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Immunosuppressive Acidic Protein in Patients with Brain Tumours: a Preliminary Report*

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Summary

The present investigation was conducted to document the serum concentrations of immunosuppressive acidic protein (IAP) in patients with intracranial tumours utilizing the single radial immunodiffusion method. Among 46 pre-operative patients, elevated serum levels of IAP were found in nine of 16 patients with gliomas, six of nine patients with metastasis, and two of 21 patients with non-glial, histologically benign intracranial tumours. The mean value of serum IAP in glial or metastatic tumours was found significantly higher than that of either non-glial or normal individuals. It was postulated that serum IAP levels could correlate with a grade of anaplasia and malignancy of the tumour. And it was also of note that serum IAP levels appeared to have a tendency to decrease in response to the treatment. In addition, serum IAP levels were found correlated with the clinical condition and course of disease as evaluated by performance status and erythrocyte sedimentation rate. Therefore, it was suggested that measurement of serum IAP could be, at least in part, useful in validating the histologic analysis of brain tumours, in following responses to treatment when used as a tumour indicator, and in monitoring the progress of the disease in patients in terms of performance status.

Keywords: Immunosuppressive acidic protein; brain tumours; tumour marker.

Introduction

It has been recognized that in cancer patients certain proteins of liver origin known as acute-phase serum protein increase as the tumour burden increased and their serum levels correlate inversely with immune competence as evaluated by both in vivo and in vitro assays of cell-mediated immunity[2, 3, 6, 8, 9, 13, 31, 33]. Isolation and identification of "immunosuppressive acidic protein (IAP)" was extensively performed by Tamura *et al.* with ascitic fluids of cancer patients utilizing the analytical isoelectric focussing method[28]. IAP is classified as one of the acute-phase serum proteins and found similar to but different from normal α_1-acid glycoprotein in terms of its chemical and biological properties[12, 24, 28]. Recent clinical studies have shown that serum levels of IAP are significantly elevated in cancer patients in contrast to those in patients with benign tumours[21, 22].

The purpose of the current investigation is to document the serum levels of IAP in a brain-tumour patient population and to examine its possible role as a tumour monitor in the management of patients with brain tumours.

Materials and Methods

Patient Population

Forty-six pre-operative patients with benign and malignant intracranial tumours hospitalized at Akita University Hospital and its affiliated hospitals were included in this study. There were 24 men and 22 women, ranging in age from 7 to 74 years. They had no concomitant diseases and the histological diagnosis was confirmed in all patients. Thirty-seven of the patients had primary brain tumours including 16 glial tumours (six glioblastoma multiforme, six astrocytomas grade I–III, three oligodendrogliomas, and one medulloblastoma) and 21 non-glial tumours (eight acoustic neurinomas, six pituitary adenomas, five meningiomas, one craniopharyngioma and one haemangioblastoma). The remainder had metastatic brain tumours of varied origin.

Blood samples were obtained by peripheral venipuncture from these 46 patients prior to initiation of any treatment and from 30 normal individuals. Ten patients were evaluated for serum IAP

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repeatedly after surgery. Normal volunteers with age and sex distributions similar to those of brain tumours collectively served as controls.

Sera from 21 additional post-operative patients, who were being either followed-up in outpatient clinics without evidence of tumour recurrence after initial therapy or hospitalized for subsequent therapy for recurrent and progressive disease, were also randomly selected for the studies. This group of patients included seven glioblastoma multiforme, ten astrocytomas, and four medulloblastomas.

Preparation of Samples and Measurement of IAP

The specimen was centrifuged at 500 G for 15 minutes, and subsequently the serum was collected and stored frozen at −80 °C until assayed for IAP. Quantitative assay of serum IAP was performed by the single radial immunodiffusion method as described by Mancini[17] using commercially available kits (IAP Plates, Kayaku Antibiotics Research Co., Japan). Briefly, agarose gel containing rabbit anti-IAP serum was prepared on a glass plate with 2.5 mm-diameter wells. Five microlitres of test serum were applied in each well, and incubated at 37 °C in a humidified atmosphere for 48 hours. Then the diameter of the precipitin ring was measured. The standard curve was made using the purified samples with the known IAP concentrations of 250 and 1,000 μg/ml. Single radial immunodiffusion is an easy, rapid and reproducible method for the determination of serum IAP concentrations within the range of 30 and 1,500 μg/ml[12, 21]. Reproducibility was confirmed by replicate determinations on the serum sample with the difference less than 4%.

