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Liver function test and its alteration in female genital and gonadal carcinoma patients

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Abstract: ***Introduction:*** *Gynecological cancer is one of the most common leading cancer in worldwide as well as India. Liver function tests are helpful to evaluate patients with hepatic dysfunction. These biomarkers may be used to identify the presence of liver disease during the follow-up period. The aim of the study was to evaluate any association between liver function parameters and pattern of liver dysfunction in metastasis of female genital and gonadal cancer patients.* ***Materials and Methods:*** *In this study 100 female genital and gonadal cancer patients and 100 women with benign genital and gonadal diseases who attended at Out Patient Door (OPD) of IPGME&R and SSKM Hospital, Kolkata, India during the period from June, 2016 to June, 2017 were included. Liver function test (LFT) was measured by semi auto analyzer by ERBA Chem - 5 Plus V2 by TRANSASIA using spectrophotometry principle. Statistical analysis was done by SPSS 20.0.1 software.* ***Results and Analysis:*** *Statistical significant association was found between ALP, albumin, globulin and ratio with disease status (Table-1). The significant difference was in ALP, albumin and globulin for the cancer patients (Table-2). As per cancer stage, t-test showed that ALT of the advance stage (stage-0, I, II) of cancer patients was significantly higher than that of early stage (stage-III, IV) (t_{98}-2.29; p=0.024) and ALP of the advance stage of cancer patients was significantly higher than that of early stage (t_{98}-2.33; p=0.022).*
Discussion and Conclusion: *Estimation of ALP levels in serum was less sensitive than imaging procedure, but it may be valuable for screening and early detection for metastases in female genital and gonadal cancer patients.*

Key Words: *Female genital and gonadal cancer, Liver function test, Alkaline Phosphatase*

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I. Introduction:

Liver function test (LFT) is a part of the workup for liver disease. The parameters that are included are:
i. Aspartate transaminase (AST) or serum glutamic oxaloacetic transaminase (SGOT)
ii. Alanine transaminase (ALT) or serum glutamic pyruvic transaminase (SGPT)
iii. Albumin
iv. Globulin
v. Bilirubin (direct and indirect)
vi. Alkaline Phosphatase (ALP)

SGOT and SGPT are important biomarkers for hepatic (liver) injury. Involvement of the liver dysfunction some diseases are of vital importance factor for development of non-hepatic disorder. Liver is a multifunctional organ and components of the liver function test rather specific to display particular componential dysfunction (S) like - functionality (e.g. albumin); some with cellular integrity (e.g. transaminase) and some with the biliary tract (eg. ALP). Liver function tests are helpful to evaluate patients with hepatic dysfunction. These biomarkers may be used to 1. to identify the presence of liver disease, 2. to distinguish among different types of hepatic disorders, 3. to determine the extent of liver damage, 4. response to treatment during the follow-up period [1].

The incidence of advanced stage carcinoma is significantly high in the Indian scenario. 6-25% of patients with metastatic breast cancer were found to have liver metastases [2]. Gynecological cancer is one of the most common leading cancer in worldwide as well as India [3]. Symptoms of cancer patients with liver metastases were upper abdominal fullness, a mass, ascites, jaundice and weight loss. CT Scan, Ultrasound and liver function tests were used to assess liver metastases in the patients [4].In postmortem report, 70% of patients who died due to metastatic cancer had bone disease [5,6] also. Usually, the axial skeleton was affected by bone

metastases. In adults, the axial skeleton includes the red marrow, the cells and extracellular matrix of which plays a major role in the formation of bone metastases. Circulating blood from anatomic sites may drain directly into the axial skeleton [6]. Biological and molecular behavior of the tumor cells and tissues influenced the pattern of metastatic spread [7-10]. Majority of the advanced breast carcinoma patients died due to metastasis of the tumor. In the process of metastasis, malignant cells spread from the primary site to the secondary site via circulatory system. Alkaline phosphatase (ALP) contains a group of isoenzymes that catalyse the hydrolysis of phosphate esters in basic medium, generating an organic radical and phosphate ions [11]. Serum ALP regulates activity of several isoenzymes found in the bone, liver, kidney and intestinal lining. In bone metastases, the skeletal isoenzyme created in osteoblasts is released in large amounts. ALP plays a major role in evaluating biliary obstruction and progression of liver disease in patients. Various studies have reported that estimation of ALP isoenzyme activity is an important factor in the diagnosis and clinical evaluation of breastcancer patients [12, 13,14]. Elevated serum ALP level was found among patients with bone metastasis compared to those without bone metastases [13-16].The aim of the study was to evaluate any association between Liver Function parameters and pattern of liver dysfunction in metastasis of female genital and gonadal cancer patients

