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Serum $\beta2-\!\!-\!\!Microglobulin$ Levels in Patients with Various Solid Cancer

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Abstract

Background: The level of β 2-M has become one of the most important prognostic factors and predictors of survival in patients with certain caner. The aim of this study was to investigate the serum levels of β 2-M in patients with various solid cancers, to find the prognostic and predictive value of serum β 2-M level elevating in patients with solid cancer.

Methods: A total of 1158 serum from 774 patients with various solid cancer and 384 patients with various solid benign tumor patients were analyzed by β 2-microglobulin ELISA kit, the data were analyzed by using statistical 36 packages for sciences (spss11.0) software.

Results: In patients with thyroid cancer, patients with breast cancer and that with liver cancer the mean β 2-microglobulin levels and positive rate were significantly higher than that in controls (p<0.05, p<0.01). In patients with other solid cancer including gastric, esophagus, intestinal and lung cancer the mean β 2-microglobulin levels have no significant difference compared with that in controls (p>0.05), and the positive rats were not significantly different compared with that in controls (p>0.05) except the patients with esophagus cancer in which the positive rate was significantly different compared with that in controls (p<0.05). In female breast cancer patients the mean

 β 2- microglobulin levels and the positive rate were significantly higher than that in breast benign tumor patients (p<0.05: p<0.05), no significant difference stages and clinical stages. In thyroid cancer patients the mean β 2-microglobulin levels and the positive rate were significantly higher than that in thyroid benign tumor patients (p<0.05, p<0.01), no significant difference in sex, ages, clinical stages, but the mean β 2-microglobulin levels and the positive rate were significantly higher in patients with follicular thyroid cancer than that in patients with mamillary thyroid 54 cancer patients.

Conclusion: β 2-M is an important tumor marker in breast, thyroid and liver cancer that would be one of assistantly diagnostic factors in patients with these cancers.

Introduction

β2-microglobulin is a low molecular weight protein consisting of a single chain of 100 amino acids which is part of the HLA antigen molecule, where it represents the invariant light chain [1,2]. It is expressed on the membrane of almost all nucleated cells, and is detectable in all body fluids as a shedding product of cell membrane [3]. Approximately 50% β 2-M is produced by lymphocytes and is filtered freely over the glomeruli. Under normal circumstances, more than 99.9% is reabsorbed in the proximal tubuli of the kidneys and metabolized there. In renal disease with damage to this segment of the nephro, eg. Acute tubuli, increased quantities of β2-M are excreted in the urine. If the rate of glomerular filtration is reduced, serum β 2-M is increased and this is also the case in persons with increased cell division despite normal renal function [4]. Therefore, the serum and urine β 2-M concentrations are used to monitor glomerular and tubular nephropathies [5], and its level is elevated in patients with certain malignancies, including solid and liquid tumors [6,7]. The increased tissues and serum level of β 2-M is associated a high 74 tumor burden and poor prognosis. Thus, the level of β 2-M has become one of the most important prognostic factors and predictors of survival in patients with certain cancers [7-9]. But, the clinical usefulness of measuring serum β 2-M in some solid tumors is controversial in the literature [10,11]. The aim of this study was to investigate the serum levels of B2-M in patients with various solid cancer.

Patients and Methods

A total of 1158 serum from 774 patients with various solid cancer and 384 patients with various solid benign tumor who were referred to the Tumor Hospital of Gansu province for treatment, proved by clinical and histopathological evidence, and all patients had normal renal function; 1002 serum from healthy individual who were referred to healthy examination center of Ren Min Hospital of Gansu province for physical examination. The patients characteristics and healthy controls are listed in table 1.

Under aseptic precautions venous blood was drawn preoperatively and serum was separated. The samples were frozen at -20°C until assay. The serum was analyzed by Enzyme Linked Immunosorbent Assay (β 2-microglobulin ELISA kit, developed by Department of Medicine Biotechnology. Medicine and Science Research Institute of Gansu province). The data were analyzed by using statistical package for sciences (spss11.0) software, p < 0.05 were considered 94 significant.