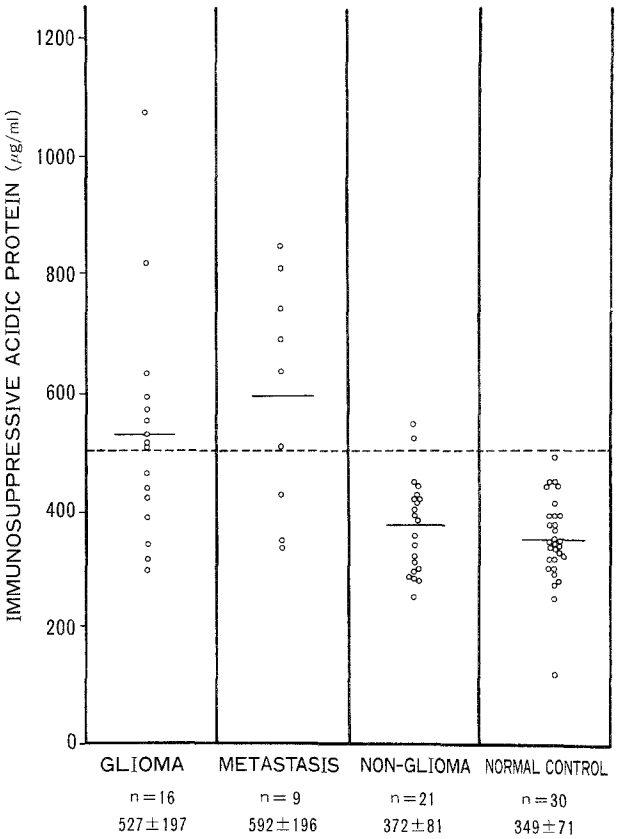

Fig. 1. Serum concentrations of immunosuppressive acidic protein (IAP) in 46 patients with brain tumours and 30 normal controls. Horizontal bars indicate the mean IAP value for each group. Dashed line indicates the IAP value of 500 μg/ml which was estimated as a maximum IAP level of the normal control. The number and the mean IAP value for each patient group are also numerically indicated. Statistical analysis of data using the unpaired Student's t-test shows that both glioma and metastasis, but not non-glioma, are statistically different from normal control ($P < 0.001$)

Results

Quantitative Measurement of IAP in Serum from Brain-Tumour Patients

Quantitative measurements of IAP in serum from 46 pre-operative patients with brain tumours and 30 normal individuals were performed utilizing single radial immundiffusion method (Fig. 1). The mean serum concentration of IAP of normal individuals was estimated to be 349 ± 71 μg/ml (mean ± SD) in the present investigation. None was higher than 2 standard deviations (491 μg/ml) above the mean value of the normal control. It was then considered reasonable to decide that the normal range of IAP was less than 500 μg/ml as reported in previous studies[12, 21, 22], and thus by this criterion abnormally elevated IAP values were designated here as any value exceeding 500 μg/ml.

The IAP concentrations in serum from 16 patients with gliomas ranged from 295 to 1,075 μg/ml with the mean value of 527 ± 197 μg/ml. Among them sera of nine patients with gliomas, mostly anaplastic and malignant, had elevated IAP levels. In contrast the serum from 21 non-glial tumours including eight acoustic neuromas, six pituitary adenomas, five meningiomas, one craniopharyngioma, and one haemangioblastoma had the mean IAP value of 372 ± 81 μg/ml. Only two patients with craniopharyngioma and acoustic neuroma showed elevated IAP levels, 545 and 520 μg/ml respectively. With respect to metastasis, six of nine patients had elevated IAP serum levels. The mean value of serum IAP in patients with gliomas or metastasis was significantly higher than that in patients with non-glial, benign tumours ($p < 0.01$) or healthy normal individuals ($p < 0.001$). There seems to be a significant tendency that serum IAP levels increase as the histological grade of anaplasia or malignancy increases and this is also well examplified in patients with primary intracranial tumours.