II. Materials and Methods:

Patient Selection

In this study 100 female genital and gonadal cancer patients and 100 women with benign genital and gonadal diseases who attended at Out Patient Door (OPD) of IPGME&R and SSKM Hospital, Kolkata, India during the period from June, 2016 to June, 2017 were included. Information related to demography of the patients was obtained by direct interview with the patients. After clinical examination all patients were subjected to true-cut biopsy or FNAC for the confirmation of their diagnosis. Information of these patients was maintained in the department of G & O in this institute. Cancer for cervix, ovary, vulva and endometrial patients will include. Intestine cancer and breast cancer were excluded.

Semi Auto Analyzer

All tests were done by semi auto analyzer by ERBA Chem - 5 Plus V2 by TRANSASIA using spectrophotometry principle. Aspartate transaminase (AST) or serum glutamic oxaloacetic transaminase (SGOT), Alanine transaminase (ALT) or serum glutamic pyruvic transaminase (SGPT), Total protein, Albumin, Globulin and Alkaline Phosphatase (ALP). The azobilirubin produced by the reaction between bilirubin and the diazonium salt of sulfanilic acid shows maximum absorbption at 550 nm in an acid medium. The intensity of the color produced is proportional to the quantity of bilirubin which has reacted. In the absence of an accelerator, only conjugated bilirubin reacts. In the presence of an accelerator, dimethylsulphoxide (DMSO), the non-conjugated bilirubin also participate in the reaction, thus determine the level of total bilirubin. AST present in the sample catalyses the transfer of the amino group from L-aspartate to 2-oxoglutarate forming oxaloacetate and L-glutamate. Oxaloacetate in the presence of Nicotinamide adenine dinucleotide (NADH) and Malate dehydrogenase (MDH) is reduced to L-malate. In this reaction NADH is oxidized to NAD. The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD. Addition of Lactate dehydrogenase (LDH) to the reagent is necessary to achieve rapid and complete reduction of endogenous pyruvate so that it does not interfere with the assay. ALT catalyzes the transfer of the amino group from L-alanine to α-ketoglutarate resulting in the formation of pyruvate and L-glutamate. LDH catalyzes the reduction of pyruvate and the simultaneous oxidation of NADH to NAD. The resulting rate of decrease in absorbance is directly proportional to ALT activity. The peptide bonds of protein react with copper II ions in alkaline solution to form a blue-violet ion complex, (the so called biuret reaction), each copper ion complexing with 5 or 6 peptide bonds. Tartrate is added as a stabiliser whilst iodide is used to prevent auto-reduction of the alkaline copper complex. The colour formed is proportional to the protein concentration and is measured at 546 nm. Albumin binds with Bromo Cresol Green (BCG) at pH 4.2 causing a shift in absorbance of the yellow BCG dye. The blue-green colour formed is proportional to the concentration of albumin, when measured photometrically between 540–630 nm with maximum absorbance at 625 nm. This method utilises 4-nitrophenyl phosphate as the substrate. At the pH of the reaction, 4-nitrophenol has an intense yellow colour. The reagent also contains a metal ion buffer system to ensure that optimal concentrations of Zinc and Magnesium are maintained. The metal ion buffer can also chelate other potentially inhibitory ions which may be present. The reaction is monitored by measuring the rate of increase in absorbance at 405 or 415 nm which is proportional to the activity of ALP in the serum

Statistical analysis

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 20.0.1 and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in

mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Significance level was set at 0.05 and confidence intervals were at 95 percent level.

III. Results and Analysis:

Distribution of age in cases and controls

The mean age (mean± s.d.) of cases was 46.06±9.88 years with range 31-70 years and the median age was 46 years. The mean age (mean± s.d.) of controls was 46.63±9.73 years with range 31-70 years and the median age was 44 years. t-test showed that there was no significant difference in mean age of the cases and controls ($p>0.05$). Thus the cases and controls were matched for age.

Association of LFT between cases and controls

In cancer patients 27(27.0%) were having high level (>35 U/L) of ALT, 27(27.0%) were having high level (>40 U/L) of AST, 24(24.0%) were having high level (>125 U/L) of ALP, 60(60.0%) were having low level (<3.5 mg/dl) of albumin, 32(32.0%) were having high level (>3.5 mg/dl) of globulin, 45(45.0%) were having low level (<1.0) of albumin-globulin ratio and 8(8.0%) were having high level of total bilirubin. In control women 20(20.0%) were having high level (>35 U/L) of ALT, 20(20.0%) were having high level (>40 U/L) of AST, 8(8.0%) were having high level (>125 U/L) of ALP, 18(18.0%) were having low level (<3.5 mg/dl) of albumin, 14(14.0%) were having high level (>3.5 mg/dl) of globulin, 12(12.0%) were having value level (<1.0) of albumin-globulin ratio and 6(6.0%) were having high level of total bilirubin. Statistical significant association was found between ALP, albumin, globulin and ratio with disease status (Table-1).

