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 subjects 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 $\mu\text{g/ml}$. The IAP level was significantly higher in the RCC than in the controls. The IAP positivity rate was 63.2% 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 $\mu\text{g/ml}$ was quite poor. In contrast, even high stage patients with IAP levels of 500 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ or less after nephrectomy also had a longer survival than those with the levels over 500 $\mu\text{g/ml}$.

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.

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Although much progress has been made in identifying tumor cell surface markers, no tumor-specific markers have yet been established for renal cell carcinoma (RCC). Immunosuppressive acidic protein (IAP), a type α_1 -acid glycoprotein, was one of the first immunosuppressive substances isolated from ascitic fluid and the serum of mice with Ehrlich ascites cancer^{1,2}. 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 unclear^{1,3~8}.

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 confirmed 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

classification¹⁰, and were divided into two groups, i.e., 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 serum^{6~7}. All values are expressed as the mean $\pm$ 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 $707.6 \pm 281.3 \mu\text{g/ml}$ in the RCC patients and $426.5 \pm 99.2 \mu\text{g/ml}$ in the controls ($p < 0.01$) (Fig. 1).

When IAP levels of 500 $\mu\text{g/ml}$ 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 ($p < 0.01$).

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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

Relationship between IAP and clinical stage.

The serum IAP level at diagnosis was 517.7 ± 72.1 $\mu\text{g/ml}$ in the low stage RCC group and 936.8 ± 120.2 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ (normal group), $500 < \leq 1,000$ $\mu\text{g/ml}$ (slightly elevated group), and $> 1,000$ $\mu\text{g/ml}$ (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

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

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 $\mu\text{g/ml}$ after the operation was significantly better than that of patients with a value over 500 $\mu\text{g/ml}$ ($p < 0.01$), 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.7 Relationship between the serum IAP level at 2 months after nephrectomy and the prognosis of 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 $\mu\text{g}/\text{ml}$ 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 $\mu\text{g}/\text{ml}$ 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

Fig.8 Postoperative changes of serum IAP in two representative patients

with malignant tumors^{2,11}). In addition, studies of patients with malignancy reduced cutaneous hypersensitivity to many recall antigens¹²). 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 leukocytes¹³).

It is generally accepted that 500 $\mu\text{g}/\text{ml}$ is the upper limit of normal for serum IAP (1). However, Ogoshi and associates defined the upper limit as 558 $\mu\text{g}/\text{ml}$, because the mean and standard deviation was 365.6 ± 100.5 $\mu\text{g}/\text{ml}$ in healthy subjects¹⁴).

Sakamoto and Nakasato suggested that a cut-off level of 580 $\mu\text{g}/\text{ml}$ might be more appropriate than 500 $\mu\text{g}/\text{ml}$ for the prognostic evaluation of gastric cancer after curative gastrectomy, and this suggested cut-off level was confirmed by a multicenter study¹⁵⁻¹⁶). In the present study, we used 500 $\mu\text{g}/\text{ml}$ as upper limit of normal on the basis of previous reports of IAP levels in patients with RCC⁷⁻⁹). 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 haptoglobulin¹⁷⁻¹⁹.

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 $\mu\text{g}/\text{ml}$ was quite poor. On the other hand, even high stage patients with an IAP levels of 500 $\mu\text{g}/\text{ml}$ or less showed longer survival than those with levels over 500 $\mu\text{g}/\text{ml}$. Although tumor stage is an important prognostic factor, the correlation between stage and prognosis is not always so high^{20,21}. 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 $\mu\text{g}/\text{ml}$ or less at 2 months after surgery had a much better prognosis than the patients with postoperative IAP level over 500 $\mu\text{g}/\text{ml}$. 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 effected by surgery, infection and collagen diseases^{13,22}.

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.

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Ehlich担癌マウスの腹水、および血清より免疫能抑制物質とし分離されたIAPは、各種腫瘍の非特異的腫瘍マーカーとして用いられている。今回、腎癌において血清IAP値の有用性について検討したので報告する。

〔対象と方法〕 腎癌と診断された38~87歳の68症例(女:16, 男:52)を対象とし、40~68歳の健康成人30人をその対象とした。臨床病期は、Robson分類に準じ、stage I~IIをlow stage, stageIII~IVをhigh stageとした。血清IAPは、IAPプレートを用いたsingle radical immunodiffusion法により測定、500 μ g/mlをcutoff値とした。

統計学的検討は、Fisherのプログラムを使用し、多群間の比較はWilcoxonの手法を、また生存率の比較はKaplan-Meierの手法により行った。

〔結果〕 ① 腎癌患者と健康成人の血清IAP値: 腎癌症例での平均IAP値は、707.6 $\pm$ 281.3 μ g/mlで、対照群の426.5 $\pm$ 99.2 μ g/mlに比較し、有意な高値を示した($p<0.01$)。500 μ g/ml以下を正常とすると、陽性例は腎癌患者68症例中43例、対照30人中5人であった($p<0.01$)。