Results

Mean levels of serum β 2-microglobulin in solid cancer patients

In order to get mean β 2-microglobulin levels in healthy individual

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to be used as controls and the 2 times mean β 2-microglobulin levels in controls was used as cut off. The mean levels of serum β 2-microglobulin and the positive rate in patients with various solid cancer and controls are given in table 2. In patients with thyroid, breast and liver cancer the mean β 2-microglobulin levels and the positive rate were significantly higher than that in controls (p<0.05, figure 1A; p<0.01, figure 1B). In patients with other solid cancer including gastric, esophagus, intestinal and lung cancer the mean β 2-microglobulin levels and the positive rats have no significant difference compared with that in controls (p >0.05, figure 1A; p > 0.05; figure 1B), except the esophagus cancer patients in which the positive rate was significantly different compared with that in control (p<0.01; figure 1B).

Mean levels of serum β 2-microglobulin in female patients with breast cancer and breast benign tumor

Group	No	sex		merages(years)	
		Men	Women	(ranges)	
Controls	1002	559	443	41.08(6-94)	
Thyroid Ca.	95	26	69	48.49(17-79)	
Thyroid benign- tumors.	243	54	189	53.9(8-79)	
Breast Ca.	205	4	201	47.7(19-78)	
Breast benign- tumors.	141	6	135	41.2(2-78)	
Liver Ca.	77	57	20	54.0 (30-80)	
Gastric Ca.	148	114	34	57.1 (25-78)	
Esophagus Ca.	72	64	8	61.2 (42-77)	
Intestinal Ca.	58	42	16	60.4 (26-84)	
LungCa.	119	78	41	56.7(17-80)	

Table 1: Patients characteristics and healthy controls.

Group	No	Serum β2-M	positive rate		
		mean ±SD	Р	%	Р
Controls	1002	0.99 ± 4.47		7.88	
Thyroid Ca.	95	2.84±4.56	<0.05	34.73	<0.01
Breast Ca.	205	2.02±4.78	<0.05	28.29	<0.01
Liver Ca.	77	2.81±6.16	<0.05	23.37	<0.01
Gastric Ca.	148	1.25±5.24	>0.05	11.48	>0.05
Esophagus Ca.	72	1.47±3.20	>0.05	18.05	<0.01
Intestinal Ca.	58	1.51±4.71	>0.05	13.79	>0.05
Lung Ca.	119	0.94±2.03	>0.05	11.76	>0.05

Table 2: Mean levels of serum $\beta 2\text{-microglobulin}$ in Patients with various solid Cancer and controls.



Figure 1: Mean level and positive rate of serum β 2-microglobulin in Patients with various solid Cancer and controls. A. mean level of serum β 2-microglobulin, 1.Thyriod Ca.,2.Breast Ca.,3.Liver Ca.,4.Gastric Ca., 5.EsophagusCa.,6. Intestinal Ca.,7.Lung Ca.,8.Controls, VI p<0.05. B. positive rate of serum β 2-microglobulin, 1.Thyriod Ca.,2.Breast Ca.,3.Liver Ca.,4.Gastric Ca.,5. EsophagusCa.,6.Intestinal Ca.,7.Lung Ca.,8.Controls VI VI P<0.01.