Comparison of LFT in cases and controls

As per liver function test, t-test showed that ALP of the patients was significantly higher than that of control (t_{198}-4.96; $p<0.001$), albumin of the patients was significantly higher than that of control (t_{198}-5.58; $p<0.001$), globulin of the patients was significantly higher than that of control (t_{198}-3.43; $p<0.001$) and albumin-globulin ratio of the patients was significantly lower than that of control (t_{198}-5.68; $p<0.001$). There was no significant difference in ALT (t_{198}-1.06; $p>0.050$), AST (t_{198}-1.21; $p>0.050$) and serum bilirubin (t_{198}-1.15; $p>0.050$) in the control and patients (Table-2).

Pattern of liver dysfunction in female genital and gonadal cancer

As per liver function test, t-test showed that high level of ALT of the patients was significantly higher than that of control (t_{198}-11.58; $p<0.001$), AST of the patients was significantly higher than that of control (t_{198}-11.72; $p<0.001$), ALP of the patients was significantly lower than that of control (t_{198}-26.84; $p<0.001$), albumin of the patients was significantly lower than that of control (t_{198}-21.43; $p<0.001$), globulin of the patients was significantly higher than that of control (t_{198}-21.47; $p<0.001$) and albumin-globulin ratio of the patients was significantly lower than that of control (t_{198}-15.46; $p<0.001$). But there was no significant difference in serum bilirubin (t_{198}-1.15; $p>0.050$) in the control and patients (Table-3).

Variation of LFT in early and advance stages of female genital and gonadal cancer

As per cancer stage, t-test showed that ALT of the advance stage (stage-0, I, II) of cancer patients was significantly higher than that of early stage (stage-III, IV) (t_{98}-2.29; $p=0.024$) and ALP of the advance stage of cancer patients was significantly higher than that of early stage (t_{98}-2.33; $p=0.022$). But there was no significant difference level of AST level (t_{98}-1.91; $p=0.059$), level of albumin (t_{98}-0.36; $p=0.720$), level of globulin (t_{98}-0.11; $p=0.909$), level of albumin-globulin ratio (t_{98}-0.26; $p=0.792$) and level of total bilirubin(t_{98}-0.59; $p=0.558$) in the advance and early stage of cancer patients.

IV. Discussion:

SGOT and SGPT both are liver enzyme and SGPT rather specific biomarkers for hepatic disease**.** Daniel S et al reported that elevated SGOT and SGPT were increased in cancer patients with liver metastasis [4]. We found high levels of SGOT and SGPT in patients with liver metastasis. ALP levels may predict bone metastases, and to some extent liver metastases [15]. B Prabasheela et al showed that higher ALP level was observed in patients with recurrence or metastases in bone or liver [13]. Various studies have reported that biochemical parameters such as ALP, γ – glutamyltransferase, SGOT, SGPT and carcinoembryonic antigen are useful for diagnosis of liver metastasis [14]. This study reported that most of the patients having high serum SGPT (ALT) activity were associated with liver metastasis, secondary to female genital and gonadal cancer. However elevated level of SGOT was noted in both metastatic and non-metastatic variety patients with breast

cancer. Increased ALP levels indicated either bone or liver metastasis. High circulating ALP was associated with an increased risk for distant metastasis [16]. Cancer patients with bone metastasis had significantly poorer prognosis compared to patients without metastasis [15,16]. The significant difference in serum ALP level was observed among patients with and without bone metastasis in this study.

High levels of ALP, ALT and AST were significant risk factors for development of female genital and gonadal cancer patients, and similarly elevated levels were associated with more advanced disease stage.ALP is raised in both bone and liver metastasis. In the case of bone metastasis, elevated ALP mainly originates from osteoblast cells, whereas in liver metastasis increased level of ALP is mainly due to intra hepatic biliary obstruction. But alteration in the synthetic function of the liver is not noted in female genital and gonadal cancer patients. Excretory and secretory functions are not significantly diminished in female genital and gonadal cancer patients, as evident by normal serum bilirubin.

