CARCINOID – A SMALL SERIES AND A REVIEW OF LITERATURE

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Abstract- The carcinoid tumour occupies a unique place among gastrointestinal tumours because of its histology, immune his to chemistry and staining characteristics. The presence of receptors now paves the way for targeted therapy.

I. INTRODUCTION
Carcinoid refers to a range of neoplasms, both benign and malignant originating from a wide range of neuroendocrine cells. Carcinoid syndrome is present in only 10% of patients. The word Karzinoide meaning “Carcinoma-like” was first coined to differentiate these tumors from adenocarcinoma by Oberndofer in 1907.

II. AIM OF OUR STUDY
The aim of our study is to look at the incidence of carcinoid tumours over a three year period from a single centre in South India, to analyse their modes of presentation and to review the immunostaining of this tumour followed by a brief review of treatment for carcinoid tumours.

III. MATERIALS & METHODS
This was a retrospective analysis of all patients with carcinoid tumours from a single centre in Chennai, India from the period of June 2007 to June 2010. All patients with histopathological evidence of carcinoid tumour were included in the study. Their case sheets were retrieved, perused, operative notes and pathology records were analysed.

IV. RESULTS
Our study population consisted of 15 patients. Of this, 33% were male and 66% were females. We also found the maximum clustering in the fifth decade of life (33%) followed by seventh decade (26%) as shown in Graph 1.
In our study, 86% of carcinoid occurred in the gastrointestinal tract followed by 14% in the lungs & bronchi. Maximum clustering of cases were seen in midgut, especially appendix (46.6%) followed by foregut. In foregut, 20% of the cases were present in stomach followed by 13.2% in duodenum. Males predominated for the foregut tumours whereas there was a marked female preponderance in midgut tumours. Lungs & bronchi comprised 13.3% of our cases and were all female patients (Table 1). The most common mode of presentation in our study was abdominal pain (46%) while 12% presented with anemia. All the patients with bronchial carcinoid presented with cough with expectoration and were treated with lobectomy/segmentectomy.

Almost 40% of our cases were diagnosed incidentally during appendicectomy. If the size of the primary was found to be more than 1cm, they underwent limited right hemicolecotony. Patients with gastric carcinoids were treated with partial gastrectomy with adequate margins. Both cases of duodenal carcinoids were treated with a whipple resection. We had one case of ileal carcinoid which was treated with limited resection of the ileum.

Only one patient in our study group presented as carcinoid syndrome presenting with flushing & diarrhea with elevated 24-hour urine 5-Hydroxyindoleacetic acid (5-HIAA) levels (11mg/24hr urine). On metastatic workup of all our patients, two of our patients were found to have metastasis to the liver with primary from the appendix and the stomach. One patient with carcinoid syndrome was further referred for chemotherapy with streptozotocin.

All the histology specimens were further evaluated with immunohistochemistry and were found to be positive for synaptophysin, chromogranin and neuron specific enolase.

V. DISCUSSION

Carcinoids are classified according to the embryonal site of origin, which includes foregut, midgut and hindgut carcinoids and was first introduced by Sandler in 1963. Carcinoid arises from the neuroendocrine cell found along the primitive gastrointestinal tract with the Kulchitsky or the enterochromaffin cell (found in the crypts of Lieberkuhn) being the cell of origin.

Carcinoid tumours are slow growing neuroendocrine tumour commonly seen in the mid gut and only rarely in foregut[1]. The median age of diagnosis is 60years with a slightly increased preponderance for females (55%). Carcinoids are incidentally discovered at appendicectomy[1].

About two-thirds of all carcinoid tumours occur in gastrointestinal tract(67.5%). Small bowel (41.8%) is the most frequent site of the gastrointestinal carcinoid tumours, followed by the rectum (27.4%) and the appendix (24.1%). The frequency of duodenal carcinoid tumours is about 2-4%[1].

Small intestinal carcinoids are biologically aggressive tumour frequently having metastases to regional lymphnode and liver. In contrast, carcinoids of hindgut are often discovered incidentally[2]. Unlike other carcinoids, foregut carcinoids have a location advantage and are often diagnosed with endoscopy and biopsy.

Carcinoid syndrome occurs when vasoactive substance like serotonin(5-hydroxytryptamine), Substance-P, histamine and kallikrein enters systemic circulation escaping hepatic degradation as is the case in hepatic metastasis. The important clinical findings and their mediators are shown in table 2.