Figure 2 illustrates the serum IAP levels for patients with primary brain tumours of varying histologies in terms of relative percentage of the normal mean. The mean IAP value of 30 normal individuals was designated here as 100% and each group of the patients was

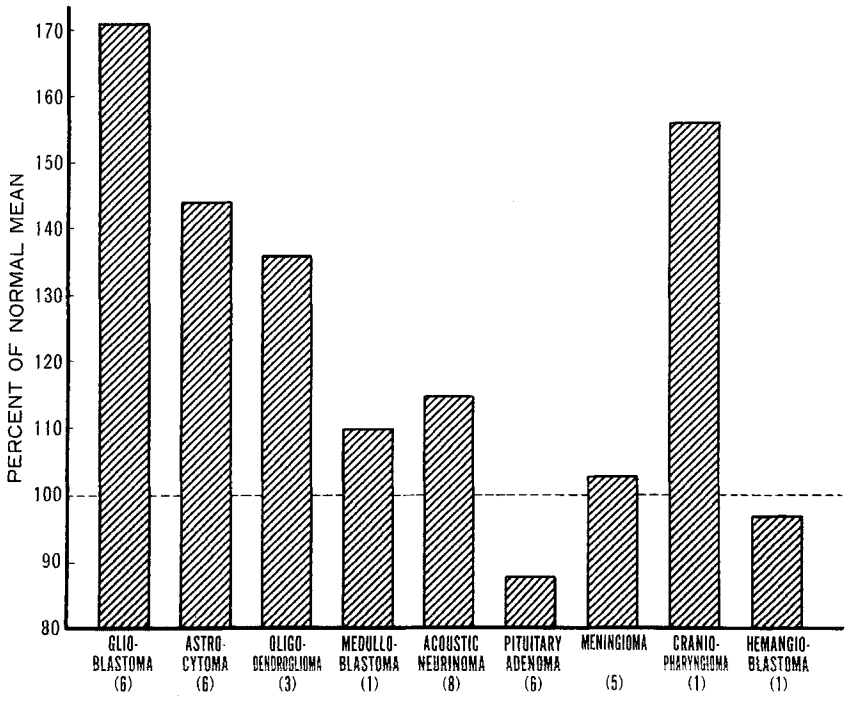

Fig. 2. Comparison of serum immunosuppressive acidic protein (IAP) in patients with gliomas and non-glial intracranial tumours. The mean IAP value of 30 normal individuals was designated here as 100%

compared. There were significant increases in serum IAP levels in patients with glioblastoma, astrocytoma and oligodendroglioma. Furthermore it was of interest that there was a clear and statistically significant distinction as to serum IAP levels between patients with glioblastoma and other less malignant glial tumours. It was therefore suggested that serum IAP levels could correlate with the grade of anaplasia and malignancy of the primary brain tumours.

Serial Evaluations of Serum IAP

Serum IAP levels were evaluated repeatedly in 10 patients during and after treatment. These included three glioblastomas, five astrocytomas and two metastatic brain tumours. As shown in Fig. 3, pre-operative IAP levels among these patients were elevated in seven with the mean value of 595 μg/ml. The same group of patients was evaluated again for serum IAP levels at discharge following treatment by surgery, radiation, and immunochemotherapy. The mean IAP value at discharge was 434 μg/ml, and found significantly lowered in comparison to that evaluated initially prior to treatment. There were three patients whose serum IAP levels either remained or rose higher than 500 μg/ml despite the multimodal treatment. In these patients biopsy rather than tumour resection was performed for histological diagnosis and further regression of the tumours was not seen on follow-up CT scans after subsequent treatment. In contrast, in five