V. Conclusion:

In this study, SGOT levels were found to be increased in female genital and gonadal cancer patients. SGOT is a nonspecific enzyme for liver. This raised concentration may be due to cellular breakdown in the malignant state. But SGPT which is a more specific liver enzyme is particularly raised in the patient of female genital and gonadal carcinoma with liver metastasis.Abnormal serum ALP was found in our research work probably due to liver or bone metastases and further study will be required to confirm our findings. Estimation of ALP levels in serum was less sensitive than imaging procedure, but it may be valuable for screening and early detection for metastases in female genital and gonadal cancer patients. We concluded that evaluation of ALP may be an important monitor for therapeutic efficiency in female genital and gonadal cancer patients.

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Table 1 Association of LFT between cases and controls

LFT		Case	Control	χ^2 value	p-value
		Number (%)	Number (%)		
ALT (U/L)	High (>35)	27(27.0)	20(20.0)	1.36	0.243
	Normal (≤35)	73(73.0)	80(80.0)		
AST (U/L)	High (>40)	27(27.0)	20(20.0)	1.36	0.243
	Normal (≤40)	73(73.0)	80(80.0)		
ALP (U/L)	High (>125)	24(24.0)	8(8.0)	9.52	0.002*
	Normal (≤125)	76(76.0)	92(92.0)		
Albumin (mg/dl)	Low (<3.5)	60(60.0)	18(18.0)	37.07	<0.001*
	Normal (3.5-5.5)	40(40.0)	82(82.0)		
Globulin (mg/dl)	High (>3.5)	32(32.0)	14(14.0)	9.15	0.002*
	Normal (2.0-3.5)	68(68.0)	86(86.0)		
Albumin:Globulin	<1	45(45.0)	12(12.0)	28.72	<0.001*
	≥1	55(55.0)	88(88.0)		
Total Bilirubin (mg/dl)	High (>1.0)	8(8.0)	6(6.0)	0.32	0.579
	Normal (≤1.0)	92(92.0)	94(94.0)		

Table 2: Comparison of LFT in cases and controls

LFT	Case (n=100)	Control (n=100)	t-statistic	p-value
	(mean±se)	(mean±se)		
ALT (U/L)	47.60±35.96	35.84±13.94	1.06	>0.050
AST (U/L)	52.12±42.80	37.34±12.34	1.21	>0.050
ALP (U/L)	108.12±71.06	70.68±25.68	4.96	<0.001*
Albumin (mg/dl)	3.35±1.05	4.10±0.83	5.58	<0.001*
Globulin (mg/dl)	3.30±0.94	2.89±0.73	3.43	<0.001*
Albumin : Globulin	1.12±0.50	1.49±0.38	5.68	<0.001*
Total Bilirubin (mg/dl)	0.84±0.13	0.77±0.18	1.15	>0.050

Table 3:Pattern of liver dysfunction in cancer patients

LFT		Case (n=100)	t-statistic	p-value
		(mean±se)		
ALT (U/L)	High (>35)	87.25±41.57	11.58	<0.001*
	Normal (≤35)	28.94±2.54		
AST (U/L)	High (>40)	105.63±53.55	11.72	<0.001*
	Normal (≤40)	32.33±3.55		
ALP (U/L)	High (>125)	226.17±36.72	26.84	<0.001*
	Normal (≤125)	70.84±19.61		
Albumin (mg/dl)	Low (<3.5)	2.58±0.41	21.43	<0.001*
	Normal (3.5-5.5)	4.52±0.49		
Globulin (mg/dl)	High (>3.5)	4.54±0.52	21.47	<0.001*
	Normal (2.0-3.5)	2.72±0.33		
Albumin :Globulin	<1	0.66±0.21	15.46	<0.001*
	≥1	1.51±0.31		
Total Bilirubin (mg/dl)	High (>1.0)	1.04±0.02	1.15	>0.050
	Normal (≤1.0)	0.82±0.12		

Table 4:Variation of LFT in early and advance stages of cancer

LFT	Early Stage(stage-0, I, II) (n=27)	Advance Stage (stage-III, IV) (n=73)	t-statistic	p-value
	(mean±se)	(mean±se)		
ALT (U/L)	34.33±21.74	52.51±38.94	2.29	0.024*
AST (U/L)	38.85±18.57	57.03±47.99	1.91	0.059
ALP (U/L)	81.48±33.89	117.97±78.51	2.33	0.022*
Albumin (mg/dl)	3.29±1.07	3.38±1. 05	0.36	0.720
Globulin (mg/dl)	3.28±0.94	3.31±0.95	0.11	0.909
Albumin : Globulin	1.10±0.48	1.14±0.52	0.26	0.792
Total Bilirubin (mg/dl)	0.85±0.12	0.83±0.13	0.59	0.558

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