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Original Research Article

Clinicopathological features and incidence of micrometastases in the bone marrow and peritoneum in advanced carcinoma of stomach in Indian patients

Anita Samraj[1]*, George Mathew[2], Aravindan Nair[2]

[1]Associate Professor, Department of General Surgery, Saveetha Medical College and Hospital, Saveetha University, Chennai, Tamil Nadu, India
[2]Department of Surgery, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

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***Correspondence:**
Dr. Anita Samraj,
E-mail: chinus.kumar9@gmail.com

ABSTRACT

Background: Gastric cancer is associated with high mortality. The current five-year survival rate is less than 20%. Preventing the development of gastric cancer or finding it at the earliest possible stage is a far more cost-effective way of dealing with this tumour than the treatment of patients with advanced local regional or metastatic disease. The introduction of immunocytological methods that using monoclonal antibodies, sensitive enough to identify even single tumour cells can now be used to detect secondary metastatic sites. The objective of this study was to evaluate the patients with advanced gastric carcinoma using various factors such as presenting symptoms, predisposing risk factors and evidence of micro metastases by analysis of bone marrow and peritoneal cytology and also to identify any specific risk factors in a group of patients and if there were evidence of early micro metastases in these patients.
Methods: Around 30 patients with histologically and endoscopically diagnosed gastric carcinoma, admitted in CMCH, surgery unit I was included in the study. All patients with gastric carcinoma had bone marrow smear and biopsy prior to surgery.
Results: In all 30 patients, the periperal bone marrow smears and the bone marrow biopsy was negative for malignant cells. Only 1 patient had evidence of atypical cells on examination of the peritoneal fluid for cytology. 14 patients had less than 3 lymph nodes positive. In 7 patients, more than 3 lymph nodes were positive. 23.3% of the patients had *H.Pylori* associated gastritis.
Conclusions: Smoking and alcohol were found to be significant risk factor. There was a significant association of *H.pylori* infection in the group. There was only one patient detected to have malignant cells in the peritoneal washings analyzed cytologically. In this study, no significant incidence of micro metastases in the bone marrow or elevated CEA levels in the peritoneal fluid were found.

Keywords: Bone marrow biopsy, Gastric carcinoma, Metastasis, Tumour

INTRODUCTION

Gastric cancer is associated with high mortality. The current five-year survival rate is less than 20%. As for most solid tumours, the survival rate is stage dependent. According to a study done on the epidemiology of gastric cancer by Alfred and co-workers, the five-year survival rate has been slowly increasing in the past 30 years.[1] This probably is because of improved diagnostic methods, in particular endoscopic visualization and biopsy of the stomach allowing early diagnosis and treatment. According to David Kelson of the Memorial Sloan-Kettering Cancer Centre, gastric carcinoma is still one of the most common human solid tumours, particularly in

Asia.[2] The high-risk countries include large parts of Central and South America, as well as most countries of the Far East. Low levels are noted in Canada, the Middle East, and various countries of the former British Common Wealth with intermediate risk for most of the countries of Europe. There are areas in which we can improve outcome for patients with gastric cancer; the first is a better understanding of the epidemiology of the disease which should lead to better prevention and screening programs. Preventing the development of gastric cancer or finding it at the earliest possible stage is a far more cost-effective way of dealing with this tumour than the treatment of patients with advanced local regional or metastatic disease.

Even after resection, the risks for recurrences are high in patients with locally advanced disease. Radical resection of primary gastric cancer with extended lymph node dissection or en bloc resection of infiltrated adjacent organs increases the prospect of a local cure for the affected patients. Despite these improvements of surgical techniques, the overall prognosis has not improved during the last decade.[3]

It has been speculated if haematogenous metastatic spread may be a relatively early event in the natural history of many carcinomas. Sub clinical tumour cell dissemination may be evidenced by micro metastasis in the bone marrow and when the peritoneal cytology is positive for malignant cells. This is indicative of advanced disease and requires adjuvant chemotherapy.[4]

Definition of the stage of subclinical tumour cell dissemination becomes critically important for further adjuvant treatment modalities. In epithelial carcinomas, minimal residual disease is difficult to be diagnosed with conventional methods. A study was conducted on patients with oesophago-gastric cancer, detected 15% of micro metastasis in the bone marrow when the samples were taken from bilateral iliac crests.[5] The introduction of immunocytological methods that using monoclonal antibodies, sensitive enough to identify even single tumour cells can now be used to detect secondary metastatic sites.[6] In various solid tumours, monoclonal antibodies directed against cytoskeleton or cell membrane differentiation antigens showed epithelial cells with excellent sensitivity in bone marrow of patients with carcinomas. Recent reports have suggested that this process of tumour cell dissemination might define a crucial step in tumour progression from local to systemic disease. In colorectal cancer and in breast cancer, as well as in neuroblastomas, the presence of disseminated tumour cells in bone marrow has been demonstrated to be of prognostic value.[7]

