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Role of C - Reactive protein In Carcinoma Esophagus In Terms Of Survival And Disease Free Progression

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Abstract

Background: Cancer esophagus carries very poor prognosis. Patients usually present at an advanced stage, when curative options are very limited. There is no independent predictive marker, currently available which may indicate the general status of the patient prior to treatment. Keeping in view the poor outcome and great load of this diseases in this part of country, we conducted this study to find out the significance of C - reactive protein levels in our set of patients.

Material and methods: A total of 153 patients with histologically confirmed carcinoma esophagus, were enrolled in the study between November 2013 to May 2015.Patient's eligibility included Squamous cell carcinoma histology, No prior treatment in the form of surgery, chemotherapy or radiotherapy. History of the patient was thoroughly taken to rule out any chronic illness. Besides CBC, biochemistry, imaging modalities used for staging workup, serum C-reactive protein levels were determined in all patients prior to treatment.

Results: In a group with CRP levels < 6mg/l, 44 (34.37%) had partial response, 42 (32.81%) had disease progression, while in group with CRP levels > 6 mg/l, 66.66% had disease progression, which was statistically significant (p=0.003). At 6 months of follow up, 95 (62.09%) patientswere lost to follow up and 12 (7.3%) had expired. 46 patients were available for further analysis. 35 patients with CRP levels< 6mg/l, showed partial response and disease progression on endoscopy and CECTof chest findings in42.85% and 40% of cases respectively and 11 patients withCRP levels >6 mg/l, had disease progression in 72.72% of cases (p=0.06).

Conclusion: Elevated C-reactive protein levels are associated with tumor progression and poor survival in patients with squamous cell carcinoma of esophagus.

Key Words: C-reactive protein, carcinoma esophagus, tumor marker, prognostic indicator.

Introduction

Cancer esophagus carries very poor prognosis, because patients usually present at an advanced stage, when curative options are very limited [1]. Squamous cell cancer is the most prevailing histological subtype in the endemic regions of the world, accounting more than 90% of all esophageal malignancies [2].High incidence of cancer of esophagus has been reported from Caspian littoral of Iran, central and east Asia, certain areas of China [3]. In India cancer of esophagus is the most common malignancy involving the gastrointestinal track in Karnataka, Tamil Nadu,Kerala,Assam and Kashmir[4-6]. Despite advances in imaging technology and treatment modalities of carcinoma esophagus,5 year survival rates for patients with localized and regional

involvement remain low at 33.7 and 16.7% respectively [7]. There is no independent predictive marker, currently available which may indicate the general status of the patient prior to treatment, help in selecting the treatment option and may suggest an opinion about the possible treatment outcome. Several studies have demonstrated that increased C- reactive protein (CRP) levels are associated with the poor prognosis in patients with esophageal cancer[8,9].Keeping in view the poor outcome and great load of this diseases in this part of country,we conducted this study to find out the significance of C - reactive protein levels in our set of patients.

Materials and Methods

A total of 153 patients with histologically confirmed carcinoma esophagus, were enrolled in the study between November 2013 to May 2015.Patients eligibility in the study included Squamous cell carcinoma histology, No prior treatment in the form of surgery, chemotherapy or radiotherapy. Patients with any chronic disease, stage IV disease, were not included in the study. History of the patient was thoroughly taken to rule out any chronic illness. Besides CBC, biochemistry, imaging modalities used for staging workup, serum C-reactive protein levels were determined in all patients prior to treatment. This was a prospective study in which patient's characteristics with regard to gender, age, presentation, locality, investigations and treatment prescribed in each case was studied in detail. The observations were statistically analyzed by using descriptive statistics (in percentage and average).3-5 ml of blood sample was collected in plain tube, serum was separated and stored at 2-8 degree Celsius till tested for C - reactive protein levels.

Estimation of CRP levels Qualitative determination**:**

CRP levels in serum were determined by latex agglutination test. Latex agglutination kit was procured from Randox Laboratories Limited, United Kingdom. The test performed as per manufacturer's instructions. Briefly One drop of test serum was mixed with one drop of latex reagent (An aqueous suspension of white latex particles coated with Anti-Human CRP antibody) spread to fill the test circle with stirring bar. The slide was rotated for 2 minutes and observed for any agglutination. Positive control and negative control provided with kit was used.Marked agglutination indicated a CRP concentration of 6 mg/l.A smooth homogenous milky suspension indicated CRP concentration of less than 6 mg/l.

Results

A total of 153 patients were enrolled in the study between November 2013 to May 2015. Of these 91 (59.47%) were male and 62 (40.50%) female in the age group ranging between 50-75 years. Patient characteristics are shown in Table 1. Allpatients presented with dysphagia at the time of diagnosis. Grade 1 and grade 2 dysphagia was seen in 35.94% and 64.05% of cases respectively. 73.2% had lesion as per endoscopy in the middle esophagus at 25-30 cm from incisor teeth. Pre-treatment CRP level of less than 6 mg/l was seen in 83.6% of the cases which was considered negative. CRP level of more than 6 mg/l was present in 16.4% ofthe cases which was considered positive Table 1. Chemo-radiation formed the main treatment modality in 39.9% of cases followed by radiotherapy alone in 32% Table 2. After completion of the treatment at 6 weeks of follow up, 2 patients, 9.25%had expired during treatment and two patients did not give consent for undergoing assessment fordisease status, thus 149 patients were available for assessing treatment response. In a group (128) with negative CRP levels,44 (34.37%) had partial response, 42 (32.81%) had disease progression.In contrast to group (21) with positive CRP levels, 66.66% had disease progression which was statistically significant(p=0.003).Stable disease was seen in 32.81% and 23.80 % of cases in CRP negative and CRP positive group respectivelyTable 3.

