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Toho Journal of Medicine Vol. 3 No. 4 掲載論文の紹介

Clinicopathological Significance of Serum NY-ESO-1 Antibodies in Patients with Gastric Cancer

Yajima S, Shimada H, Nemoto T, Ito M, Suzuki T, Nanami T, Oshima Y, Shiratori F, Kuwajima A, Kaneko H
Toho J Med 3 (4): 101—106, 2017

要約 :

Background: Although clinicopathological significance of serum NY-ESO-1 antibodies has been evaluated in patients with esophageal cancer, little information was available in the patients with gastric cancer. We, therefore, evaluated pathological and prognostic significance of serum NY-ESO-1 antibodies (s-NY-ESO-1-Abs) in patients with gastric cancer.

Methods: Serum samples were obtained from 75 patients with gastric cancer before surgery. Serum samples were analyzed using an enzyme-linked immunosorbent assay system to detect s-NY-ESO-1-Abs. A cut-off optical density value was fixed at 0.165 (mean plus three standard deviations for serum samples from the healthy controls). Clinicopathological factors and patients prognosis were compared between seropositive and seronegative patients. Tissue microarray of surgically resected tumor specimens were evaluated for NY-ESO-1 immunoreactivities.

Results: The overall positive rate for s-NY-ESO-1-Abs was 8% (4.9% of stage I, 0% of stage II, 13% of stage III, and 38% of stage IV patients). s-NY-ESO-1-Abs was significantly associated with distant metastases ($P < 0.001$) and stage progression ($P = 0.005$). Although seropositive patients showed worse survival rates than seronegative patients, the difference was not statistically significant ($P = 0.106$). Based on the tissue microarray, the association between serum antibodies and immunoreactivities was not confirmed.

Conclusions: Although s-NY-ESO-1-Abs was significantly associated with distant metastasis and tumor progression, the prognostic impact of s-NY-ESO-1-Abs was not found to be statistically significant. The association between immunoreactivities and autoantibodies reaction was not confirmed in the current study using tissue microarray.

KEYWORDS: NY-ESO-1, gastric cancer, serum autoantibody, tissue microarray

Diagnostic and Prognostic Impact of Serum p53 Antibody Titration in Colorectal Cancer

Suzuki T, Funahashi K, Ushigome M, Koike J, Nemoto T, Shimada H
Toho J Med 3 (4): 107—115, 2017

要約 :

Background: Although s-p53-Abs titers of cancer patients are distributed in wide range, the diagnostic and prognostic significance of preoperative and perioperative s-p53-Abs titers have not been evaluated in detail.

Methods: Preoperative and postoperative s-p53-Abs titers were assayed in 527 consecutive colorectal cancer patients surgically treated at Toho University Hospital between January 2010 and December 2014, and their associations with prognostic and clinicopathological variables were evaluated. To evaluate the clinical impact of s-p53-Abs titers, seropositive patients were divided into four groups by antibody titer as follows: 1.3 – 10 U/mL (very low); 10.1 – 50 U/mL (low); 50.1 – 200 U/mL (medium-high); and >200 U/mL (extremely high). The impact of perioperative change in the titer on survival was also evaluated.

Results: Among 527 patients, 155 (29.4%) were positive for s-p53-Abs. The positive rate of combination with CEA, CA19-9, and s-p53-Abs was significantly higher than the combination with CEA and CA19-9. Tu-mor depth, lymphatic invasion, and CA19-9 were significantly associated with s-p53-Abs status. Although the overall prognostic value of s-p53-Abs was not significant, the subgroup analysis found that extremely high titers were not associated with recurrence or poor survival. Tumor recurrences were more likely to occur in patients with medium-high titers. Although the medium-

high-titer group showed poor survival, the extremely high-titer group showed better survival than the other groups.

Conclusions: Combination assay with CEA, CA19-9, and s-p53-Abs was useful to increase positive rates to detect colorectal cancers. Although s-p53-Abs seropositivity itself was not independently associated with survival, high titers of s-p53-Abs had a paradoxical impact on tumor recurrence and patient survival.

