SQUAMOUS CELL CARCINOMA RELATED ANTIGEN IN UTERINE CERVICAL CARCINOMA

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Summary

Squamous cell carcinoma-related antigen (SCC-Ag), first described by Kato and Torigoe in 1977, has been cited by various workers as a serological marker for some epithelia1 neoplasms. The most well-studied is its association with carcinoma of the uterine cervix. In January 1989, we embarked on a prospective, multivariate study at the University Hospital, Kuala Lumpur to assess the usefulness of serologically assaying SCC-Ag (using the Abbott RIA diagnostic kit) in our patients with carcinoma of the uterine cervix. We were also interested to ascertain whether SCC-Ag is a 'general' marker for all histological types of cervical carcinoma or specific for squamous carcinoma. From the time of commencement to June 1990, 35 newly-diagnosed and histologically-proven cases were entered into the study. Of these, 4 were keratinising squamous carcinoma, 18 large cell non-keratinising carcinoma, 3 adenosquamous carcinoma, 7 adenocarcinoma and 3 carcinoma-in-situ. Our preliminary results show that all keratinising squamous carcinoma and 1/3 each of large cell non-keratinising carcinoma, adenosquamous carcinoma and carcinoma-in-situ had positive pre-therapy serum SCC-Ag levels (i.e > 2 ng/ml, 2 ng/ml being an arbitrarily selected 'cut-off' value). In contrast, no adenocarcinoma was serologically positive. In addition, keratinising squamous carcinoma had the highest mean pre-therapy serum SCC-Ag level. The results imply that serum SCC-Ag is related to the (1) presence of squamous and not glandular differentiation and (2) degree of squamous differentiation.

Key words: SCC-Ag, Squamous cell carinoma-related antigen, cervical carcinoma, differentiation.

INTRODUCTION

Squamous cell carcinoma related antigen (SCC-Ag) is a glycoprotein recently described in carcinomas from various sites including the uterine cervix,[1-11] head and neck,[12-14] lung,[15-16] and oesophagus.[17-18] It is one of 14 subfractions of Tumour-associated antigen-4 (TA-4), TA-4 being a protein purified from squamous cell carcinoma of the uterine cervix. Originally described by Kato and Torigoe[19] in 1977, TA-4 and its subfraction, SCC-Ag, are being increasingly recognised as potential markers for neoplasms of the above sites. We embarked in early 1989 on a prospective, multivariate study to assess the applicability of SCC-Ag as a marker for cervical neoplasia in our local population. As a preliminary we were interested in determining whether SCC-Ag is a 'general' marker for all histological types of cervical carcinoma or, as its name implies, specific for squamous carcinoma.

MATERIALS AND METHODS

Commencing from January 1989, we have been assaying the pre-therapy serum SCC-Ag levels, using the Abbott RIA diagnostic kit, of all patients in the University Hospital, Kuala Lumpur who have undergone biopsy or definitive surgery for a tentative or previously histologically-proven diagnosis of invasive or in-situ carcinoma of the uterine cervix whenever blood samples are available for analysis. Only newly-diagnosed cases were considered for the study while those who presented with recurrent disease were excluded. The histological sections of all the tissue specimens procured from the operative procedures were re-examined and classified according to the World Health Organisation

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Classification (1975). Special stains were performed whenever necessary. Only cases with a positive tissue diagnosis which could be histologically re-confirmed were finally entered into the study. This cohort is being followed-up at the Gynaecology Unit with periodic serum SCC-Ag assays. The serum SCC-Ag levels of 19 healthy, female medical staff were also assayed and served as normal controls.

RESULTS

Over the 18-month period from January 1989 to June 1990, 35 newly-diagnosed cases of either invasive or in-situ cervical carcinoma with histologically-proven and re-confirmed diagnoses, were entered into the study. Of these, 32 had invasive carcinoma and 3 squarnous carcinoma-in-situ. Among the

TABLE 1
PRE-THERAPY SERUM SCC-AG LEVELS VERSUS HISTOLOGICAL TYPE OF TUMOUR

Case	Type	SCC (ng/ml)
1	KS	34.0
2	KS	21.0
3	KS	9.6
4	KS	7.0
5	LCNK	78.0
6	LCNK	14.0
7	LCNK	9.2
8	LCNK	3.1
9	LCNK	2.4
10	LCNK	2.3
11	LCNK	1.8
12	LCNK	1.7
13	LCNK	1.6
14	LCNK	1.5
15	LCNK	1.5
16	LCNK	1.4
17	LCNK	1.4
18	LCNK	1.3
19	LCNK	1.2
20	LCNK	0.9
21	LCNK	0.7
22	LCNK	0.6
23	AS	7.6
24	AS	1.3
25	AS	1.0
26	AD	1.7
27	AD	1.3
28	AD	1.3
29	AD	1.2
30	AD	1.1
31	AD	1.0
32	AD	1.0
33	CIS	2.4
34	CIS	1.1
35	CIS	0.8

