serra S: Nuclear E-cadherin immunoexpression: from biology to potential applications in diagnostic pathology. Adv Anat Pathol *15*: 234-240, 2008.
32 Morell-Quadreny L, Rubio J, Lopez-Guerrero JA, Casanova J, Ramos D, Iborra I, Solsona E and Llombart-Bosch A: Disruption of basement membrane, extracellular matrix metalloproteinases and E-cadherin in renal cell carcinoma. Anticancer Res *23*: 5005-5010, 2003.
33 Chu YQ, Ye ZY, Tao HQ, Wang YY and Zhao ZS: Relationship between cell adhesion molecules expression and the biological behavior of gastric carcinoma. World J Gastroenterol *14*: 1990-1906, 2008.
34 Mitselou A, Ioachim E, Peschos D, Charalabopoulos K, Michael M, Agnantis NJ and Vougiouklakis T: E-cadherin adhesion molecule and syndecan-1 expression in various thyroid pathologies. Exp Oncol *29*: 54-60, 2007.
35 Schwarzenberger K and Udey MC: Contact allergens and epidermal proinflammatory cytokines modulate Langerhans cell E-cadherin expression *in situ*. J Invest Dermatol *106*: 553-558, 1996.
36 Cumberbatch M, Dearman RJ and Kimber I: Adhesion molecule expression by epidermal Langerhans cells and lymph node dendritic cells: a comparison. Arch Dermatol Res *288*: 739-744, 1996.
37 Fujita H, Asahina A and Tamaki K: Ligation of E-cadherin molecules on murine resident Langerhans cells inhibits their maturation and chemokine production. J Dermatol Sci *43*: 152-155, 2006.
38 Riedl E, Stockl J, Majdic O, Scheinecker C, Knapp W and Strobl H: Ligation of E-cadherin on *in vitro*-generated immature Langerhans-type dendritic cells inhibits their maturation. Blood *96*: 4276-4284, 2000.
39 McElligott J, McMichael A, Sangueza OP, Anthony E, Rose D and McLean TW: Spontaneous regression of Langerhans cell histiocytosis in a neonate with multiple bony lesions. J Pediatr Hematol Oncol *30*: 85-86, 2008.
40 Yamaguchi S, Oki S and Kurisu K: Spontaneous regression of Langerhans cell histiocytosis: a case report. Surg Neurol *62*: 136-140, 2004.
41 Jang KA, Ahn SJ, Choi JH, Sung KJ, Moon KC and Koh JK: Histiocytic disorders with spontaneous regression in infancy. Pediatr Dermatol *17*: 364-368, 2000.
42 Miller MJ, Lonardo EC, Greer RD, Bevan C, Edwards DA, Smith JH, Freman JJ: Variable responses of species and strains to white mineral oils and paraffin waxes. Regul Toxicol Pharmacol *2*: 55-68, 1996.
43 Bansal D, Marwaha RK, Trehan A, Gupta V and Varma N: Langerhans' cell histiocytosis: experience from a single center. Indian Pediatr *45*: 685-688, 2008.
44 Goyal R, Das A, Nijhawan R, Bansal D and Marwaha RK: Langerhans cell histiocytosis infiltration into pancreas and kidney. Pediatr Blood Cancer *49*: 748-750, 2007.
45 Terracciano L, Kocher T, Cathomas G, Bubendorf L and Lehmann FS: Langerhans cell histiocytosis of the stomach with atypical morphological features. Pathol Int *49*: 553-556, 1999.
46 Geissmann F, Emile JF, Andry P, Thomas C, Fraitag S, De Prost Y, Brousse N: Lack of expression of E-cadherin is associated with dissemination of Langerhans' cell histiocytosis and poor outcome. J Pathol *181*: 301-304, 1997.
47 Kapur P, Erickson C, Rakheja D, Carder KR and Hoang MP: Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease): ten-year experience at Dallas Children's Medical Center. J Am Acad Dermatol *56*: 290-294, 2007.
48 Leenen PJ and Egeler RM: Langerhans' cell histiocytosis is caused by dysregulation of the E-cadherin–beta-catenin cascade: a hypothesis. Immunol Cell Biol *77*: 460-467, 1999.
49 Beavon IR: The E-cadherin–catenin complex in tumour metastasis: structure, function and regulation. Eur J Cancer *36*: 1607-1620, 2000.
50 Wijnhoven BP, Dinjens WN and Pignatelli M: E-cadherin–catenin cell–cell adhesion complex and human cancer. Br J Surg *87*: 992-1005, 2000.
51 Nakamura E, Sugihara H, Bamba M and Hattori T: Dynamic alteration of the E-cadherin/catenin complex during cell differentiation and invasion of undifferentiated-type gastric carcinomas. J Pathol *205*: 349-358, 2005.
52 Wiseman SM, Masoudi H, Niblock P, Turbin D, Rajput A, Hay J, Filipenko D, Huntsman D and Gilks B: Derangement of the E-cadherin/catenin complex is involved in transformation of differentiated to anaplastic thyroid carcinoma. Am J Surg *191*: 581-587, 2006.
53 Cepek KL, Shaw SK, Parker CM, Russell GJ, Morrow JS, Rimm DL and Brenner MB: Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the αEβ7 integrin. Nature *372*: 190-193, 1994.
54 Marchal T, Dezutter-Dambuyant C, Fournel C, Magnol JP and Schmitt D: Electron microscopic study of canine cutaneous histiocytoma: a benign Langerhans cell tumor. Adv Exp Med Biol *378*: 549-551, 1995.

Received January 16, 2009
Revised March 17, 2009
Accepted April 2, 2009