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Characteristics of MHC antigen expression and tumor-infiltrating mononuclear cells in renal cell adenomas and carcinomas

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Summary. We compared the expression of major histocompatibility complex (MHC; HLA class I and II) antigens and the presence of tumor-infiltrating mononuclear cells presenting S100 protein (S100), CD68 antigen, or CD45RO antigen in formalin-fixed, paraffin-embedded tissue sections of 10 renal cell carcinomas and 9 renal cell adenomas using immunohistochemistry. The expression of ß2-microglobulin (B2MG) as an HLA class I antigen in all 10 cases (100%) and that of HLA-DR/α as an HLA class II antigen in 7 of 10 cases (70%) of carcinoma was stronger than that in the adjacent proximal convoluted tubule, but was respectively not different to weaker in 8 of 9 cases and not different to markedly weaker in all cases of adenoma. Furthermore, there was comparatively dense infiltration by S100(+) antigen-presenting cells in the carcinomas, but almost none in the adenomas and generally dense infiltration by CD45RO(+) T cells and CD68(+) macrophages in the carcinomas, but little to none in the adenomas. We concluded that the generally enhanced expression of MHC antigens in carcinomas must be an immunophenotypic deviation from not only the adjacent proximal convoluted tubule but also adenomas, and that the predominant infiltration of antigen-presenting cells, T cells and macrophages in the carcinomas, but not in the adenomas, reflects the anti-cancer immune reaction

Key words: MHC antigen, HLA class I and II antigens, Tumor-infiltrating mononuclear cell, Renal cell adenoma, renal cell carcinoma, Immunohistochemistry

Introduction

Class I HLA-A, -B, -C antigens are expressed by most somatic cells and are fundamental to the recognition of foreign antigens by T cells (Bjorkman et al., 1987; Dasgupta et al., 1987). Class II HLAD/DR, DP, DQ antigens play an important role in the regulation of the immune response to T-cell dependent antigens as key antigens in the T to B and T to T cell recognition process that is the basis of the immune response network (Winchester and Kunkel, 1979). The distribution of HLA class I antigens in normal tissues of non-lymphoid origin have been examined (Natali et al., 1984). HLA class II antigens have a more restricted tissue distribution than HLA class I antigens and are normally presented on the surface of B cells, tumor-infiltrating mononuclear cells such as activated T cells, monocytes/macrophages and antigen-presenting dendritic cells, endothelial cells, and some epithelial tissue (Daar et al., 1984; Edwards, 1985). In the renal epithelial tissue, HLA class I and II antigens are consistently expressed in the proximal convoluted tubule (Natali et al., 1984; Heinemann et al., 1987). The aberrant (enhanced or decreased) expression of HLA class II antigens in epithelial tumors has been reported (Edwards, 1985; Stefanini et al., 1989; Banner et al., 1990). There have been many studies on the relationship between tumor prognosis and tumor-infiltrating mononuclear cells (Heinemann et al., 1987; Maruno et al., 1989; Stefanini et al., 1989; Banner et al., 1990; Furihata et al., 1992). However, to our knowledge, there have been no reports of an immunohistochemical observation of the intensity of MHC antigen expression and the density of tumor-infiltrating mononuclear cells in renal cell carcinomas, particularly in comparison to the adjacent proximal convoluted tubule and renal cell adenomas.

In this paper, we describe the generally enhanced expression of MHC antigen expression and comparatively dense presence of tumor-infiltrating mononuclear cells, particularly S100(+) cells (antigen-presenting cells) (Kapsenberg et al., 1986), CD68(+) cells (macrophages) (Pulford et al., 1989) and CD45RO(+) cells (subtypes of T cells including activated T cells of the helper/inducer subtype (Smith et al., 1986), in renal cell carcinomas, but not in renal cell adenomas, and discuss the anti-tumor immune reaction.

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Materials and methods

Samples, 2-4 mm thick, taken from sagittal halves of single kidneys fixed in 10% formalin solution from autopsy cases were embedded in paraffin, and each paraffin-embedded block was cut into 5 µm-thick tissue sections which were stained with haematoxylin-and eosin (H&E). We selected 9 out of 14 cases of renal cell adenoma (from 7 kidneys) found by microscopic observation of these H&E-stained sections. Regarding histological type, of the 9 adenomas, 2 cases (#3 and #4) were the granular cell/cystic papillary type and 7 cases were the granular cell/papillary type. Next we selected 10 cases of renal cell carcinoma from the surgical pathology files of Ehime University Hospital (8 cases) and the Matsuyama Adult Disease Center (2 cases). Of the 10 carcinomas, 7 cases (#1 to #7) were the clear cell/alveolar type, 2 cases (#8 and #9) were the granular/papillary type and 1 case (#10) was the granular cell/alveolar type. Regarding the tumor stage of the carcinomas, 1 case (#6) was T1, 7 cases were T2 and 2 cases (#5 and #9) were T3. Two cases (#9 and #10) showed a broad area of necrosis with innumerable infiltrates of neutrophil.