KEYWORDS: serum p53 antibody, antibody titer, colon cancer, surgery, monitoring

Preoperative Chemotherapy, Previous Deep Vein Thrombosis/Pulmonary Thromboembolism, and Old age are Predictors of Preoperative Deep Vein Thrombosis

Sugano T, Uzawa M, Koda K, Tagami M, Kitamura T

Toho J Med 3 (4): 116—124, 2017

要約 :

Background: The purpose of this study was to identify predictors for preexisting thrombi before surgery so that a decision can be made as to the advisability of intermittent pneumatic compression, which is contraindicated in patients with thrombi, among the methods to prevent perioperative deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE).

Methods: Plasma D-dimer was measured preoperatively in 521 consecutive patients aged ≥ 20 years who underwent elective surgery. With a D-dimer level ≤ 0.72 $\mu\text{g/mL}$, thrombi were considered absent. With a D-dimer level > 0.72 $\mu\text{g/mL}$, lower limb venous ultrasonography was performed, and the presence/absence of thrombi was recorded. Multivariate logistic regression analysis was performed with presence/absence of thrombi as the response variable and predictors for DVT as explanatory variables.

Results: After excluding 14 patients in whom lower limb venous ultrasonography could not be performed because of fractures or skin lesions, the analysis included 507 patients. The p values for chemotherapy, previous DVT/PTE, and for age were < 0.05 . On receiver operating characteristic curve analysis with age, the threshold value at which the sum of sensitivity and specificity was the largest was 64 years. When patients with age ≥ 65 years, chemotherapy, or previous DVT/PTE were assumed to have thrombi, the positive predictive value was 0.14 and the negative predictive value was 0.99. Among patients with one or more of these three factors, 27 patients had actual thrombi; additionally, 22 of the 27 patients had no restrictions on daily living.

Conclusions: Chemotherapy, previous DVT/PTE, and old age are predictors of preoperative DVT.

KEYWORDS: preoperative deep vein thrombosis, prediction, intermittent pneumatic compression, D-dimer, lower limb venous ultrasonography

Presence of Autoantibodies against Ras-like GTPases in Serum in Stage I/II Breast Cancer

Kubota Y, Ogata H, Otsuka S, Kuwajima A, Saito F, Shimada H

Toho J Med 3 (4): 125—130, 2017

要約 :

Background: Ras-like GTPases, RalA, and RalB, are members of the Ras superfamily of small GTPases. Their aberrant activation is a major cause of human tumorigenesis induced by oncogenic Ras. Serum anti-RalA antibodies (s-RalA-Abs) are induced in patients with esophageal carcinoma, but there have been no reports regarding their presence in patients with breast cancer.

Methods: Serum samples from 100 patients with breast cancer and 73 healthy individuals were analyzed using an enzyme-linked immunosorbent assay system specifically developed for s-RalA-Abs. Positive rates of s-RalA-Abs and serum p53 antibodies (s-p53-Abs) were evaluated for two cut-off optical density values of 0.26 and 0.33 (i.e., the control

mean + 2 and 3 standard deviations), respectively.

Results: Overall positive rates for s-RalA-Abs at the two cut-offs were 24% and 11%, respectively, with no statistically significant differences between stage I and stage II cancers. The positive rate increased significantly in a combination assay of s-p53-Abs with s-RalA-Abs, and s-RalA-Abs was shown to be inversely associated with s-p53-Abs.

Conclusions: s-RalA-Abs in combination with s-p53-Abs may be a candidate serum antibody marker for breast cancer.

KEYWORDS: RalA, serum autoantibody, tumor marker, breast cancer, ELISA

Assessment of Pharmacological Effects of Mongolian Medicinal Plant *Adonis mongolica* in Guinea Pigs *in vivo* and *in vitro*

Izumi-Nakaseko H, Li W, Cao X, Nakamura Y, Ando K, Tanaka K, Enkhsaikhan A, Gotov C, Purevjav B, Chultemsuren Y, Nyambayar K, Dorjsuren N, Hagiwara-Nagasawa M, Naito A.T, Koike K, Sugiyama A
Toho J Med 3 (4): 131—141, 2017

要約 :

Background: *Adonis mongolica* (Ranunculaceae) is one of the endemic plants in Mongolia and has been used as a medicinal herb in Mongolian traditional medicine to treat patients with congestive heart failure showing tachycardia and edema. Although the plant has been empirically used in the last three decades, the precise information regarding its cardiovascular profile is still limited.