Figure 2: Mean level and positive rate of serum β 2-microglobulin in female patients with breast cancer and breast benign tumor, patients with thyroid cancer and thyroid benign tumor. A. mean level of serum β 2-microglobulin in patients with breast cancer. 1.female patients with breast cancer, 2. female patients with breast benign tumor, 3. contorls. B. positive rate of serum β 2-microglobuli in patients with breast cancer. 1.female patients with breast cancer, 2. female patients with breast cancer, 2. female patients with breast cancer, 1.female patients with breast cancer, 2. female patients with breast benign tumor, 3. contorls. VI p<0.05. C. Mean level of serum β 2-microglobulin in patients with thyroid cancer. 1.patients with thyroid cancer, 2. patients with thyroid benign tumor, 3. contorls,VI p<0.05, .D.positive rate of serum β 2-microglobulin in patients with with thyroid cancer, 1.patients with thyroid cancer, 2. patients with thyroid benign tumor, 3. contorls, VI p<0.05, .D.positive rate of serum β 2-microglobulin in patients with with thyroid cancer, 1.patients with thyroid cancer, 2. patients with thyroid benign tumor, 3. contorls, VI p<0.05, .D.positive rate of serum β 2-microglobulin in patients with with thyroid cancer, 1.patients with thyroid cancer, 2. patients with thyroid benign tumor, 3. contorls, VI p<0.05, .D.positive rate of serum β 2-microglobulin in patients with with thyroid cancer, 1.patients with thyroid cancer, 2. patients with thyroid benign tumor, 3. contorls, VI p<0.05, .D.positive rate of serum β 2-microglobulin in patients with with thyroid cancer, 1.patients with thyroid cancer, 2. patients with thyroid benign tumor, 3. contorls, VI p<0.01.

The mean β 2-microglobulin levels and the positive rats in female patients with breast cancer and breast 112 benign tumor were analyzed, the 2 times mean β 2-microglobulin levels in control were used as its cut off. The results were showed in table 3. In female patients with breast cancer the mean β 2-microglobulin levels and the positive rate were significantly higher than that in control and patients with breast benign tumor (p<0.05 figure 2A, p<0.05; figure 2B). In patients with breast benign tumor the mean β 2-microglobulin level has no significant difference compared with that in control, but the positive rate was significantly higher than that in control (p>0.05 figure 2A: p<0.05, figure 2B). In female patients with breast cancer the mean β 2microglobulin levels have no significant difference at ages and clinical stages, but the positive rate in ages of \geq 60 years was significantly lower than that in ages of < 60 years (p<0.01).

Mean levels of serum β 2-microglobulin in patients with thyroid cancer and thyroid benign tumor

The mean β 2-microglobulin levels in patients with thyroid cancer and thyroid benign tumor were analyzed, the 2 times mean β 2-microglobulin level in controls was used as its cut off, and the results were showed in table 3. In patients with thyroid cancer the mean β 2-microglobulin levels and the positive rate were significantly higher than that in control and patients with thyroid benign tumor (p<0.05, p<0.01; figure 2C,D). the mean β 2-microglobulin levels and the positive rate have no significant difference between controls and patients with thyroid benign tumor (p>0.05, p>0.05; figure 2C,D) In patients with thyroid cancer the mean β 2-microglobulin levels and the positive rate have no significant difference at sex, and ages, except the age of 40-60 years in that the positive rate have significant difference compared with that in age <40 years. The mean β 2-microglobulin levels and the positive rate have no significant difference in clinical stages I-III (p> 0.05, p>0.05) but having significant difference in clinical

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Group	No	Serum β2- <i>M (mg/L,)</i> (mean L SD)	Р	positive rate (%)	Р
Controls	1002	0.9 9±4.47		7.88	
Female benign tumor	141	1.19±2.55	>0.05	20.00	<0.05
Female breast Ca.	201	2.0 5±4.81	< 0.05	30.84	<0.05
Female breast Ca,					
ages:					
< 40years	46	2.51± 6.64		39.13	
40-60years	127	2.15± 4_47	>0.05	28.34	>0.05
>60years	19	0.84±1.75	>0.05	7.14	< 0.01
cilinical stages					
I	14	1.77±2.48		28.57	
II	116	2.50±3.61	>0.05	34.48	>0.05
III	24	2.18 ± 4.15	>0.05	33.33	>0.05
IV	14	0.74±1.85	>0.05	28.57	>0.05
Benign tumor	243	0.68±2.20	> 0.05	7.81	> 0.05
Thyroid Ca.	95	2.84±4.56	<0.05	34.73	<0.01
Thyroid Ca.:					
Male:	26	1.71±2.88		23.07	
female:	69	3.26±5.00	> 0.05	36.23	> 0.05
ages:					
< 40years	31	2.04±4.35		22.58	
40-60years	45	3.66±4.96	> 0.05	46.67	<0.05
> 60years	19	2.17±3.71	> 0.05	26.31	> 0.05
cilinical stages					
1	28	2.07±4.18		28.57	
11 - 111	18	2.15±1.674.95	> 0.05	33.33	> 0.05
IV	20	0.23±1.35	< 0.01	0	<0.01
Cell types					
Follicularthyroid adenoma	42	2.07±3.75		19.07	
Papillary-thyroid adenoma	18	2.71±4.25	> 0.05	44.44	<0.05

