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Review

Carcinoid Tumors: Insights into Etiology, Classification, Clinical Presentation, Prognosis and Management

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Abstract

There are few types of tumor growths that are midway between the two traditional classifications of benign and malignant. Carcinoid tumors are the most commonly occurring of these rare types of "midway" growths. They have been considered as cancers in slow motion because even though they usually have the potential for ultimately being fatal. They mostly tend to grow so slowly that people affected with these tumors usually live for many years, indeed sometimes for a normal life time. The wide variety of treatment now available makes the outlook for most victims of the more aggressive Carcinoid tumors more hopeful than it was in the past. This review sheds light on the recent perspectives regarding the etiology, classification, clinical presentation, prognosis and management of Carcinoid tumors.

Keywords: Carcinoid; Tumors; Patients; Diagnosis; Management

Introduction

Carcinoid tumors are midway between carcinomas and adenomas. They were found to arise from the cells of the diffuse neuroendocrine system, enterochromaffin cells that are widely distributed in the body but are found in greatest amounts in the small intestine and then in decreasing frequency in the appendix, rectum, lung, pancreas and very rarely in the ovaries, testes, liver, bile ducts and other locations [1]. These cells have special peculiar features that make them identifiable under the microscope. They stain in a special way when put in contact with silver containing chemicals. Special stains for the particular hormones that enterochromaffin cells can secrete will identify

the hormone substances in Carcinoid tumor cells and confirm the diagnosis of the microscopic exam on biopsied Carcinoid tumors [2]. Naalsund et al. [3] reported that Carcinoids are rare malignant tumors that are, in most cases, resectable. They found that the main cause of death in most cases of Carcinoid tumors was metastasis/locally advanced tumor at presentation or recurrent disease following surgical resection. Cidon [4] stated that treatment of unresectable and/or metastatic Carcinoids may necessitate a combination of surgical resection, systemic therapy and liver-directed therapies to alleviate symptoms of peptide release and control tumor growth. The aim of this review was to shed light on the recent perspectives regarding the etiology, classification, clinical picture, diagnosis, prognosis and management of Carcinoid tumors.

Prevalence of Carcinoid Tumors

The incidence of Carcinoid tumors is thought to be 1.5-2 cases per 100,000 of the general population [1]. Recent studies have reported an increase in incidence to 3.84-8.4 per 100 000 population. The highest incidence is reported in patients around 50-70 years old. The incidence is equal between males and females. Appendiceal Carcinoid tumor is an exception as it seems to develop at an earlier age and more frequently in women, which is thought to parallel the mean age at appendectomy [5].

Etiology of Carcinoid Tumors

Family History

Carcinoid tumors develop more often than usual in people who have a rare family syndrome called multiple endocrine neoplasia

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type 1 (MEN1) [2]. Around 1 in 10 people with MEN1 (10%) develop Carcinoid tumors. They are more likely to be diagnosed with Carcinoid tumors at a younger age than average. The physician should ask the patient about family history of cancer [6].

Ethnic Background and Gender

Carcinoid tumors are slightly more common in black people of African descent than in white people. There are slightly more women than men that may develop Carcinoid tumors [7].

Diabetes

Studies have found that people who have diabetes for a long time have an increased risk of Carcinoid tumors. The risk is especially increased in women [8].

Past History of Cancer

A previous cancer occurrence, for example cancer oesophagus, cancer colon, renal cell carcinoma, prostate cancer or lymphoma, may be associated with an increased risk of Carcinoid tumors of the small bowel [9].

Other Medical Conditions

A long term inflammation of the stomach lining called chronic atrophic gastritis is associated with a slightly higher risk of Carcinoid tumor of the stomach [5]. A higher risk of Carcinoid tumor of the stomach is also associated with a condition called Zollinger-Ellison syndrome, where the stomach lining makes too much acid [4].