Immunostaining

Formalin-fixed and deparaffinized serial tissue sections 5µm thick were stained by the streptoavidin-biotin immunocomplex technique-alkaline phosphatase method (LsAB al-phos) using a commercial kit (DAKO Co., Santa Barbara, Cal, USA). Tissue sections were incubated in methanol/0.3% hydrogen peroxide solution for 30 minutes and then incubated in 10% normal goat serum for 30 minutes at room temperature. Primary antibodies were applied for 14 hours (overnight) in a refrigerator at 4 ºC, incubated with a biotin-linked second antibody, which was ß2-microglobulin (B2MG) (Bjorkman et al., 1987), HLA-DR/α (Epenetos et al., 1985), S100, CD68 (KP-1), or CD45RO (UCHL 1), for 10 minutes at room temperature, and incubated with HRP-labelled streptoavidin solution for 10 minutes at room temperature. Between each incubation the sections were rinsed 5 times for 5 minutes each in 0.05 M TRIS-buffered saline (pH 7.6). Immunoreactive sites were visualized with 3% AEC (3-amino-9-ethyl-carbazol)-hydrogen peroxide solution. Finally, the sections were counterstained with Meyer's haematoxylin solution for 10 seconds. As the negative control, normal rabbit serum was substituted for the primary antiserum. As the positive control, neighbouring normal proximal convoluted tubule was used for B2MG and HLA-DR/α, peripheral nerves for S100 and infiltrating inflammatory mononuclear cells for CD68 and CD45RO. The tissue sections for CD68 antigen only were digested with pepsin for 10 minutes before processing. The characteristics of the primary antibodies used are summarized in Table 1.

Grading the immunoreactivity of the lesions and the presence of tumor-infiltrating mononuclear cells

The degree of mean staining intensity of the lesions was estimated microscopically in comparison with that of the adjacent PCT as follows: 2-, markedly weaker; 1-, slightly to moderately weaker; +/-, no difference; 1+, slightly to moderately stronger; 2+, markedly stronger. The presence of immunostaining-positive mononuclear inflammatory infiltrates in and around the lesions was estimated by microscopy at x100 as follows: 0, none; +/-, very few (no more than 3 infiltrates); 1+, a few (4 to 19 infiltrates); 2+, many (more than 20 but numerable infiltrates); 3+, innumerable.

Results

Intensity of HLA class I (ß2-microglobulin) and HLA Class II (HLA-DR/α) expression (Table 2)

As is shown in Table 2, in the 9 cases of adenoma, B2MG expression was stronger in 1 (case #1), weaker in 2 (cases #6 and 9), and not different in 6 (Fig. 1a); HLA-DR/α expression was weaker in 3 (cases #3, 5 and 6), markedly weaker in 3 (cases #4, 7 and 8) (Fig. 1b), and not different in 3 (cases #1, 2 and 9). In the 10 cases of carcinoma, B2MG expression was markedly stronger in 9 cases (Fig. 2a) and stronger in 1 (case #1); HLA-DR/α expression was weaker in 2 (cases #1 and 6), markedly weaker in 1 (case #8), stronger in 7 (cases #2-5, 7 and 10) ((Fig. 2b) and markedly stronger in 1 (case #9).

Table 1. Characteristics of antibodies used.

ANTIGEN	ANTIGEN SOURCE	IMMUNE ANIMAL	POLY-/MONO-CLONAL	ANTIBODY CONCENTRATION (µg/ml)	COMMERCIAL SOURCE	STAINING METHOD
B2MG	Human	Rabbit	Poly.	10.0	DAKO	LsAb
HLA-DR/α	Human	Mouse	Mono.	19.8	DAKO	LsAB
S100	Cow	Rabbit	Poly.	Kit dilution x 10	Biomeda	LsAB
CD68	Human	Mouse	Mono.	19.0	DAKO	LsAB
CD45RO	Human	Mouse	Mono.	6.5	DAKO	LsAB

B2MG: ß2-microglobulin; LsAB: streptoavidin-biotin immunocomplex technique-alkaline phosphatase method.