Table 3: Mean levels of serum β2-microglobulin in female breast cancer patients , thyroid cancer patients and benign tumor patients.

stages IV(p<0.001, p<0.01). The mean β 2-microglobulin levels have no significant difference in cell types (p>0.05), but the positive rate were significantly higher in patients with folliculaire thyroid cancer than that in patients with mamillary thyroid cancer patients (p<0.05). Because of the cases are little, the data of male patients with thyroid cancer was not analyzed. Most patients with live cancer cannot have operation and the cases are little, the data of patients with live cancer was not analyzed.

Discussion

Elevated levels of β 2-microglobulin have been observed in a variety of patients with advanced malignancy and the level of β 2-M has 149 become one of the most important prognostic factors and predictors of survival in patients with certain cancers [6-9,12-15]. In the present study, the serum elevated levels of β 2-microglobulin in patients with breasts cancer, thyroid cancer and liver cancer have been observed to be significantly higher than that in the controls, and the positive rate was respectively 28.85% for breast cancer, 34.78% for thyroid cancer and 23.76% for liver cancer, significantly higher than that in the controls (7.88%), but the serum level elevating of β 2-microglobulin and the positive rate in patients with gastric cancer, esophagus cancer, intestinal cancer and lung cancer have no significant difference compared with the controls except the esophagus cancer in which the positive rate was 18.05%, significantly higher than that in the controls. The results demonstrates that serum β 2-microglobulin may be valuable marker in the diagnosis of breasts cancer, thyroid cancer, liver cancer and esophagus cancer, but as a independent tumor marker, the clinical valuation of serum level elevating of β 2-microglobulin in the diagnosis of gastric cancer, intestinal cancer and lung cancer seems limited, agreeing with the literature [11,12,14].

In order to avoid false positive results and decide the reliable cut off level, the serum level changing of β 2-microglobulin of healthy individuals 167 during at different ages and sex were analyzed, the results showed that the β 2-M level in healthy individuals have no significant difference in sex and age except the females of \leq 40 years in whom the β 2-M level was significantly lower than that of >40 years, suggesting that when evaluated the β 2-M level was used to elevate the positive rate in female patients with cancer, the individual cut off levels was needed.

In femal patients with breast cancer the mean β 2-microglobulin levels and positive rate have no significant difference at ages, clinical stages and cell type, but the positive was highest in patients of \leq 40 years, suggesting that detecting serum β 2-microglobulin level in patients of \leq 40 years may have more clinical valuation than that in the patients of > 40 years.

In patients with thyroid cancer the mean β2-microglobulin levels

and positive rate have no significant difference at sex, age and clinical stages but positive was highest in patients in range 40-60 years, and in patients with folliculaire thyroid cancer the mean β 2-microglobulin levels and the positive rate were significantly higher than that in patients with mamillary thyroid cancer, suggesting that detecting serum β 2-microglobulin level in range 40-60 years may have more clinical valution than that in the patients of 185<40 years and >60 years, and more senstive in folliculaire thyroid cancer than in other cell type.

