Serum immunosuppressive acidic protein in renal cell carcinoma

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No useful tumor makers for renal cell carcinoma (RCC) have yet been established. In the present study, the serum IAP level was assessed as a diagnostic and follow-up marker for RCC. The subject were 16 women and 52 men with RCC (28–87 years old) and 30 healthy adult controls (20–68 years old).

Serum IAP levels were assayed by the single radial immunodiffusion method and the cut-off level was set at 500 µg/ml. The IAP level was significantly higher in the RCC than in the controls. The IAP positivity rate was 63.9% in the RCC patients and 16.7% in the controls. Elevation of IAP was related to clinical stage. The IAP Positivity rate was 83.9% in patients with high stage RCC and 35.1% in those with low stage RCC. The prognosis of low stage RCC with IAP level over 1,000 µg/ml was quite poor. In contrast, even high stage patients with IAP levels of 500 µg/ml or less had a longer survival compared with those having elevated IAP levels. Additionally, in the low stage patients, the IAP level decreased significantly after radical nephrectomy compared with that at diagnosis. Patients with the IAP levels of 500 µg/ml or less after nephrectomy also had a longer survival than those with the levels over 500 µg/ml.

Based on these results, it was concluded that IAP may be a useful marker for RCC, although it appears valuable for assessing the prognosis than for diagnosis. A more accurate assessment of the prognosis of RCC was possible using a combination of the IAP value and clinical stage.


Key words: IAP, RCC, Tumor marker

Although much progress has been made in identified tumor cell surface markers, no tumor-specific markers have yet been established for renal cell carcinoma (RCC). Immunosuppressive acidic protein (IAP), a type α1-acid glycoprotein, was one of the first immunosuppressive substances isolated from ascitic fluid and the serum of mice with Ehrlich ascites cancer1,2). It has been reported that serum IAP levels are high in patients with advanced gastric, colon, gynecologic, and urogenital cancers including RCC, although the pathophysiological role of this protein remains unclear3–8).

The present study investigated the clinical usefulness of IAP as a diagnostic or follow-up marker for RCC.

Patients and methods

Serum IAP levels were evaluated in 68 patients (16 women and 52 men) with histologically confirmation of RCC between October 1984 and December 1992. The patients ranged in age from 38 to 87 years (mean: 68 years). As a control, IAP levels were also evaluated in 30 healthy adults aged 40 to 68 years (mean: 65 years). The patients were staged according to Robson's classification14), and were divided into two groups, ie., a low stage group (stages I and II) and a high stage group (stages III and IV).

Serum IAP levels were assayed by the single radial immunodiffusion method using an agarose plate containing anti-IAP goat serum (Sanko Pure Chemical Ind., Tokyo). The assay had a cut-off level of 500 µg per 1 ml of serum6–7). All values are expressed as the mean ± standard deviation (SD). Data were analyzed by the generalized Wilcoxon test using Fisher statistical software. Differences in survival were analyzed according to the Kaplan-Meier method using the same software.

Results

Serum IAP levels of the patients and controls.

The IAP levels of the RCC patients at diagnosis were significantly higher than those of healthy controls (p<0.01). The mean IAP value was 707.6 ± 281.3 µg/ml in the RCC patients and 426.5 ± 99.2 µg/ml in the controls (p<0.01) (Fig.1).

When IAP levels of 500 µg/ml or less were defined as normal and those higher were defined as positive, IAP was positive in 43 of the 68 RCC patients and 5 of the 30 controls and there was a significant difference of the positivity rate between the two groups (p<0.01).
Fig. 1 Serum IAP levels in the patients with renal cell carcinoma and the controls

Fig. 2 Serum IAP levels in the patients with low and high stage renal cell carcinoma

Fig. 3 Relationship between the serum IAP level at diagnosis and the prognosis of renal cell carcinoma

Fig. 4 Relationship between the serum IAP level at diagnosis and the prognosis of high stage renal cell carcinoma

Relationship between IAP and clinical stage.