The objective of this study was to evaluate the patients with advanced gastric carcinoma using various factors such as presenting symptoms, predisposing risk factors and evidence of micro metastases by analysis of bone marrow and peritoneal cytology. And to identify any specific risk factors in a group of patients and if there were evidence of early micro metastases in these patients.

METHODS

All patients with histologically and endoscopically diagnosed gastric carcinoma, admitted in CMCH, surgery unit I was included in the study. Informed consent for performing a bone marrow procedure was obtained from each patient. The study was done after obtaining prior permission from the college officially.

Inclusion criteria

- Age 29-60 years
- All cases of histologically proven carcinoma of the stomach
- Patients with proven gastric carcinoma by endoscopic biopsy.

Exclusion criteria

- Patients unable to give informed consent
- Patients with concurrent malignancy elsewhere
- Patients with history of previously treated malignancy
- Patients with chronic liver disease
- Hepatitis B virus or HIV positive patients
- Patients diagnosed to have tuberculosis
- Patients who had previously diagnosed bone marrow disease.

Sample size

Thirty patients with advanced gastric carcinoma were included in the study so as to obtain and 80% sensitivity with the presumption of 15% within 95% confidence interval.

Study plan

All patients with endoscopically and histologically proven gastric carcinoma had bone marrow smear and biopsy one to seven days prior to surgery. The procedure was performed under sterile conditions. The skin at site of the biopsy was shaved, if necessary. It was then cleaned with disinfectant solution. The skin, subcutaneous tissue and periosteum in the area of biopsy were anaesthetized with a local anesthetic such as 1% lidocaine using a 25-gauge needle. Care was taken to fully anaesthetize the periosteum, where most of the bone fibers are located. After the anesthetic had taken effect, a small incision was made in the skin overlying the biopsy site. The posterior superior iliac spine was the site of choice for the bone marrow aspiration and biopsy. The bone marrow aspiration needle is inserted through the skin, subcutaneous tissue and the bone cortex with a slight rotating motion. Entrance of the needle into the bone marrow cavity is sensed as a slight give or increase

in spread of needle advancement. The needle obturator is removed and the needle is attached to a 10ml syringe. Aspiration of the marrow is achieved by rapid suctioning with syringe so that 0.2 to 2ml of fluid is obtained. The bone marrow was stored in formalin. The marrow was stained with haematoxylin and eosin and monoclonal antibody to cytokeratin. Pre-operatively, immediately after the peritoneal cavity was opened 100ml of normal saline was instilled into the sub hepatic space if no ascites was present. Care was taken not to mobilize or handle the bowel or cause spillage of bowel contents into the peritoneal cavity. After the saline was instilled we waited for about 5 minutes before collecting the peritoneal washings in a sterile conical flask. The conical flask was sent for cytological examination to the pathology department immediately.

RESULTS

There were 30 patients with gastric carcinoma. All had bone marrow smear and biopsy performed on them, preoperatively. The routine staining with haematoxylin and eosin did not reveal any bone marrow micro metastases including in one patient who had bone micro metastases on bone scan. Hence the decision to the study monoclonal antibody to cytokeratin was made. This test is more specific though expensive. It was also decided to estimate CEA levels in peritoneal fluid as it was thought that it would increase the sensitivity of picking up peritoneal disease. 30 patients with advanced Gastric Carcinoma were included in the study. 7 patients were below the age of 40 and 8 patients were above 60 years. There were 15 patients in the age group 40 to 60 years. Of the 30 patients studied 12 were female patients and 18 were male patients. The patient past medical history was taken (Table 1).

Table 1: Patient's past medical history.

Past medical history	Patients	Percentage
Smoking	8	26.6%
Alcohol	7	23.3%
Jaundice	2	6.6%
Blood transfusion	2	6.6%
Gastro jejunostomy	1	3.3%
Treament with omeprazole	6	20%

The liver was palpable in 6.6% of the patient 10% had ascites clinically. 6.6% had a palpable left supraclavicular lymph node, 6.6% had secondary deposits on rectal examination.