Another observation that emerged from the current study is the serum levels elevating of β 2-M have no significant diagnostic valuation in thyroid cancer and breast cancer patients of \geq 60 years. These observation are not in line with previous report showing that the serum β 2-M levels have independent prognostic role in patients with AML who are \geq 60 years old [7]. This observation may be explained that the serum β 2-M levels elevated in normal individual of \geq 60 years under normal physiological condition may be due to the β 2-M metabolizing decreasing. Therefore, the serum β 2-M level elevating in patients of \geq 60 years has no significant difference compared with normal individual.

The mechanism of altered β 2-M level is not yet clearly understood. Various Possibilities for increased serum level of β2-M suggested are an increased cellular activity in malignancy being responsible for an increased release of β 2-M, β 2-M being a constituent of HLA molecules ,cell membrane turnover or cell division could increased the shedding of β 2-M [16]. β 2-M and HLA molecules variably expressed on the surface of tumor cells [17-23]. Because the HLA class I antigen 203 are key component of the immune system, the recognition of tumor-specific antigen by cytotoxic T cell is dependent on intact HLA expression. Malignant cells with modified or lacking of HLA expression may escape from the normal host immune response and proliferate uncontrollably [24-26]. A structural defect of the HLA complex may also result in changes in epitope expression and increased release of β 2-M in serum [27-30]. This mechanism is consistent with the observation that serum β2-M levels reflect tumor burden and cell turnover [27,28,31,32]. This mechanism also can explain why the mean β 2-microglobulin levels in patients with breast, thyroid and liver cancer were significantly higher than that in patients with benign tumor in present study, the reason may be that the cancer cell burden and turnover more quickly than benign tumor.

We cannot explained the reason why the mean elevated β_2 microglobulin level significantly higher in patients with breast, thyroid and liver cancer than that in patients with other solid cancer, but we noted that the breast cancer and thyroid cancer have same feature that the breast cancer and thyroid cancer both are glandular cancer and both are correlated with the estrogen receptor (ER), progesterone receptor (PR) and HER2/neu [33,34]. Whether β_2 -microglobulin have any correlation with the ER, PR and 222 HER2/neu in breast and thyroid cancer need further studying.

The another possibility of the mechanism responsible for an increase in β 2-M expression during the progression of cancer is that the tumors contain three β 2-M alleles instead of one. Recently, Nomura et al.[36] demonstrated that promoted growth of β 2-M in human renal cell carcinomas while interrupting the β 2-M signaling pathway lead to apoptosis of tumor cells Huang et al. [37] reported that β 2-M is a signaling and growth promoting factor for human prostate cancer bone metastasis, β 2-M stimulate growth and enhance osteocalcin(OC) and bone sialoprotein (BSP) gene expression in human prostate cancer cells by activating cyclic AMP(cAMP)-dependent protein kinase A signaling pathway Chen et al. [35] reported that β 2-M may act as an effective growth promoting factor to facilitate tumor progression, invasion,

and migration in oral cavity squamous cell carcinoma. Yang et al. [38] discovered that monoclonal antibodies (mAbs) specific to human β 2-M induce apoptosis in vitro and were therapeutic in mouse models of myeloma and other hematological tumor cells via recruiting MHC class I molecules to lipid rafts and activating Lyn and PLC γ 2, leading to activated JNK and inhibited P13K/Akt and ERK, compromised mitochondrial integrity, and caspase-9-dependent cascade activation [38]. Accordingly, these finding address 241 that β 2-M must play a farreaching function than just a housekeeping gene or role on stabilization and presentation of MHC class I molecule in cells, an elevated serum β 2-M may become one of important diagnosis factor, prognostic factor and survival predictors. The correlation of β 2-M with Development, progression and differentiation of tumor need further studying.

In conclusion, we found that the serum elevated level of β_2 microglobulin in patients with breasts cancer, thyroid cancer and liver cancer have been observed to be significantly higher than that in the controls, suggesting that β_2 -M is an important tumor marker in breast, thyroid and liver cancer that would be one of important assistantly diagnostic factors in patients with these cancer.

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