Density of tumor-infiltrating mononuclear cells immunoreactive to HLA-DR/α, S100, CD68 or CD45RO (Table 2)

HLA-DR/α positive infiltrates (B cells, subtypes of T cells, monocytes/macrophages and antigen-presenting dendritic cells): very few in 3 (cases #1, 2 and 9), a few in 5 (Fig. 1b) and many in 1 (case #6) of the 9 cases of adenoma; very few in 2 (cases #7 and 8), many in 3 (cases #2, 3 and 6) and innumerable in 5 (Fig. 2b) of the 10 cases of carcinoma. S100-positive infiltrates (antigen-presenting dendritic cells, T-zone histiocytes): none in 5 (cases #1, 4, 5, 8 and 9) and very few in 4 (Fig. 3a) of the 9 cases of adenoma; very few in 6 (cases #2, 4, 7-10), a few in 1 (case #3) and many in 3 (cases #1, 5 and 6) (Fig. 4a) of the 10 cases of carcinoma. CD68-positive infiltrates (macrophages): none in 3 (cases #1, 5 and 9), very few in 4, a few in 1 (case #6) and many in 1 (case #7) (Fig. 3b) of the 9 cases of adenoma; many in 6 (Fig. 4b) and innumerable in 4 (cases #1, 4, 9 and 10) of the 10 cases of carcinoma. CD45RO-positive infiltrates (subtypes of T cells including activated T cells of the helper/inducer subtype): none in all 9 adenomas (Fig. 3c); and a few in 4 (cases #1, 3, 8 and 10), many in 5 and innumerable in 1 (case #5) (Fig. 4c) of 10 carcinomas.

Discussion

To date, there have been many studies concerning the expression of HLA class I and II antigens by tumor cells and the characteristics of inflammatory infiltrates for various types of carcinoma: renal cell carcinoma (Natali et al., 1984; Heinemann et al., 1987; Banner et al., 1990; Onishi et al., 1993); gastric carcinoma (Natali et al., 1984); laryngeal carcinoma (Eteban et al., 1990), hepatocellular carcinoma (Paterson et al., 1988);

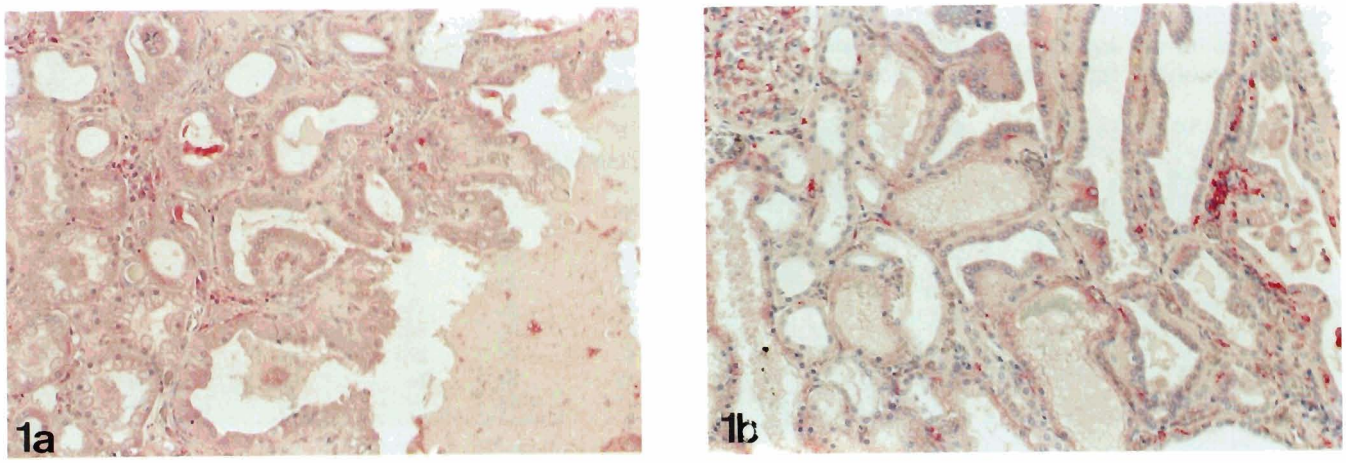


Fig. 1. Immunohistochemical stain for B2MG **(a)** and HLA-DR/α **(b)** of adenoma cells (case #7) showing no difference (a) and markedly weaker (b) in comparison to proximal convoluted tubules. Endothelial cells of blood vessels are strongly positive to HLA-DR/α and a few HLA-DR/α-positive infiltrates are seen (b). LsAB method-haematoxylin, x 50