The serum IAP level at diagnosis was 517.7 ± 72.1 µg/ml in the low stage RCC group and 936.8 ± 120.2 µg/ml in the high stage group (p<0.01) (Fig. 2).

IAP was positive in 13 out of 37 low stage patients and in 26 out of 31 high stage patients. There was a significant difference of the positivity rate between the two groups (p<0.01).

Relationship between IAP levels and the prognosis

The patients were divided into the following three groups according to their IAP levels: ≤ 500 µg/ml (normal group), 500 < ≤ 1,000 µg/ml (slightly elevated group), and > 1,000 µg/ml (elevated group). IAP levels at the time of diagnosis were evaluated first. The normal group had a significantly better survival than the slightly elevated and elevated groups (p<0.01 for both groups). Additionally, the survival rate of the slightly elevated group was also significantly better than that of the elevated group (p<0.05) (Fig. 3).

In the high stage RCC patients, the survival rate of the normal group was significantly better than that of the slightly elevated or elevated groups (p<0.01 for both groups), while there was no difference in survival between the slightly elevated and elevated groups (Fig. 4). In the low stage patients, the survival rate of the elevated group was significantly worse than that of the slightly elevated or normal groups (p<0.01) (Fig. 5).

The relationship between IAP level at 2 months after radical nephrectomy and the prognosis was also studied, since this was a time when IAP values were no longer affected by the operation. Postoperative changes of the IAP level were evaluated in 15 patients who were IAP positive at diagnosis. A significant decrease of the postoperative level was observed in the low stage patients (p<0.05), although there was no significant change in the high stage patients (Fig. 6).

The survival rate of the patients with an IAP level ≤ 500 µg/ml after the operation was significantly better than that of patients with a value over 500 µg/ml (p<0.01), while there was no difference in survival between the slightly elevated and elevated groups (Fig. 7).
Fig. 5 Relationship between the serum IAP level at diagnosis and the prognosis of low stage renal cell carcinoma

Fig. 6 Postoperative changes of serum IAP in the patients with low and high stage renal cell carcinoma

Postoperative changes of IAP in two representative patients.

Case 1 was a 59-year-old man with a serum IAP level of 1,055 µg/ml at diagnosis and no evidence of metastatic disease. Right radical nephrectomy was performed under a diagnosis of stage II RCC. The IAP level decreased to below the cut-off value at 2 months after the operation. However, it increased progressively over time following the appearance of lung and bone metastases.

Case 2 was a 70-year-old man with an IAP level of 720 µg/ml at diagnosis. Right radical nephrectomy was performed under a diagnosis of stage III RCC. The IAP level fell to below the cut-off value at 2 months after surgery and has remained for 4 years with no evidence of recurrence (Fig. 8).

Discussion

Impairment of cellular immunity is common in hosts with malignant tumors\(^2,11\). In addition, studies of patients with malignancy reduced cutaneous hypersensitivity to many recall antigens\(^12\). This immunosuppression has been attributed to the presence of a variety of soluble factors such as IAP, an acidic protein with a molecular weight of 50,000 and isoelectric focusing at pH 3.0, which is released by hepatocytes, macrophages, and polymorphonuclear leukocytes\(^13\).

It is generally accepted that 500 µg/ml is the upper limit of normal for serum IAP (1). However, Ogoshi and associates defined the upper limit as 558 µg/ml, because the mean and standard deviation was 365.6 ± 100.5 µg/ml in healthy subjects\(^14\).

Sakamoto and Nakasato suggested that a cut-off level of 580 µg/ml might be more appropriate than 500 µg/ml for the prognostic evaluation of gastric cancer after curative gastrectomy, and this suggested cut-off level was confirmed by a multicenter study\(^15-16\). In the present study, we used 500 µg/ml as upper limit of normal on the basis of previous reports of IAP levels in patients with RCC\(^7-9\). However, further studies might be required to define a more appropriate cut-off value for...
patients with RCC.