Operative findings

Out of the 30 patients with advanced carcinoma stomach 9 were considered inoperable due to either extensive intraperitoneal metastasis, posterior infiltration of tumour, gross ascites and extensive liver, serosal or pelvic deposits. The cardiac end alone was involved in two patients. The entire stomach was involved in eight patients. The antrum was involved in eleven patients. In 9 patients, there was evidence of metastasis.

The sign and symptoms of the patient were observed and noted (Figure 1 and 2).

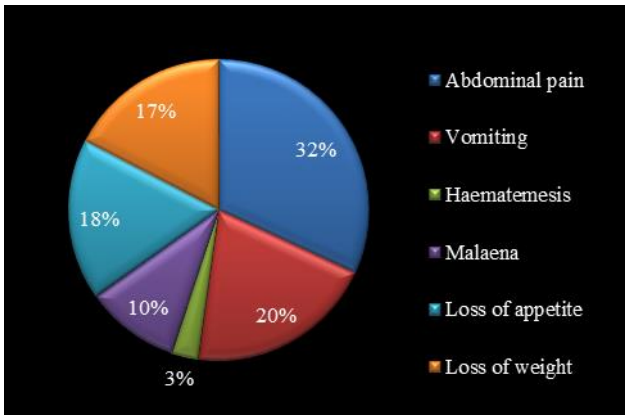

Figure 1: Symptoms of the patient.

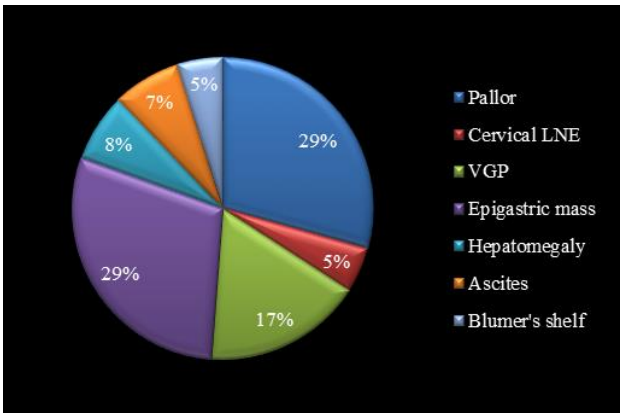

Figure 2: Signs of the patient.

Pre-operatively all of the patients who had gastric resection done had lymph node involvement, 14 patients had less than 3 lymph nodes positive. In 7 patients, more than 3 lymph nodes were positive. In all these patients, the paragastric lymph nodes was sent along with the specimen for histopathological examination, for evidence of malignant spread to the lymph nodes. 23.3% of the patients had *H.Pylori* associated gastritis. Bone marrow findings were given in the graph 3. In all 30 patients, the periperal bone marrow smear and the bone marrow biopsy was negative for malignant cells.

Presence of malignant cells in bone marrow: Routine bone marrow smear and biopsy was negative for malignant cells in all the 30 patients studied. This could be due to the fact that bone marrow involvement by malignant cells is patchy. Hence the biopsy taken from the posterior superior iliac spine may not be representative.

Presence of malignant cells in peritoneal fluid: Only 1 patient had evidence of atypical cells on examination of the peritoneal fluid for cytology.

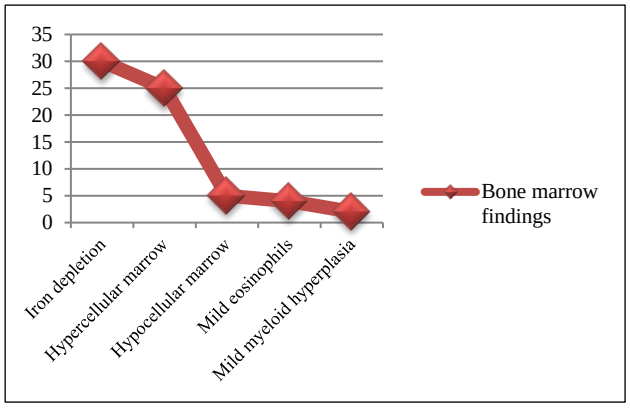

Figure 3: Bone marrow findings.

DISCUSSION

Gastric cancer is predominantly a disease affecting middle and old age group individuals.[8] In this study 15 patients (50%) were in the age group 40-60 years. 8 patients were above the age of 60 years (26.6%) and 7 patients were in the age group of 20-40 years (23.3%). This is in keeping with the published world literature where majority of the patients are in the age group 40-60 years. Most population studies have reported a ratio of 2:1 for male: female incidence.[9] In our study, we had a ratio of 1.5:1 for male: female patients.