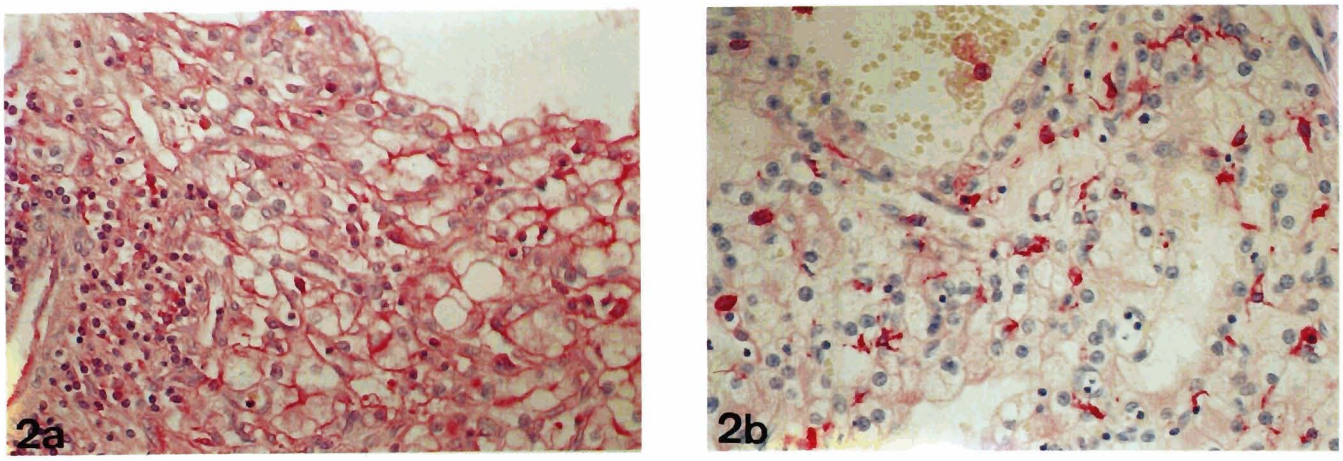


Fig. 2. Immunohistochemical stain for B2MG **(a)** and HLA-DR/α **(b)** of carcinoma cells (case #5) showing markedly stronger (a) and stronger (b) in comparison to proximal convoluted tubules. Endothelial cells of blood vessels are strongly positive to HLA-DR/α antigen and innumerable HLA-DR/α-positive infiltrates are seen (b). LsAB method-haematoxylin, x 100

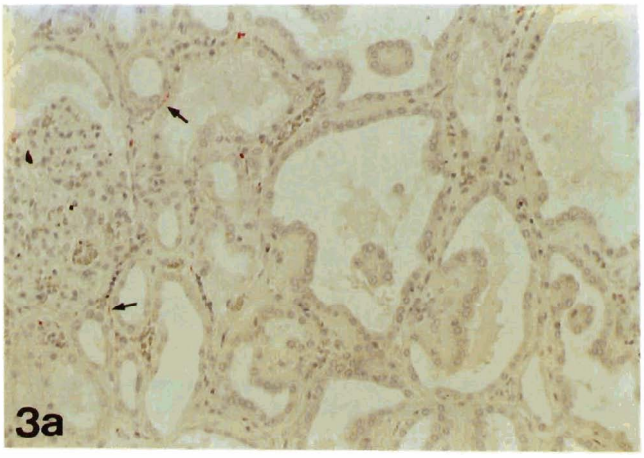
colorectal carcinoma (Van den Ingh et al., 1987); transitional cell carcinoma (Stefanini et al., 1989); esophageal squamous cell carcinoma (Furihata et al., 1982); and cervical squamous cell carcinoma (Glew et al., 1992). HLA class I antigens, which are presented in nearly all nucleated cells in man, are fundamental to the recognition of foreign antigens by T cells (Dasgupta et al., 1987). HLA antigen expression has been particularly studied in correlation with tumor prognosis (Schröder et al., 1988; Colloby et al., 1992; Furihata et al., 1992) in association with the presence of tumor-infiltrating mononuclear cells, such as S100(+) cells (Schröder et al., 1988; Ambe et al., 1989; Tsujitani et al., 1990; Furihata et al., 1992) or tumor-infiltrating lymphocytes (Onishi et al., 1993) or interleukin-2-receptor(+) cells (Maruno et al., 1989), in the tumor tissue, which may signal a favourable prognosis.