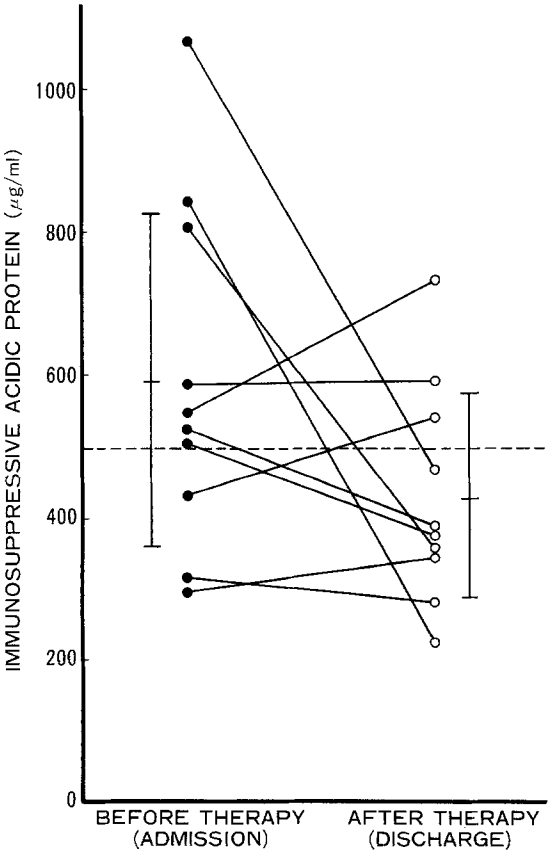

Fig. 3. Sequential changes of serum immunosuppressive acidic protein (IAP) in 10 patients before and after the treatment by surgery, radiation, and immunochemotherapy. Short bars indicate 1 standard deviation from the mean IAP level for each group. Dashed line represents the IAP value of 500 μg/ml. Statistical analysis of data using the paired Student's shows that IAP values before treatment are statistically different from those after treatment ($P < 0.01$)

among seven patients with elevated IAP levels who had decreased levels of serum IAP after treatment, the tumours were removed partially or subtotally and computed tomographic evidence of tumour regression was obtained in accordance with clinical remission. It was thus postulated that serum IAP levels appeared to have a tendency to decrease in response to the treatment, and therefore quantitative serial measurements of serum IAP were found useful for the evaluation of responses to treatment and progression of the disease.

The following are two illustrative cases in which serum IAP levels appeared to correlate with responses to therapy. Fig. 4 shows serial IAP levels of a 62-year-old woman with a three-month history of progressive left hemiparesis and dysarthria. A CT scan revealed an enhanced mass lesion in the right parietal region with marked oedema and ventricular shift. Initial serum IAP was 1,075 μg/ml. Craniotomy provided the histologic diagnosis of glioblastoma multiforme and the tumour was partially resected. She further underwent cranial irradiation (6,000 rads) and immunochemotherapy. Immunochemotherapeutic regimen contained a combination of nimustine [1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride; ACNU: 1 mg/kg), tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil: 750 mg/day] and protein-bound polysaccharide (PS-K: 3.0 g/day). During a course of treatment the serum IAP levels gradually decreased to the normal range pari passu with clinical remission.

Fig. 5 shows serial IAP levels of a 32-year-old man with symptoms of increased intracranial pressure. Physical examination revealed an enlarged testicle on the left side. A CT scan demonstrated a right occipital mass lesion of homogeneously high density with perifocal oedema. Orchiectomy and craniotomy provided the diagnosis of testicular tumour metastasizing to the brain (seminoma combined with embryonal carcinoma). The intracranial tumour was subtotally removed. Alphafetoprotein (AFP) and human chorionic gonadotropin (HCG) levels were undetectable. After surgery the patient received three courses of multiagent systemic chemotherapy with cisplatinum (20 mg/m^2), vinblastin (0.3 mg/kg), and bleomycin (0.5 mg/kg). 5,000 rads of whole-brain irradiation were also added. The patient improved clinically and IAP levels decreased accordingly. The initial IAP level on admission was 810 μg/ml, and after chemotherapy it decreased to 535 μg/ml and finally to 360 μg/ml.