Methods: We assessed the cardiohemodynamic and electrophysiological profile of the water-soluble extract of *A. mongolica* using the guinea pig *in vivo* model ($n = 4$) and *in vitro* preparation ($n = 5 - 17$). In addition, the onset mechanism of the extract-induced effects on the heart rate and blood pressure *in vivo* ($n = 4$), and the atrial rate and contractile force *in vitro* ($n = 4 - 5$) were pharmacologically analyzed.

Results: The extract exerted the positive chronotropic, negative dromotropic, and vasopressor effects in addition to the proarrhythmic action *in vivo*. Meanwhile, it modestly decreased the atrial rate and aortic tension but increased the atrial contractile force *in vitro*. The pretreatment of *dl*-propranolol and prazosin significantly suppressed the positive chronotropic and vasopressor actions induced by the extract *in vivo*, indicating that the extract increased the sympathetic tone. Also, liquid chromatography-mass spectrometry analysis showed that water-soluble extract of *A. mongolica* contained eight kinds of cardiac glycosides.

KEYWORDS: cardiovascular, *Adonis mongolica*, Mongolian traditional medicine, LC-MS

Persistent Serum p53 Antibody Titer Following Mastectomy for Locally Advanced Breast Cancer Is Associated with the Recurrence of Cancer in the Central Nervous System

Kubota Y, Ogata H, Saito F, Nemoto T, Shimada H
Toho J Med 3 (4): 142—145, 2017

要約 :

Serum p53 antibody (s-p53-Abs) is induced by p53 overexpression in cancer cells. Therefore, residual cancer cells may be the cause of seropositivity even after radical surgery. Only few reports have evaluated perioperative changes and long-term monitoring of s-p53-Abs titers in patients with breast cancer. This case report presents long-term monitoring of s-p53-Abs titers in a patient with locally advanced breast cancer who developed recurrence in the central nervous system after radical surgery. The s-p53-Abs titer was monitored for 3 years during neoadjuvant chemotherapy and radical surgery in a 38-year-old woman with clinical stage IIB (T2N1M0) breast cancer. The levels of both the

carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) were within the normal range, but s-p53-Abs test result (54.8 U/ml) was positive. Neither computed tomography nor bone scintigraphy showed any distant metastasis before treatment. The patient received neoadjuvant chemotherapy (epirubicin, 100 mg/m²; cyclophosphamide, 500 mg/m²; and fluorouracil, 500 mg/m²; followed by docetaxel, 75 mg/m²). One and a half year after surgery, s-p 53-Abs results remained positive (5.66 U/ml), and brain metastasis was found. Despite resection for brain metastasis, s-p53-Abs titer remained high (5.88 U/ml), and carcinomatous meningitis was found. During the entire clinical course, although s-p53-Abs titers reflected the presence of residual cancer cells, both CEA and CA15-3 results were negative. The perioperative s-p53-Abs titer might be a useful marker for monitoring residual cancer cells in a patient with breast cancer. Recurrence in the central nervous system might be detected using s-p53-Abs monitoring.

KEYWORDS: serum p53 antibody, breast cancer, metastasis

Development of an Educational Equipment “Dock-kun” to Help School Children Master High-quality Cardiac Massage

Nakamura Y, Miyamoto T, Yamada M,

Goto A, Hagiwara-Nagasawa M, Izumi-Nakaseko H,

Ando K, Honda M, Naito A.T, Yoshihara K, Lurie K.G, Sugiyama A

Toho J Med 3 (4): 146—151, 2017

要約 :

One of the most effective ways to increase the cardiopulmonary resuscitation (CPR) rate of lay rescuers is through education of school children. We developed a learning tool called “Dock-kun” to help school children understand and master high-quality manual cardiac massage. With “Dock-kun,” school children can visually learn about the physiology of CPR and how to correctly perform this life-saving technique by checking the amount of water, a surrogate for blood, being pumped out of the model heart and sucked back into the heart with each compression-decompression cycle. The forward flow was maximized when the high-quality cardiac massage was performed with a depth of 4.5-5.0 cm and a rate of 105-110 compressions per minute. The real-time flow of “water” and feedback to the rescuer provide a means for school children to learn high-quality cardiac massage technique and understand its related mechanophysiology. Workshops using this new educational tool will greatly contribute to widespread knowledge of the high-quality cardiac massage among school children.

KEYWORDS: high-quality cardiac massage, Dock-kun, education, school children, mechanophysiology