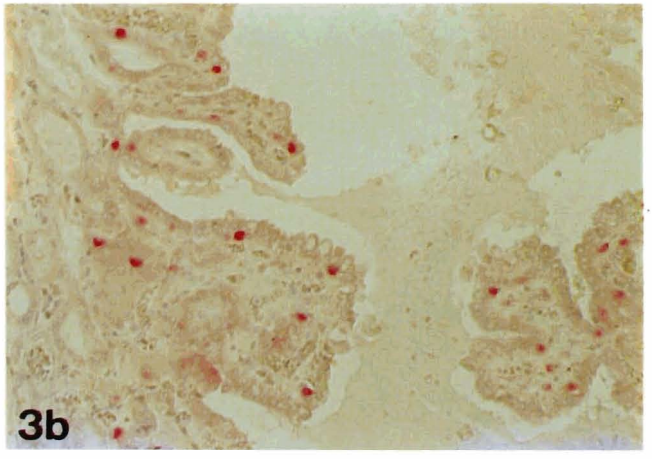
In our study, we examined the expression of HLA class I and II (B2MG and HLA-DR/α) antigens in comparison with that of the adjacent proximal convoluted tubule and the presence of three different immunophenotypic tumor-infiltrating mononuclear cells in renal cell adenomas and carcinomas, and considered the relationships between the findings. The origin of renal cell carcinomas and adenomas has been immunohistochemically confirmed to be the tubular epithelial cells lining the proximal convoluted tubule (Oosterwijk

Table 2. Intensity of major histocompatibility complex antigen (B2MG as HLA Class I and HLA-DR/α as HLA Class II) expression in comparison with adjacent proximal convoluted tubules and density of antigen-positive tumor-infiltrating mononuclear cells.

LESION	INTENSITY OF ANTIGEN EXPRESSION		DENSITY OF ANTIGEN-POSITIVE TIMC			
	B2MG	HLA-DR/α	HLA-DR/α	S100	CD68	CD45RO
Adenomas						
#1	1+	+/-	+/-	0	0	0
#2	+/-	+/-	+/-	+/-	+/-	0
#3	+/-	1-	1+	+/-	+/-	0
#4	+/-	2-	1+	0	+/-	0
#5	+/-	1-	1+	0	0	0
#6	1-	1-	2+	+/-	1+	0
#7	+/-	2-	1+	+/-	2+	0
#8	+/-	2-	1+	0	+/-	0
#9	1-	+/-	+/-	0	0	0
Carcinomas						
#1	1+	1-	3+	2+	3+	1+
#2	2+	1+	2+	+/-	2+	2+
#3	2+	1+	2+	1+	2+	1+
#4	2+	1+	3+	+/-	3+	2+
#5	2+	1+	3+	2+	2+	3+
#6	2+	1-	2+	2+	2+	2+
#7	2+	1+	+/-	+/-	2+	2+
#8	2+	2-	+/-	+/-	2+	1+
#9	2+	2+	3+	+/-	3+	2+
#10	2+	1+	3+	+/-	3+	1+

Intensity of B2MG (ß2-microglobulin) and HLA-DR/α expression and density of antigen-positive tumor-infiltrating mononuclear cells. Intensity: 2-, markedly weaker; 1-, weaker; +/-, no difference; 1+, stronger; 2+, markedly stronger. Density: 0, none; +/-, very few; 1+, a few; 2+, many; 3+, innumerable.





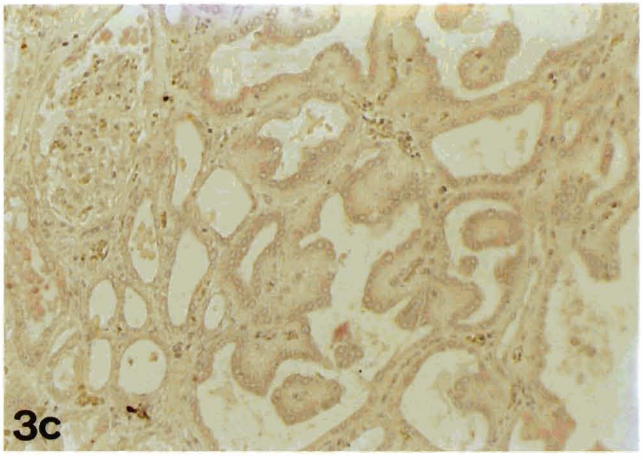


Fig. 3. Immunohistochemical stain for S100 **(a)**, CD68 **(b)** and CD45RO **(c)** of adenoma (case #7) in serial section of Figure 1. Infiltrates of S100(+) cells are very few, CD68(+) cells are many and CD45RO(+) cells are none. Nerve fibres (arrows) are strongly positive to S100 (a). LsAB method-haematoxylin, x 50