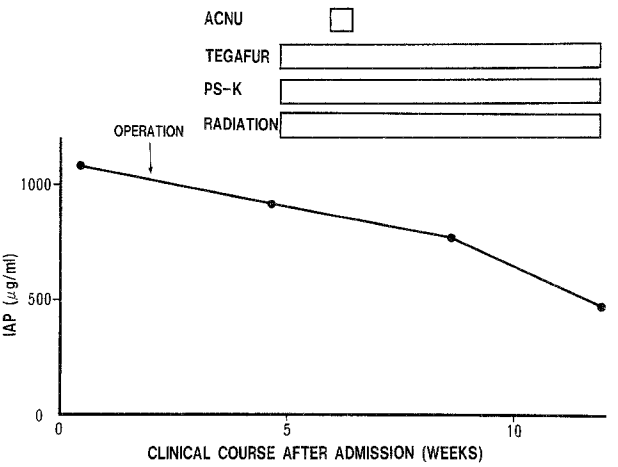

Fig. 4. Graph showing serial serum levels of immunosuppressive acidic protein (IAP) in a 62-year-old female patient with glioblastoma multiforme before and after the initiation of multimodality treatment by surgery, radiation and immunochemotherapy. Abbreviations; ACNU: 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride; PS-K: protein-bound polysaccharide, a nonspecific immunopotentiator

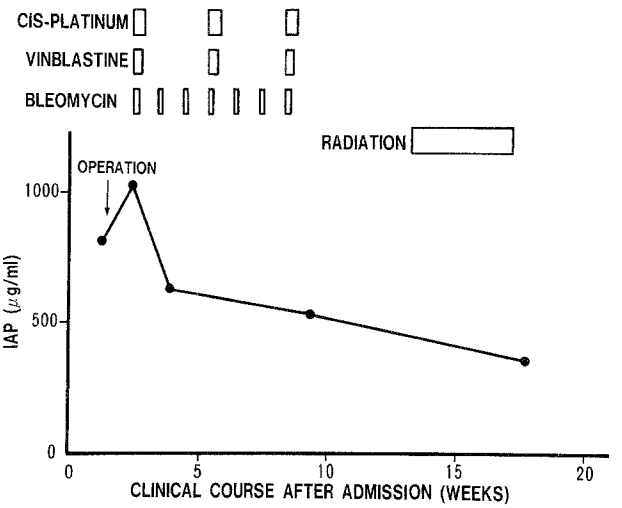

Fig. 5. Graph showing serial serum levels of immunosuppressive acidic protein (IAP) in a 32-year-old male patient with mixed seminoma and embryonal carcinoma before and after the initiation of multimodality treatment by surgery, radiation and chemotherapy. Operation consisted of orchiectomy and craniotomy

Correlation Between Serum IAP Levels and Clinical Status of the Patients

Since 17 of 46 pre-operative patients with brain tumours had elevated serum IAP levels in our studies according to the defined criteria, a search was made for variable(s) which could affect this distribution but making no use of the histological grade of malignancy of the brain tumours. For this purpose in reviewing the clinical data in our patients with brain tumours, no pharmacologic agents such as steroids or anticonvulsants were used prior to IAP evaluations. Serum IAP levels were then investigated and correlated with the clinical post-operative state of the patients as evaluated by performance status, and erythrocyte sedimentation rate, whether there was a recurrence or not.

Fig. 6 shows the distribution of serum IAP levels in the group of patients with varying performance status initially evaluated prior to treatment. The performance status was defined and classified into five grades according to the Radiation Therapy Oncology Group (11) as follows: grade 0; normal, 1; symptoms, but ambulatory, 2; in bed, up to 50% of the time, 3; in bed,