② 腎癌患者の血清IAP値と臨床病期の関係: Low stage例の平均IAP値は515.1 $\pm$ 72.1 μ g/mlで、high stage例の936.8 $\pm$ 120.2 μ g/mlに比較し、有意の低値を示し($p<0.01$)、その陽性例は各々37症例中13例、31症例中26例と両群間に有意の差異を認めた($p<0.01$)。

③ 腎癌患者の血清IAP値と予後の関係: 腎癌患者を、便宜上、IAP値により3群に分類した。正常群($\leq 500\mu$ g/ml)の予後は、やや高値群(500μ g/ml $<\leq 1,000\mu$ g/ml)および高値群($>1,000\mu$ g/ml)に比較し良好で($p<0.01$)、やや高値群は高値群に比し良好であった($p<0.05$)。high stage例において、正常群は、やや高値群および高値群に比較し予後良好であり($p<0.01$)、また、low stage症例において、高値群は正常群およびやや高値群に比較し予後不良であった($p<0.05$)。さらに、low stage症例では、入院時に比較し手術後、有意に減少し($p<0.05$)、その正常群では、他の2群に比較し予後は良好であった($p<0.01$)。

〔考察〕 腎癌患者の血清IAP値は、健康成人に比較し有意に高値を示し、その陽性率は症例全体で63.2%、対照で16.7%であった。さらに、high stageに限ると83.9%となり、従来報告されていたb-FP、TPA、血清鉄、ハプトグロブリンなどの陽性率より高率ではあるが、腎癌スクリーニングにおける診断マーカーとしての役割、特にlow stage例においては、限られたものであると考えられた。

一方、予後と血清IAP値の関係では、low stage症例でもIAP 1,000 μ g/dl以上の症例では予後不良であり、またhigh stage症例でも500 μ g/dlでは予後が良好であった。また、IAP値の変動は、臨床経過をよく反映し、術後IAP正常群では長期生存が期待された。

以上より、IAPは予後マーカーであり、臨床病期診断を併用によりその有用性は増すと考えられた。

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乳腺の分泌癌は別名若年性癌ともよばれ、乳癌取扱い規約にも記されているが、まだその報告は非常にまれである。今回筆者らは、穿刺吸引細胞診にて特徴的な所見を呈した成人の乳腺分泌癌を経験したので報告する。

症例は55歳女性で、右乳腺腫瘍を主訴に来院した。触診では右乳房BED領域に1.5cm大の弾性硬、境界明瞭で可動良好な腫瘍を触知したが、皮膚変化は認めず、腋窩リンパ節も触知しなかった。超音波検査では、腫瘍触知部に一致して境界鋭、不整型で内部エコーはほぼ均一な低エコー像を認めた。マンモグラフィーでは、触診と同じ部位に、径1.7cmの辺縁やや不明瞭な円形腫瘍陰影を認めたが、微細石灰化像は明らかではなかった。以上の所見より乳癌を疑い、穿刺細胞診を行った結果、Class Vで右乳癌(T1 N0 M0)と診断し、非定型乳房切除術を施行した。

細胞診所見では、核小体の目立つ核を有する細胞の重積ないしシート状の細胞集塊がみられた。細胞質は豊富で淡く空胞や粘液を有しており、核は三日月型で偏在しているものも認められた。これらの細胞集塊はあたかも“ぶどうの房”様であった。

組織所見では、大小不同の管腔を形成し、管腔内と細胞質にPAS、Alcian-blue陽性の分泌物を認めた。また、腫瘍は間質に富むscirrhousな像を呈し、一部で乳腺外脂肪組織への浸潤を認めた。以上の所見より乳腺分泌癌と診断した。

なお、腫瘍組織内ER、PgRはともに陰性であった。術後経過は順調で、現在再発の兆候はない。

分泌癌は、1966年にMcDivitらが、腫瘍細胞が著名な分泌像を示し、PAS陽性物質が細胞内、腺房様腔内にみられる組織学的特徴を有する3歳から15歳の7例の若年性乳癌を最初報告した。しかし、1980年にTavassoliらは、成人においても同様な組織像を呈する乳癌を提示し、若年者のみにみられるものではないことを報告した。筆者らが調べ得た限りでは、本邦では14例の報告があるが、穿刺吸引細胞診について述べた報告はほとんどみあたらない。Shinagawaらは最近、分泌癌の穿刺吸引細胞診において、本症例においても認められた“ぶどうの房”様の細胞診所見が特徴的であることを述べている。

本疾患の予後に関しては、他の乳癌より良好という報告もあるが、本邦報告14例についてみると、42%にリンパ節転移が認められており、今後症例を重ねて検討していく必要があると思われる。