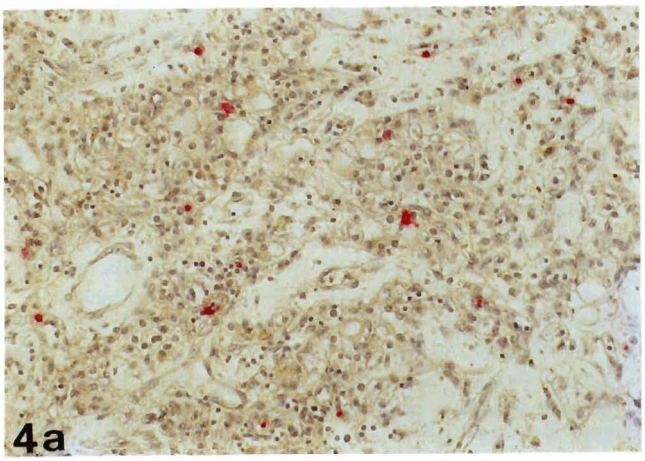
et al., 1986). Natali et al. (1984) examined the distribution of HLA class I antigen in normal and malignant tissues of nonlymphoid origin and reported that the proximal convoluted tubule and 9 out of 10 renal cell carcinomas expressed it. Heinemann et al. (1987) reported that HLA class I and II antigens were consistently expressed by the glomeruli and proximal convoluted tubule of the normal kidney, as was found in our study, but that in 10 carcinomas, the antigens were not present in 8, which had more tumor-infiltrating mononuclear cells, composed principally of macrophages, in the tumor tissue than the other 2 carcinomas, which did express the antigens and in which there were fewer tumor-infiltrating mononuclear cells, composed principally of T cells; they then suggested that the absence of HLA antigens on carcinoma cells mitigates attempts to potentiate the patient's immune response to the tumor. On the other hand, Banner et al. (1990) reported that tumor cells expressed B2MG (HLA class I antigen) in 4 of the 13 cases of carcinoma (30.8%) and HLA-DR (HLA class II antigen) in 9 of the 12 cases of carcinoma (75.0%) available for examination.

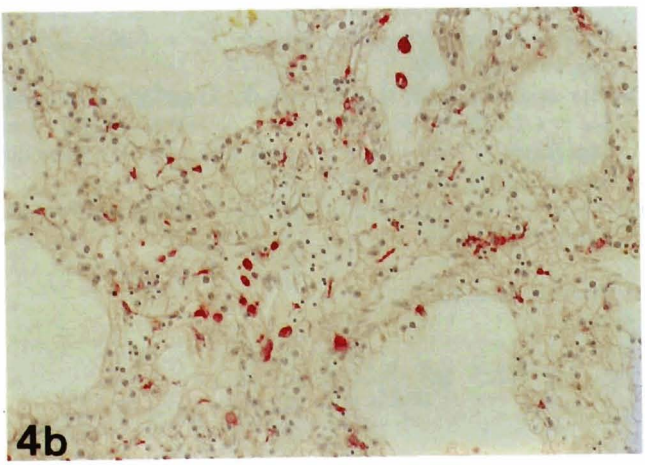
In each of the studies described above, the expression of MHC antigen in the proximal convoluted tubule was always observed, but in the carcinomas it was not, which may indicate enhanced or decreased expression in comparison with that of the adjacent proximal convoluted tubule. In addition, the observations of Banner et al. (1990) of HLA-DR expression and tumor-infiltrating mononuclear cells in carcinomas were similar to those of our study. That is, HLA-DR expression by tumor cells tended to correlate with increasing stage and grade, T-helper cells and monocytes infiltrated the carcinomas, but dendritic cells (antigen-presenting cells) were infrequent in carcinomas.