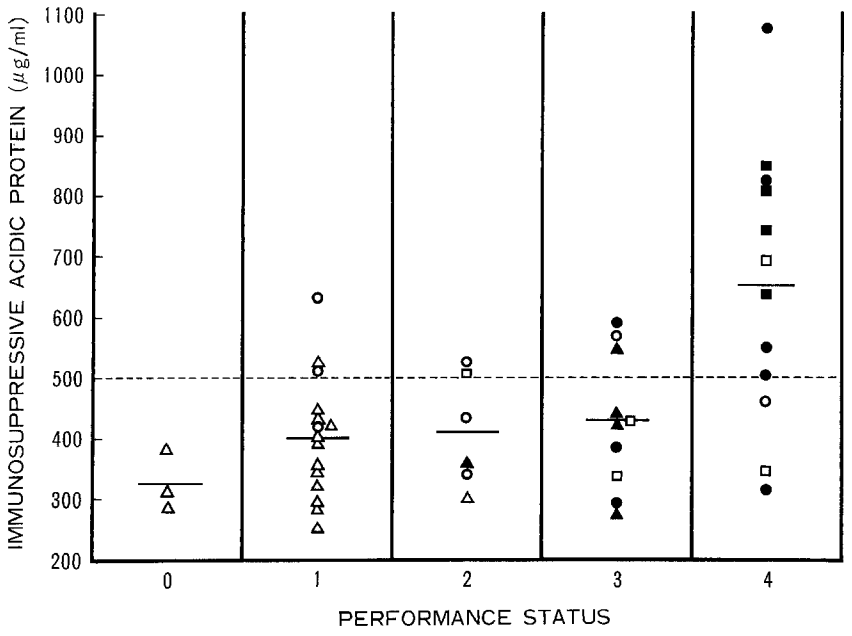

Fig. 6. A distribution of serum immunosuppressive acidic protein (IAP) in patients with varying performance status. The performance status is defined here according to the Radiation Therapy Oncology Group as follows: grade 0; normal, 1; symptoms, but ambulatory, 2; in bed, up to 50% of the time, 3; in bed, more than 50% of the time, 4; 100% bedridden. Forty-six pre-operative patients are represented here as circles, triangles and squares corresponding to gliomas, non-glial tumours, and metastatic brain tumours respectively. Closed ones indicate patients presenting with signs and symptoms of increased intracranial pressure. Statistical analysis of data using the unpaired student's t-test shows that grade 4 is statistically different from any other group ($P < 0.01$)

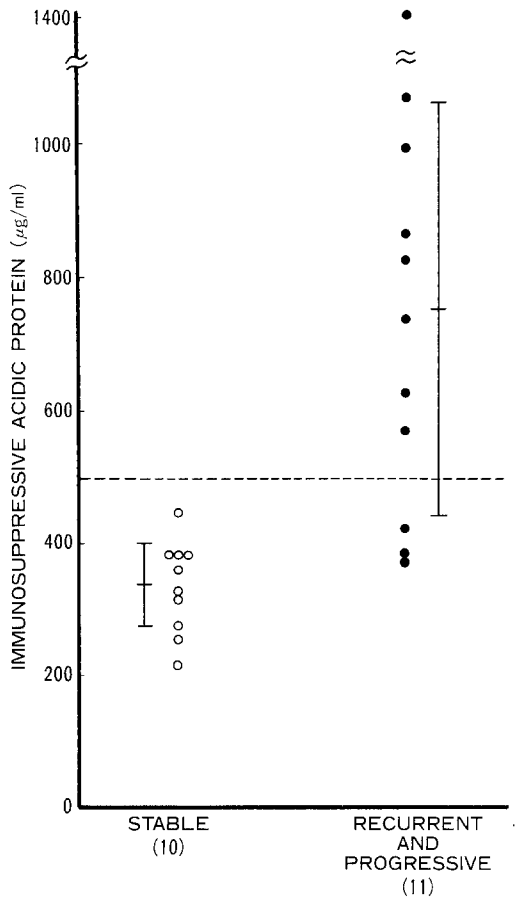

Fig. 7. Serum immunosuppressive acidic protein in 21 post-operative patients who had either stable or progressive disease. A statistically significant difference between these two groups of patients is seen ($P < 0.001$). The number in parenthesis indicates the number of patients belonging to each group

more than 50% of the time, 5; 100% bedridden. It was obvious that grade 4, mainly consisting of patients with glial and metastatic tumours, showed elevated IAP levels. In spite of the significant role in deterioration of performance status, increased intracranial pressure was not found directly related to an elevation of serum IAP.