### Table 2

<table>
<thead>
<tr>
<th>Organ</th>
<th>Symptoms (%)</th>
<th>Mediator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>flushing (84%)</td>
<td>5-HT, Substance-P, Histamine, Kallikrein</td>
</tr>
<tr>
<td>Gastrian</td>
<td>Diarrhea (7%)</td>
<td>Gastomin, Substance-P, VIP</td>
</tr>
<tr>
<td>Heart</td>
<td>Incapciation (10%)</td>
<td>5-HT, Substance-P</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Wheezing (19%)</td>
<td>5-HT, Histamine</td>
</tr>
<tr>
<td>Other system</td>
<td>Arthritis (19%)</td>
<td>5-HT, Histamine</td>
</tr>
</tbody>
</table>

24-hour urine 5-HIAA, a degradation product of serotonin and plasma glycoprotein chromogranin A (more common in midgut carcinoids) are elevated in case of carcinoid syndrome. More recently, Turner et al identified neuropeptide A (a breakdown product of Chromogranin A) as an independent predictor of prognosis[3].

Histology/Immunohistochemistry

All gastrointestinal carcinoids have malignant potential but it varies with size, depth of invasion, histopathological growth pattern(Table 3) and site( Ileal and appendicular more than duodenal).

### Table 3

<table>
<thead>
<tr>
<th>Histology</th>
<th>Median survival (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed glandular</td>
<td>4.4</td>
</tr>
<tr>
<td>Glandular insular</td>
<td>2.9</td>
</tr>
<tr>
<td>Trabecular</td>
<td>2.5</td>
</tr>
<tr>
<td>Mixed insular</td>
<td>2.3</td>
</tr>
<tr>
<td>Trabecular glandular</td>
<td>0.9</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>0.5</td>
</tr>
</tbody>
</table>

On histopathological examination, these tumours are characterized by their staining patterns due to their shared secreted products and cytoplasmic proteins most important of which is their staining with silver, hence the name argentaffinoma. Characteristically, they either take up and reduce silver (argentaffin reaction) or take up and do not reduce silver (argyrophilic reaction). They also stain with potassium chromate (enterochromaffin). Foregut carcinoids are characteristically argyrophilic whereas midgut tumours
are argentaffin positive. Hindgut carcinoids are argentaffin negative (75%) or occasionally argentophilic (55%). Table 4 shows the staining pattern of the tumour. Chromogranin-A, Neuron specific enolase (NSE) and synaptophysin are generally used now in immunohistochemistry (IHC)[4].

Table 4

<table>
<thead>
<tr>
<th>IHC</th>
<th>Foregut</th>
<th>Midgut</th>
<th>Hindgut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverstaining</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative(75%)</td>
</tr>
<tr>
<td>Argentaffin</td>
<td>Positive</td>
<td>Positive</td>
<td>Occasional(55%)</td>
</tr>
<tr>
<td>Argyrophilic</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Neuron-specific enolase</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive (42%)</td>
</tr>
</tbody>
</table>

**Imaging**

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) helps in localisation of tumour, operability and metastasis. Computed Tomography (CT) has been the commonest imaging modality used to evaluate the carcinoid tumours. Unfortunately the sensitivity of CT is only 55%. CT may be especially useful in identifying locally advanced lesions and to identify liver metastasis.

Somatostatin receptor scintigraphy (SRS) or OctreoScan [5] localise the presence of somatostatin receptor in carcinoids. Indium-111 labelled octreotide is used and it not only helps in localisation of the tumour but also predicts the tumour response to octreotide analogues in treatment. The diagnostic sensitivity is around 80% for carcinoid tumour and exceeds 90% in cases of carcinoid syndrome. But octreotide scan is not helpful in cases with active octreotide therapy because of receptor saturation.

Metaiodobenzylguanidine (MIBG) scintigraphy is nowadays used as an alternative to octreoscan. The sensitivity varies from 60-70% in various studies but when used with octreoscan, the sensitivity exceeds 95%.

Small bowel follow through (SBFT) and enteroclysis may occasionally show the tumour. Single photon emission computerized tomography (SPECT) is a new technique involving nuclear medicine tomographic imaging using gamma rays that can localise the tumour. In selective cases, PET scans and Mesenteric angiography are helpful in diagnosis[5].

**Treatment**

Surgical resection remains the standard therapy for complete cure. Localised resection of the tumour and anastomosis is done. For gastric carcinoids, if the tumour is less than 1-2 cm is removed endoscopically and if more than 2 cm, gastrectomy is considered. Small intestinal carcinoids can spread to nodes and mesentry which in turn can cause desmoplastic reaction presenting with intestinal obstruction. These tumours are treated with segmental resection with the associated mesentery nodes if involved[6].

Surgical management of appendiceal carcinoids depends on the tumour size, lymph nodal spread and involvement of mesoappendix. Simple appendectomy is adequate for tumour less than 1 cm. For tumour more than 2 cm and tumours with lymph nodal involvement, right hemicolecctomy is indicated. Colorectal carcinoids are managed with formal hemicolecctomy regardless of the tumour size. Rectal lesions less than 2 cm can be managed with local excision. For lesions more than 2 cm, either abdominoperineal resection or low anterior resection is performed depending on distal clearance[7].