To study the usefulness of IAP in screening for RCC, IAP levels were measured in RCC patients at the time of diagnosis and in healthy adults. The IAP level in the RCC patients was significantly higher than that in the controls, and the IAP level in high stage patients was higher than levels in the low stage patients and controls. The IAP positivity rate was 63.2% in RCC patients and 16.7% in the controls, respectively. The positivity rate increased with advancing clinical stage, and the rate was 83.9% in the high stage patients but only 35.1% in the low stage patients. Thus, the positivity rate of IAP was higher than that of any other RCC markers, including serum basic fetoprotein, tissue polypeptide antigen, serum iron, and haptoglobin.\(^{17-19}\)

However, it still seems that the usefulness of IAP for detection of RCC is somewhat limited, especially in the case of low stage disease.

Next, we studied the usefulness of serum IAP for monitoring the progress of RCC. The prognosis of patients with raised IAP levels was generally poor. The patients were divided into the low and high stage groups and were also divided into three groups according to their IAP levels. The prognosis of low stage patients with an IAP level over 1,000 \(\mu\)g/ml was quite poor. On the other hand, even high stage patients with an IAP level of 500 \(\mu\)g/ml or less showed longer survival than those with levels over 500 \(\mu\)g/ml. Although tumor stage is an important prognostic factor, the correlation between stage and prognosis is not always so high.\(^{16,21}\) Our results indicate that a more accurate assessment of prognosis is possible using a combination of the IAP level and the clinical stage.

The early detection of tumor recurrence is of great clinical importance. It has been reported that IAP levels were increased in patients with recurrent RCC. In our patients with low stage RCC, the IAP level decreased significantly after nephrectomy. However, the changes of IAP in the high stage group were not uniform. The patients with IAP levels of 500 \(\mu\)g/ml or less at 2 months after surgery had a much better prognosis than the patients with postoperative IAP level over 500 \(\mu\)g/ml. Our study of the postoperative changes in IAP suggested that it could be used to indicate the presence of recurrence or metastasis. However, IAP production is also stimulated by various inflammatory conditions and the level of this acute phase reactant is affected by surgery, infection and collagen diseases.\(^{16,22}\)

In conclusion, serum IAP level can be used as a prognostic marker for RCC, and also provides a tool for the early detection of recurrence or metastasis.

References
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Aim of the study: To evaluate the usefulness in the detection of renal cell carcinoma of serum immunosuppressive acidic protein (IAP) concentration.

Method: The IAP concentrations of 25 patients with renal cell carcinoma and 25 healthy individuals were measured. IAP was analyzed with a single radial immunodiffusion method by using a 500 μg/ml cutoff value.

Results: The mean IAP concentration in renal cell carcinoma patients was significantly higher (p<0.01) than that in healthy individuals. The IAP levels were also significantly higher in high-stage patients (p<0.01) compared to low-stage patients. The IAP level was significantly lower in patients with a low disease stage compared to those with a high disease stage (p<0.01).

Conclusions: Serum IAP is a useful biomarker for the detection of renal cell carcinoma, particularly for high-stage patients. The test results should be interpreted in conjunction with other clinical factors.

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Secretory carcinoma of the breast diagnosed by aspiration biopsy cytology: report of a case  
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Aims of the study: To report a case of secretory carcinoma of the breast diagnosed by aspiration biopsy cytology.

Method: A 55-year-old female patient with a palpable mass in the right breast was referred for further evaluation. The lesion was aspirated and cytology was performed.

Results: The aspirate specimen showed a high nucleus:cytoplasm ratio with vacuolated cytoplasm consistent with secretory carcinoma. Immunohistochemistry was positive for keratin and negative for estrogen and progesterone receptors.

Conclusions: Secretory carcinoma of the breast is a rare subtype of breast cancer. This case highlights the importance of careful cytologic examination in the diagnosis of this entity.