Fig. 7 illustrates well, a potential correlation between serum IAP levels and the clinical condition of post-operative patients. All patients with stable disease had no evidence of tumour enhancement on CT scan, and their serum IAP levels were less than 500 μg/ml. The mean IAP level in this group was 338 ± 62 μg/ml. The serum IAP levels of this group did not statistically differ from those of normal controls. Serum IAP levels were greater than 500 μg/ml in 8 patients with recurrent and progressive disease. None had clinical evidence of infection, but most were taking steroids, an indication of the progressive status of their disease with performance status being either grade 3 or 4. The mean serum IAP in this group was 756 ± 315 μg/ml and significantly higher than that of the stable group.

The erythrocyte sedimentation rate was also evaluated in 34 pre-operative patients in conjunction with their serum IAP levels. As is clearly shown in Fig. 8, there is a significant correlation between serum IAP levels and erythrocyte sedimentation rate. The erythrocyte sedimentation rate is commonly elevated in many patients despite the lack of evidence of inflammatory processes, and may represent the disease status of the patients with regard to some aspect of tumour-host interactions.

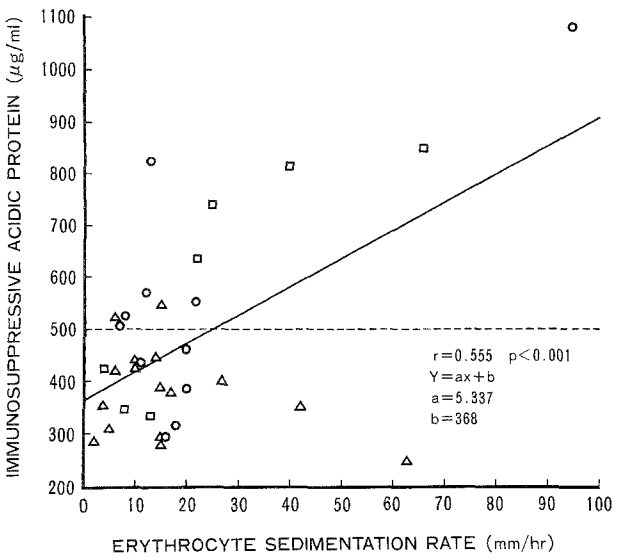

Fig. 8. A significant correlation between the serum levels of immunosuppressive acidic protein (IAP) and erythrocyte sedimentation rate (ESR) in 34 pre-operative patients consisting of gliomas (circles), non-glial tumour (triangles), and metastatic brain tumours (squares). Solid line represents a regression line expressed as $Y = 5.337x + 368$, where Y indicates IAP values and x indicates ESR. Regression coefficient abbreviated here as r is 0.555

Discussion

Several previous studies have demonstrated an increase of certain serum components in cancer patients referred to as acute-phase proteins[9, 31, 33]. It has also been shown that these proteins increase as the tumour burden increases and that their serum levels correlate inversely with immune competence as evaluated by both in vivo and in vitro assays of cell-mediated immunity[2, 3, 6, 8, 13]. Recently, isolation and identification of acidic glycoprotein was extensively performed by Tamura *et al.* with ascitic fluids of cancer patients utilizing analytical isoelectric focussing in polyacrylamide gel at pH 2.5 to pH 5[28]. This acidic protein was designated as "immunosuppressive acidic protein (IAP)" and found similar to but different from normal α_1-acid glycoprotein in term of molecular weight, carbohydrate content, isoelectric point, and suppressive effect upon the blastogenesis of mitogen-stimulated lymphocytes[24, 28]. Several investigators have documented to date elevated serum IAP levels in a high percentage of patients with a variety of cancers and have mentioned that the quantitative measurement of serum IAP was highly useful in the diagnosis and evaluations of these patients[12, 21, 22].