Regardless of the location of the primary tumour, 75% of the patients will develop liver metastasis. Widely metastatic disease is managed by cytoreductive surgery or surgical debulking to improve survival and control symptoms. In a recent metaanalysis by Que et al[8], it was noted that following surgical debulking of the hepatic metastasis, complete resolution of symptoms was found in 86% of patients and a 5 year survival rate of more than 70%.

Patients presenting with carcinoid syndrome are treated symptomatically along with somatostatin analogues which neutralises the serotonin by binding with somatostatin subtype receptors (SSTR). Two drugs are commercially available now, the short acting octreotide and the longer acting lanreotide. Although effective in arresting tumour growth and prolonging survival, tachypylaxis is common after 12 months of treatment.

Antiseroatin agents like methysergide maleate is not used nowadays because of its serious side effect of retroperitoneal fibrosis.

Besides octreotide, interferon therapy[9] is the common chemotherapeutic option used for metastatic carcinoid disease. Interferon alfa acts by inhibiting protein synthesis, hormone synthesis and angiogenesis in tumour cells.

Cytotoxic agents are used nowadays as first line of treatment for carcinoid tumours with elevated proliferation index (Ki-67 antibody). Combination therapy are more effective than single agent treatment. The commonest cytotoxic drugs used are streptozocin, 5-flourouracil and doxorubicin.

Other recent advances in the management of hepatic carcinoid metastases include radio frequency ablation (RFA) and hepatic chemoembolisation[10]. RFA uses thermal coagulation to destroy isolated tumour tissue. In a metaanalysis by Eriksson et al, total clearance of liver metastasis was found in 17% of foregut carcinoids and 41% of midgut carcinoids. Similarly symptomatic improvement was noted in 71% of patients with carcinoid syndrome[10].

Hepatic chemoembolization was done with either or combination of cisplatin, mitomycin and doxorubicin. Improvement of symptoms and abilization of tumour burden was noted in 90% of patients by Yao[2]. Patients with previous surgical debulking or liver metastasis of less than 5 cm were found to have a sustained response to hepatic chemoembolization.
Future targeted therapies

Radiolabelled somatostatin analogues are being developed by several research groups and has been showing promising results in various trials. Carcinoid tumour cells frequently exhibit somatostatin subtype receptors (SSTR). Radiolabelled receptor-binding somatostatin analogues are used as vehicles to guide radioactivity to tissues expressing SSTRs. Number of isotopes with varying physical properties have been developed. Auger electron and γ-emitter 111In-diethylenetriaminepenta-acetic acid (DTPA)0,octreotide when used in high doses showed considerable symptomatic relief but very less tumor response[11]. 90Y-1,4,7,10-tetraazacyclododecane-N,N,N”,N”-tetraacetic acid (DOTA)0,Tyr3,octreotide (90Y-DOTATOC, OctreoTher) has been shown to have a better response in large tumours and showed 30% objective tumor response. More recently, 177Lu-DOTA0,Tyr3octreotate (177Lu-DOTATATE) has been developed and shown to have a much higher affinity for SSTRs[12].

Vascular endothelial growth factor inhibitors such as bevacizumab has shown promising result in advanced carcinoid disease. In a study done by Yao et al [13], comparing bevacizumab with interferon alpha, bevacizumab therapy showed better tumour response, reduction of tumour blood flow and longer progression free survival.

Epidermal growth factor receptor (EGFR) plays an important role in tumorigenesis of many neoplasms including carcinoid. In a study by Papouchado et al, patients with activated EGFR expression had significantly poorer prognosis compared to the patients who did not express EGFR[14]. These findings implicate a potential targeted therapy against EGFR in advanced carcinoid tumours.

More recently, mammalian target of rapamycin (mTOR) inhibitors are being investigated. mTOR is a protein kinase in the phosphoinositide 3-kinase/Akt/p70S6K signaling pathway, an important mediator of various cellular functions such as proliferation, differentiation, apoptosis, tumorigenesis and angiogenesis. mTOR inhibitors such as everolimus has shown promising result in recent clinical trials although further trials are needed before it can be applied clinically[15].

Insulin like growth factor-1 (IGF-1) is been shown to be an autocrine regulator of neuroendocrine tumors and blockage of IGF-1 is considered to be one of the effects of somatostatin analogues and therefore appears to be a promising therapeutic strategy[16].

Phosphatidylinositol 3-kinase (PI3K)-Akt signaling inhibits apoptosis and has been shown to have a role in tumor growth and neuroendocrine hormone secretion in carcinoid[17]. Hence inhibition of PI3K-Akt may provide another potential pathway for carcinoid tumors.

VI. CONCLUSION

The increasing identification of receptors in carcinoid paves the way for targeted therapy. The limitation of any treatment modality analysis will be the small number of study subjects. But certainly targeted therapy promises to be the future in treatment of carcinoid.

REFERENCES:

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