At 6 months of follow up, out of 149 patients, 95 (62.09%) were lost to follow up and 12 (7.3%) had expired. 46 patients were available for further analysis which included 35 patients withnegative CRP levels and 11 patients with positive CRP levels. Of the 35 patients 42.85% and 40% of cases showed partial response and disease progression on endoscopy and CECT of chest findings. While as out of 11 patients with positive CRP levels, 72.72% patients had disease progression (p=0.060) Table 3.

Table 1. Patient characteristics

Variable	n	%
No. of patients	153	
AGE		
Range (50-70y)	126	82.4
Mean Age	64	
Median Age	65	
GENDER		
Male	91	59.47
Female	62	40.50
PRESENTATION		
Dysphagia	153	
Grade 1	55	35.94
Grade 2	98	64.05
ENDOSCOPIC LEVEL		
Upper	18	11.8
Middle	112	73.2
Lower	23	15.03
PRE-TREATMENT CRP		
<6mg/l	128	83.6
>6mg/l	25	16.4

Table 2. Treatment

variable	n	%
Surgery Alone	5	3.26
RT Alone	49	32
CT Alone	12	7.8
CT+RT	61	39.9
CT+RT+SURGERY	9	5.9
DEFAULT	16	10.4
EXPIRED	1	0.65

RT=Radiotherapy, CT= Chemotherapy, CT+RT= Chemotherapy + Radiotherapy

Table 3. Response

variable	6 weeks			6 months		
Disease status	**<6 mg/l** n=128 (%)	**>6 mg/l** n=21(%)	**p-value**	**<6 mg/l** n=35(%)	**>6 mg/l** n=11(%)	**p-value**
Partial response	44(34.7)	--	--	15(42.85)	2(18.18)	0.143
Progression	42(32.81)	14(66.66)	0.003	14(40.0)	08(72.72)	0.060
Stable	42(32.81)	5(23.80)	0.412	06(17.14)	01(9.09)	0.521

Discussion

Esophageal cancer including squamous cell carcinoma and adenocarcinoma is an aggressive malignancy with respect to prognosis [10]. Incidence of this cancer is higher in males and rises steadily with advancing age [6, 11, 12]. The current study also revealed a male preponderance with 59.47% of cases in the age group of 50-70 years Table 1.The patients usually present at an advanced stage with dysphagia to solids when more than half of the lumen gets involved with the disease. More than 64.05% presented with grade 2 dysphagia in the current study.73.2% of patients had lesion in the middle of esophagus which is similar with other studies [5, 13].Since majority of the patients are diagnosed in advanced stage a surgical intervention cannot be planned as in the current study. Chemo-radiotherapy (39.9%) formed the main treatment modality followed by radiotherapy alone in 32% of cases Table 2. There is no independent predictive marker in carcinoma esophagus which may indicate the general status of the patient prior to treatment, guide in the selection of appropriate treatment option, and may suggest the prognosis, survival period of the patient. Several studies have revealed that increased serum C - reactive protein (CRP) levels are associated with poor prognosis in carcinoma esophagus [8, 14]. We also observed poor outcome in patients who had C- reactive protein levels more than 6mg/l Which is depicted by the fact that diseases progression at 6 weeks of follow up was seen in 32.81% in a group with C- reactive protein <6mg/l, and 66.66% in a group with C- reactive protein >6mg/l. which wasstatistically significant (p=0.003), similarlyat 6 months of follow-up 40% had progression of disease in a group with C- reactive protein <6mg/l, in comparison to a group with C- reactive protein >6mg/l had disease progression in 72-72% (p=0.060) Table 3. The Prognostic significance of serum C-reactive protein has been demonstrated in a variety of patients with primary malignancies including esophageal,esophagogastric,colorectal cancer,pancreatic cancer and other cancers[14-16]. Many clinical trials have been used nonsteriodal anti-inflammatory drugs and have shown promise in lowering the incidence of esophageal,gastric,prostate,breast and some other cancers[17, 18].Thus defends the clinical significance of C- reactive protein in many types of malignancies. Our study justifies the prognostic significance of C- reactive protein in carcinoma esophagus.

Conclusion: Elevated C-reactive protein levels are associated with tumor progression and poor survival in patients with squamous cell carcinoma of esophagus. However to include C-reactive protein in the list of prognostic factors of carcinoma esophagus, Larger sample size needs to be studied. Serum C-reactive protein level analysis is simple, cheap and available in daily practice. In future lowering CRP agents may play a role in prevention and therapy of this cancer.

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