

## Potential Utility of the Tumour Marker RCAS1 for Monitoring Patients with Invasive Extramammary Paget's Disease

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Sir,

Extramammary Paget's disease is a rare neoplasm that most commonly occurs in areas rich in apocrine glands, such as the anogenital region (1). As long as the tumour stays within the epidermis as an *in situ* lesion, it can be cured by surgical treatment. However, once it invades the dermis, metastasis can occur with a poor prognosis (2). Although carcinoembryonic antigen (CEA) is only used as a tumour marker for follow-up of patients, serum levels of CEA are not always elevated until widespread metastasis occurs (3, 4).

Receptor-binding cancer antigen expressed on SiSo cells (RCAS1) is a tumour-associated antigen that was first identified in gynaecological carcinomas (5). It is a 40-kDa type II membrane protein inducing apoptosis of receptor-bearing cells (6). Its clinical significance as a prognostic biomarker has been reported in various neoplasms, such as pancreatic and uterine carcinomas (7, 8). In addition, expression of this antigen has been reported in tumour cells of extramammary Paget's disease (9).

We reported previously a case of extramammary Paget's disease with liver metastases that showed elevated serum levels of RCAS1 in spite of normal serum ranges of other tumour markers (10). However, the significance of serum RCAS1 as a biomarker in extramammary Paget's disease has not been elucidated. Therefore, we studied the potential utility of RCAS1 in several other patients with extramammary Paget's disease.

### PATIENTS AND METHODS

Six patients (5 men and 1 woman, age range 65–87 years, mean age 73.7 years) with extramammary Paget's disease were included in this study after informed consent had been obtained. The diagnosis was based on histopathological examination. Tissue and serum samples from patients (2 with *in situ* extramammary Paget's disease and 4 with invasive extramammary Paget's disease) were obtained between April 2005 and March 2007, during follow-up after surgery. Immunostaining was performed using Envision-labelled polymer reagent (DAKO, Carpinteria, CA, USA) and anti-RCAS1 Ab (MBL, Nagoya, Japan) by the biotin-streptavidin method. Serum levels of CEA were assayed by chemiluminescent immunoassay (Abbot Japan, Matsudo, Japan) at Fukuoka University Hospital, whereas those of RCAS1 were assayed using a RCAS1 ELISA kit (MBL). The normal RCAS1 level is less than 4.9 U/ml on average (8).

### RESULTS

Immunohistochemically, tumour cells were positive for RCAS1 in all cases (not shown). The serum RCAS1 le-

vels in patients with extramammary Paget's disease after surgery are shown in Table I. There was no evidence of lymph node metastases or distant metastases in the patients before treatment. These patients had received neither chemotherapy nor immunotherapy after surgery. Of the 4 patients with invasive extramammary Paget's disease, elevated levels of RCAS1 were observed in 2 (cases 3 and 6) and slightly elevated levels in one patient (case 4) during the follow-up period, whereas the 2 patients with *in situ* extramammary Paget's disease had normal levels. In contrast, serum levels of CEA, measured at the same time, were within the normal range in all patients (not shown). In 2 of the 3 patients (cases 3 and 6) with elevated serum levels of RCAS1, inguinal lymph node metastases appeared later, although no obvious symptoms were seen.

### DISCUSSION

Various tumour-related antigens have been used for the diagnosis or evaluation of treatment for cutaneous neoplasms. Serum CEA has been reported to be useful as a tumour marker for extramammary Paget's disease (3, 4). However, since elevated serum levels of CEA are usually seen only in patients with widespread metastases, it is not a sensitive tumour marker. The utility of other tumour-related antigens commonly used for adenocarcinomas, e.g. carbohydrate 19-9, as tumour markers for extramammary Paget's disease has not

Table I. Serum RCAS1 levels in extramammary Paget's disease

Case	Sex/age (years)	Stage	Duration (months)*	Serum RCAS1 (U/ml)
1	M/70	In situ	36	4.4
			44	4.2
2	M/69	In situ	27	3.8
3	M/65	Invasive	27	9.0
			39†	11.0
4	F/83	Invasive	24	5.4
			31	5.2
5	M/68	Invasive	0	3.1
			7	2.8
6	M/87	Invasive	22†	12.4

\*Period after the initial treatment

†Inguinal lymph node metastases were revealed at this point.

The normal RCAS1 level is less than 4.9 U/ml on average.

RCAS1: receptor-binding cancer antigen expressed on SiSo cells.

been proven. Although recent immunohistochemical studies on erbB-2 (11) and mucin core proteins (12) have revealed that these antigens are associated with tumour progression in extramammary Paget's disease, their clinical usefulness as serum biomarkers in extramammary Paget's disease has not been elucidated.

RCAS1 is a tumour-associated antigen that was identified in gynaecological carcinomas and has been reported to be expressed and associated with prognosis in various carcinomas (5–8). Tumour cells in extramammary Paget's disease express this antigen (9) and secrete a soluble form of RCAS1 in the advanced stage, thus being presumed to escape from immune surveillance (10). Accordingly, we studied the potential utility of RCAS1 as a biomarker for monitoring patients with extramammary Paget's disease. Immunohistochemically, RCAS1 was detected in tumour cells, as reported previously (9). There was no difference in positivity between *in situ* and invasive lesions. Furthermore, we measured serum RCAS1 as well as serum CEA in 6 patients after initial treatment. Remarkably, 3 of the 4 patients with invasive lesions showed elevated levels of RCAS1, although there was no clinical evidence of metastasis at this point. Serum CEA levels had always been within the normal range, but the levels were gradually increased and regional lymph node metastases were detected by computerized tomography in 2 patients. These results indicate that serum RCAS1 might be useful for monitoring of patients with invasive extramammary Paget's disease. It seems that the sensitivity of RCAS1 is higher than that of CEA in extramammary Paget's disease. However, we have to be careful about the specificity of RCAS1 in extramammary Paget's disease because RCAS1 is expressed in various types of tumours (7, 8).

In conclusion, our findings suggest that serum RCAS1 could be useful as a tumour marker and that it might contribute to the diagnosis and estimation of tumour progression in invasive extramammary Paget's disease. The number of patients in the present study was relatively small, and further study is needed to determine the clinical value of RCAS1 in extramammary Paget's disease.

*Conflict of interest:* None declared.

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