Similar attempts have previously been made to investigate whether or not there are any changes or abnormalities in the serum proteins of patients with brain tumour in order to utilize these proteins as tumour monitors for their management[1, 10, 15, 19, 23, 26, 32]. The present investigation may indicate that the serum IAP increases in response to the intracranial growth of malignant tumours. In this preliminary study a definite elevation of serum IAP was demonstrated in nine of 16 patients (56%) with gliomas and six of nine patients (67%) with metastasis. Furthermore a significant difference as to serum IAP levels was also seen between patients with glioblastoma multiforme and those with less malignant glial tumours. In contrast, the mean value of serum IAP for patients with non-glial, histologically benign intracranial tumours was 372 ± 81 μg/ml, which was not significantly higher than that of normal controls. It is of interest that there appears to be a difference between the serum IAP levels of benign and malignant cases and that serum IAP levels may correlate with the grade of anaplasia and malignancy of the tumour. A similar observation was also briefly reported by Tanaka and Sobue, suggesting measurements of serum IAP as a useful means for distinguishing high and low grade astrocytomas[29]. Thus, it may be further suggested that estimation of serum IAP could possibly act as a tumour indicator for differentiating between malignant and benign intracranial lesions.

The significance of IAP assays as a tumour indicator was well illustrated in the our case of metastatic seminoma in whom such conventional tumour markers as AFP and HCG were at an undetectable level even for a sensitive radioimmune assay. AFP identified in serum from tumours of germ cell origin, embryonal carcinoma, or more specifically, primitive yolk sac remnant is discussed in these papers[16, 27]. The beta unit of HCG appears to be produced by the trophoblastic elements of the germ cell tumours, and may be elevated in choriocarcinoma and embryonal carcinoma with numerous trophoblastic components[16, 25]. The histological evaluation of germ cell tumours is important with respect to both prognosis and choice of initial therapy. As is clearly shown in Fig. 5, it is suggested that serial changes of serum IAP levels correlated with the clinical course of the patients who were responsive to treatment, and yet in whom AFP and HCG evaluations were not useful as tumour markers. This may further imply an important role of IAP assays in the evaluation of patients with primary intracranial germ cell tumours, some of which do not have currently detectable markers.

However, caution should be exercised in utilizing IAP as a tumour indicator since elevated IAP has also

been found in patients with acute or chronic inflammatory conditions and collagen diseases[12]. It is therefore apparent that the usefulness of elevated IAP as a tumour indicator for malignant brain tumours is limited by a lack of specificity for glial tumours. Indeed, in the present investigation the mean value of the serum IAP in patients with gliomas or metastases was significantly higher than that in patients with non-glial, benign tumours or in healthy individuals. However, a difference of the serum IAP values did exist in patients with gliomas alone, ranging from 295 to 1,075 μg/ml, and 56% of them had elevated IAP values. Nevertheless, it is of great interest that serial measurements of serum IAP levels in patients with brain tumours are useful in evaluating responses to treatment and therefore in monitoring the course of the disease. Several other recent studies have also demonstrated that serum α_1-acid glycoprotein, which is similar to but different from IAP, provides prognostic information in patients with both glioblastoma multiforme[18] and cancer[7] elsewhere.

Impaired cellular immunity was been well documented by a number of investigators in patients with intracranial tumours, as evidenced by diminished in vivo cutaneous delayed hypersensitivity reaction and/or depressed in vitro lymphocyte responsiveness to either mitogens or antigens[4, 5, 20, 30, 34]. Brooks *et al.*[5] demonstrated that the IgG fraction of serum from patients with glioblastoma multiforme inhibited mitogen-induced lymphocyte blastogenesis as measured by tritiated-thymidine incorporation. He suggested that serum "blocking" factors identified as an IgG played a significant role in modifying lymphocyte function in this patient population. Kikuchi *et al.*[14] demonstrated significant suppression of mitogen-induced activation of normal lymphocytes in the presence of cyst fluid from glial tumours, indicating that brain-tumour cells may locally produce suppressive factors responsible for the inhibition of lymphocyte function. Preliminary identification of the factors present in tumour cyst fluid revealed that they were non-dialyzable and did not appear to be an IgG. The possible role of IAP upon immune competence in the brain-tumour patient population is currently being investigated in our laboratory.

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