The predominant symptom was abdominal pain or abdominal discomfort. According to literature 70% of patients complain of abdominal pain and this is the predominant presenting symptom.[10] In this study 73.3% of the patients presented with abdominal pain. Vomiting was a symptom in 46.6% of the patients, 6.6% of whom had haematemasis. 40% of the patients gave a significant history of loss of appetite or weight (Figure 1). This is in keeping with published data from the rest of the world.[11] There is a definite association between cigarette smoking and carcinoma stomach. There was a history of smoking in 26.6% of the patients in our study group. A study has reported that cigarette smoking is a risk factor for stomach cancer.[12] One reported that only when smoking was combined with alcohol was it a significant risk factor for adenocarcinoma of the cardia. These findings have led to the hypothesis that a smoker share a common risk factor that increases their risk to stomach cancer. In our study, 23.3% of the patients had a history of alcohol intake. Among those who regularly consumed alcohol history of smoking was also documented. There was a combined risk factor of alcohol and smoking in 23.3% of the patients in this study group (Table 1).

Balfour was the first to notice an increased risk for stomach cancer in patients who had gastrectomies.[13] The risk after vagotomy was substantially higher. One patient in the study group had undergone gastrojejunostomy in the past.

The hypothesis that infection with *Helicobacter Pylori* could increase the risk of stomach cancer.[14] Prospective serologic studies showed a threefold increase in the risk of gastric cancer for those with *H-Pylori* infection. The bacterium is commonly found in chronic gastritis with disappearance of the inflammatory reaction with antibiotic treatment. In this study, 7 out of 30 patients had associated *H.Pylori* infection. There was an incidence of 23.3% in this group of *H.Pylori* infection. Several studies have established that there was no increased risk of stomach cancer from the use of H2 blockers. However, an increased incidence was noticed in the first 2 years after starting the drug and probably represents pre-existing gastric cancer which was missed.[15] All the patients with *H.Pylori* infection in this study had been treated with omeprazole.

On clinical examination, 40% of the patients had pallor. Anaemia is a predominant finding in gastric carcinoma, due to blood loss. In 6.6% the liver was palpable and 10% of the patients had ascites. 6.6% had secondary deposits on rectal examination. Abdominal mass was found in 40%, Hepatomegaly was noted in 6.6%.

In this study, the presentation of the patients with advanced gastric cancer was with the following symptoms abdominal pain 70%, abdominal tumour 40%, anaemia-40%, cachexia-40%, symptoms of obstruction-23.3%, malaena-23.3% and haematemesis - 6.6%. In our study, it was found to have the following distribution. Pylorus -52.3% Body of stomach - 38.1 % Cardia - 6.6% (Figure 2). Although there are reports documenting that the world trend indicates that the tumours are becoming more proximal, in this study most of the tumours were distal in situation in the stomach.

Lymph nodal spread in gastric cancer is both by emboli and permeation. All the patients had lymph nodal involvement and 46.6% have less than 3 lymph nodes positive for malignant cells.

All the patients who had their bone marrow studied showed depleted iron stores (100%). This could be explained because of blood loss and most patients presenting with anaemia. 83.3% of the patients had a hypercellular marrow. This is due to the fact that the bone marrow tries to produce more cells when depleted of iron. 16.6% had a hypocellular marrow; there was mild easinophilia in 13.3% and mild myeloid hyperplasia in 6.6%. There were no malignant cells detected in the bone marrow in any of the patients studied (Figure 3).

Peritoneal findings

The cytological study of the peritoneal fluid revealed that one patient had malignant cells in the peritoneal cavity. Among the patients who had CEA levels estimated in the

peritoneal fluid, none of the samples had elevated CEA levels.

CONCLUSION

The age group and situation of the tumour in the stomach is in keeping with data already reported in world literature. The tumours predominantly were distal in position in the stomach. Smoking and alcohol were found to be significant risk factor. There was a significant association of *H.pylori* infection in this group. There was no bone marrow metastasis detected in this group with the either of the techniques used. There was only one patient detected to have malignant cells in the peritoneal washings analyzed cytologically there were no patients with significantly elevated CEA levels in the peritoneal fluid. In this study, no significant incidence of micro metastases in the bone marrow or elevated CEA levels in the peritoneal fluid were found. A study in larger population is proposed to validate the findings of the study and analyze if this is a valid finding in Indian patients.

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Ethical approval: The study was approved by the institutional ethics committee

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