KS = keratinising squamous carcinoma,
LCNK = large cell non-keratinising carcinoma,
AS = adenosquamous carcinoma,
AD = adenocarcinoma, CIS = carcinoma-in-situ

invasive carcinomas, 4 were keratinising squamous carcinoma, 18 large cell non-keratinising carcinoma, 3 adenosquamous carcinoma and 7 adenocarcinoma. The histological type of tumour versus the pre-therapy serum SCC-Ag level is shown in Table 1 while Table 2 shows the mean and range of the levels in relation to the histological type. Keratinising squamous carcinoma had the highest mean pre-therapy serum SCC-Ag level of 17.9 ng/ml while adenocarcinoma had the lowest (1.2 ng/ml). Table 3 shows that none of the normal controls or adenocarcinoma had serum SCC-Ag levels above the arbitrarily selected 'cut-off' value of 2 ng/ml,' while one-third each of adenosquamous carcinoma, large cell non-keratinising carcinoma and carcinoma-in-situ and all keratinising squamous cell carcinoma had values above this.

TABLE 2
PRE-THERAPY SERUM SCC-AG LEVELS :
MEAN AND RANGE VERSUS HISTOLOGICAL TYPE OF TUMOUR

Type	No. tested	Mean (ng/ml)	Range (ng/ml)
KS	4	17.9	7.0 — 34.0
LCNK	18	6.9	0.6 — 78.0
AS	3	3.3	1.0 — 7.6
AD	7	1.2	1.0 — 1.7
CIS	3	1.4	0.8 — 2.4
Controls	19	0.7	0.2 — 1.2

KS = keratinising squamous carcinoma,
LCNK = large cell non-keratinising carcinoma,
AS = adenosquamous carcinoma,
AD = adenocarcinoma. CIS = carcinoma-in-situ

TABLE 3
DISTRIBUTION OF PRE-THERAPY SERUM SCC-AG LEVELS
IN RELATION TO HISTOLOGICAL TYPE OF TUMOUR

Type	No. tested	No. > 2 ng/ml
KS	4	4 (100)
LCNK	18	6 (33)
AS	3	1 (33)
AD	7	0 (0)
CIS	3	1 (33)
Controls	19	0 (0)

KS = keratinising squamous carcinoma,
LCNK = large cell non-keratinising carcinoma,
AS = adenosquamous carcinoma,
AD = adenocarcinoma, CIS = carcinoma-in-situ

DISCUSSION

Although the limited number of cases precludes statistical analysis, there appears to be an association between pre-therapy serological SCC-Ag positivity (i.e. values >2ng/ml) and squamous differentiation. In contrast to the findings of Duk et al,[20] none of the adenocarcinoma studied were positive. Keratinising squamous carcinoma were uniformly positive and large cell non-keratinising carcinoma, adenosquamous carcinoma, and carcinoma-in-situ showed a 33% positivity rate. This suggests that squamous differentiation is a pre-requisite for pre-therapy serological SCC-Ag positivity. In addition, the pre-therapy levels appear to be related to the degree of squamous differentiation. This is inferred from the mean pre-therapy serum SCC-Ag values of the different histological types, with keratinising squamous carcinoma showing the highest of 17.9 ng/ml. The cases of large cell non-keratinising carcinoma and carcinoma-in-situ were not quantitated for the degree of squamous differentiation in each tumour and it is not obvious at this point how much squamous maturation is required to give a serological SCC-Ag positivity. Similarly, the case of adenosquamous carcinoma which was positive was also not quantitated for the amount of squamous component present. While quantification would have been ,informative in the above cases, it would have entailed processing and studying all the tumour tissue available which was not done. Although keratinising squamous carcinoma as a group was noted to have the highest mean pre-therapy serum SCC-Ag level, we observed one case of large cell non-keratinising carcinoma with a value of 78 ng/ml. This implies that apart from the degree of squamous differentiation other factors probably contribute to the final pre-therapy serum SCC-Ag level obtained. Tumour stage, tumour volume, depth of stromal invasion and lymph node metastases are among some of the suggested participant factors.[1,3,11] From our results it may appear that pre-therapy serum SCC-Ag assay cannot differentiate invasive from non-invasive lesions and this would seem to contradict the finding of others.' It is opportune to clarify that the highest pre-therapy serum SCC-Ag level in the carcinoma-in-situ category was 2.4 ng/ml. Perhaps, the arbitrary 'cut-off' value of 2 ng/ml adopted is too low and should be revised. Finally, it is worthwhile to note that serum SCC-Ag elevation has also been detected in some benign lung lesions, renal failure, and dermatological conditions eg. pemphigus, psoriasis, and generalised eczema.[21-23] These conditions have to be kept in mind when interpreting serum SCC-Ag assays.

In conclusion, this study so far indicates that squamous differentiation is required for pre-therapy serological SCC-Ag elevation. The degree of squamous maturation probably in conjunction with other factors not currently studied, then determines the final level of serum SCC-Ag attained. In other words, SCC-Ag is a serological marker for cervical tumours with squamous differentiation. Sensitivity increases with increasing degree of differentiation and serum SCC-Ag assay is most profitable in well-differentiated keratinising squamous carcinoma.

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