In our study, MHC antigen expression was generally stronger than that of adjacent proximal convoluted tubule in renal cell carcinomas but not in adenomas, and tumor-infiltrating mononuclear cells were generally dense in carcinomas but infrequent to absent in adenomas. That is, antigen-presenting (S100+) cells were comparatively dense in carcinomas but there were almost none in adenomas. Therefore, the markedly stronger MHC antigen expression, and generally/comparatively denser S100+, CD68+, and CD45RO+ tumor-infiltrating mononuclear cells in carcinomas than in adenomas must be significant. The marked infiltration in 2 cases of carcinoma (cases #9 and #10) by CD68(+) cells (macrophages) together with numerous neutrophils would indicate scavengers responding to the presence of tumor necrosis.

The report by Furihata et al. (1992) that esophageal squamous cell carcinomas with dense infiltration by HLA-DR antigen-positive and S100-positive dendritic cells suggest a good prognosis, is of much interest. In our study, the carcinomas exhibited a markedly enhanced expression of HLA class I and II antigens and generally dense infiltration of tumor-infiltrating mononuclear cells.

We concluded that, firstly, the enhanced expression of MHC (HLA class I and II) antigens, that is, B2MG





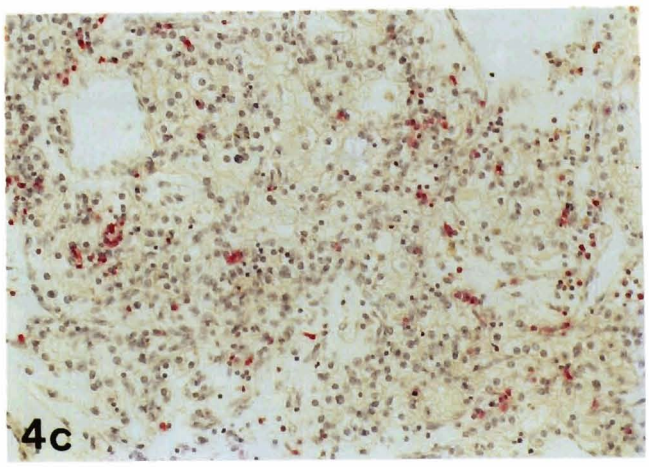


Fig. 4. Immunohistochemical stain for S100 **(a)**, CD68 **(b)** and CD45RO **(c)** of carcinoma (case #5) in serial section of Figure 2. Infiltrate of S100(+) cells and CD68(+) cells are many and CD45RO(+) cells are innumerable. LsAB method-haematoxylin. x 50

and HLA-DR/α, may be one of the characteristics of carcinomas, which may be associated with malignant transformation and, secondly, the comparatively dense infiltration of antigen-presenting cells in carcinomas may reflect its malignant biological behaviour and suggest a poor prognosis, whereas that never occurs in adenomas.

References

Ambe K., Mori M. and Enjoji M. (1989). S-100 protein-positive dendritic cells in colorectal adenocarcinomas. Cancer 63, 496-503.

Banner B.F., Burnham J.A., Bahnson R.R., Ernstoff M.S. and Auerbach H.E. (1990). Immunophenotypic markers in renal cell carcinoma. Modern Pathol. 3, 129-134.

Bjorkman P.J., Saper M.A., Samraoui B., Bennet W.S., Strominger J.L. and Wiley D.C. (1987). The foreign antigen binding site and T cell recognition regions of class I histocompatibility antigens. Nature 329, 506-512.

Colloby P.S., West K.P. and Fletcher A. (1992). Is poor prognosis really related to HLA-DR expression by malignant melanoma cells? Histopathology 20, 411-416.

Daar A.S., Fuggle S.V., Fabre J.W., Ting A. and Morris P.J. (1984). The detailed distribution of MHC class II antigens in normal human organs. Transplantation 38, 293-298.

Dasgupta J.D., Cernach K., Dubey D.P., Yunis E.J. and Amos D.B. (1987). The role of class I histocompatibility antigens in the regulation of T-cell activation. Proc. Natl. Acad. Sci. USA 84, 12094-1098.

Edwards P.A.W. (1985). Heterogeneous expression of cell-surface antigens in normal epithelia and their tumors, revealed by monoclonal antibodies. Br. J. Cancer 51, 149-160.

Epenetos A.A., Bobrow L.G., Adams T.E., Collons G.M., Isaacson P.G. and Bodmer W.F. (1985). A monoclonal antibody that detects HLA-D region antigen in routinely fixed, wax-embedded sections of normal and neoplastic lymphoid tissues. J. Clin. Pathol. 38, 12-17.

Eteban F., Ruiz-Cabello F., Conchas A., Perez-Ayala M., Sánchez Rozas J.A. and Garrido F. (1990). HLA-DR expression is associated with excellent prognosis in squamous cell carcinoma of the larynx. Clin. Exp. Metastas. 8, 319-328.

Furihata M., Ohtsuki Y., Ido E., Iwata J., Sonobe H., Araki K., Ogosahi S. and Ohmori K. (1992). HLA-DR antigen-positive and S-100 protein-positive dendritic cells in esophageal squamous cell carcinoma - their distribution in relation to prognosis. Virchows Arch. (B) 61, 409-412.

Glew S.S., Duggan-Keen M., Cabrera T. and Stern P.L. (1992). HLA class II antigen expression in human papilloma virus-associated cervical cancer. Cancer Res. 52, 4009-4016.

Heinemann D., Smith P.J.B. and Symes M.O. (1987). Expression of histocompatibility antigens and characterisation of mononuclear cell infiltrates in human renal cell carcinomas. Br. J. Cancer 56, 433-437.

Kapsenberg M.L., Teunissen M.B.M., Stiekema F.E.M. and Keizer H.G. (1986). Antigen-presenting cell function of dendritic cells and macrophages in proliferative T cell response to soluble and particulate antigens. Eur. J. Immunol. 16, 345-350.

Maruno K., Baba S., Muraki J., Jitsukawa S., Ueno M., Hata M., Tachibana M., Tazaki H. and Deguchi N. (1989). Immunologic study of human combinant inerleukin-2 (low-dose) in patients with advanced renal cell carcinoma. Urology 33, 219-225.

Natali G., Bigotti A., Nicotra M., Viola M., Manfredi D. and Ferroni S. (1984). Distribution of human class I (HLA-ABC) histocompatibility antigens in normal and malignant tissues of non-lymphoid origin. Cancer Res. 44, 4679-4687.

Onishi T., Machida T., Imagawa K., Tomoshige T., Nakagawa M. and Natori T. (1993). Assessment of biological characteristics in renal cell carcinoma through patterns of tumor-infiltrating lymphocytes. Cancer J. 3, 123-129.

Oosterwijk E., Ruiter D.J., Wakka J.C., Huiskens V.D., Meuj J.W., Jonas V., Fleuren G-J., Zwartendijk J., Hoedemaeker P. and Warnaar S.O. (1986). Immunohistochemical analysis of monoclonal antibodies to renal antigens. Application in the diagnosis of renal cell carcinoma. Am. J. Pathol. 123, 301-309.

Paterson A.C., Sciot R., Kew M.C., Callea F., Duskeiko G.M. and Desmet V.G. (1988). HLA expression in human hepatocellular carcinoma. Br. J. Cancer 57, 369-373.

Pulford K.A., Rigney E.M., Micklem K.J., Jones M., Stross W.P., Gatter K.C. and Mason D.Y. (1989). KP 1-a new monoclonal antibody that detects a monocyte/macrophage associated antigen in routinely processed tissue sections. J. Clin. Pathol. 42, 414-421.

Schröder S., Schwarz W., Rehpenning W., Löning T. and Böcker W. (1988). Dendritic/Langerhans cells and prognosis in patients with papillary thyroid carcinomas. Am. J. Clin. Pathol. 89, 295-300.

Smith S.H., Brown M.H., Rowe D., Callard R.E. and Beverley P.C.L. (1986). Functional subsets of human helper-inducer cells defined by a new monoclonal antibody UCHL 1. Immunology 58, 63-70.

Stefanini G.F., Bercovich E., Mazzeo V., Grigioni W.F., Emili E., D'Errico A., Lo Cigno M., Tanagnini N. and Mazzetti M. (1989). Class I and class II antigen expression by transitional cell carcinoma of the bladder: correlation with T-cell infiltration and BCG treatment. J. Urol. 141, 1449-1453.

Tsujitani S., Kakeji Y., Watanabe S., Kohnoe S., Maehara Y. and Sugimachi K. (1990). Infiltration of dendritic cells in relation to tumor invasion and lymph node metastasis in human gastric cancer. Cancer 66, 2012-2016.

Van den Ingh H.F., Ruiter D.J., Griffioen G., Van Muijen G.N.P. and Ferrone S. (1987). HLA antigens in colorectal tumors - low expression of HLA class I antigens in mucinous colorectal carcinoma. Br. J. Cancer 55, 125-130.

Winchester R.J. and Kunkel K.G. (1979). The human Ia system. Adv. Immunol. 28, 221-292.

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