Classification of Carcinoid Tumors

Up to 85% of the Carcinoid tumors in the gastrointestinal tract (GIT) can be classified according to their anatomical site of origin either in the foregut, midgut or hindgut [10]. While these GIT Carcinoid tumors have a common cell of origin, they are heterogeneous with a range of morphological appearances and biological behaviours [11]. It is of clinical value to note that the classical features of Carcinoid tumor are associated with development in the foregut and midgut, whereas those in hindgut rarely develop 5-hydroxytryptamine or 5-hydroxytroptophan, and malignant Carcinoid syndrome are more likely in metastatic disease from the primary midgut tumors [12,13]. Differentiation of malignant from benign primary Carcinoid tumors cannot be made reliably on histology. Furthermore, the different types of Carcinoid tumors have variable biologic behaviour and are all generally considered to have a malignant potential [14].

Clinical Presentation of Carcinoid Tumors

Carcinoid tumors are asymptomatic in up to 60% of the patients and autopsy studies showed that up to two thirds of jejunoileal Carcinoids remain undetected in life [7]. When symptoms occur, they are often non-specific and vary according to the location of the lesion [15]. These non-specific symptoms include abdominal pain, discomfort, diarrhea, malaise, nausea, vomiting, skin flushing, abdominal distension, early satiety and weight loss [7]. The average time of onset of symptoms to diagnosis is reported to exceed 9 years, by which it has usually metastasized [8]. Up to 50% of patients may present with symptoms of small bowel obstruction. Other patients may present with bleeding, ischemic enteritis or a palpable mass [10]. Patients first become symptomatic with symptoms of hormonal hypersecretion rather than symptoms related to the tumor bulk [16].

The Carcinoid syndrome was first recognized by Thorson in Sweden and Isler in Switzerland [1]. The prevalence of Carcinoid syndrome was reported to be 0.5 per 100,000 populations [17]. This is more common with tumors of the ileum and jejunum [5]. As 5-hydroxytryptamine (5HT) and amines are cleared rapidly by the liver, therefore the syndrome is uncommon unless the liver is largely replaced by metastases or if the tumor has direct access to the systemic circulation [7]. However, patients can have extensive liver metastases without having Carcinoid syndrome [9]. The symptoms are caused by the tumor's secretory products, with 5HT being the major one [4]. The urinary 5-hydroxytryptamine metabolite, 5-hydroxyindoleacetic acid (5-HIAA) was found to be virtually always elevated in the Carcinoid syndrome [18]. 5HT, the precursor of 5-HIAA is one of the mediators of diarrhea, which is often watery and explosive [4]. Kinins appear to cause cutaneous flushing, especially in patients with midgut tumors, in addition to 5HT and prostaglandin [12]. This flushing occurs in the face and upper trunk, often provoked by alcohol, tyramine containing food or exertion, lasting a few minutes but occurring several times a day [7]. Patients with foregut Carcinoids may experience a more intense and prolonged flushing accompanied by skin thickening and telangiectasia [4]. Carcinoid heart disease is a late complication associated with Carcinoid syndrome leading to right sided heart failure [2]. This is secondary to the high concentration of circulating amines which cause fibrosis and damage to the tricuspid and pulmonary valves, which has been shown to be the cause of death in one third of the patients. The aortic and mitral valves are usually spared due to the clearance of 5HT by monoamine oxidase present in the lung [1].

Diagnosis of Carcinoid Tumors

The World Health Organization (WHO) classification scheme classifies the neuroendocrine tumors within the GIT by considering well-defined histopathological and biological features such as cellular grading, primary tumor size and site, lymphovascular invasion, mitotic counts, Ki-67 labelling index, production of biologically active markers, invasion of adjacent organs, presence of metastases and functional status [19]. The diagnosis is usually

based on the clinical features and supported by the presence of high levels of 24-hour urinary 5-HIAA which is the breakdown product of serotonin. This has a sensitivity of 73-75% and a specificity of 90-100% [20]. False negative results may occur in patients taking salicylates or L-dopa, in those with malabsorption syndromes, or ingestion of tryptophan or serotonin-rich foods [21]. Serial measurement has been commonly used for monitoring patients with metastatic tumors [14]. Tumor marker chromogranin A is a 49-kD protein that is contained in neurosecretory vesicles of neuroendocrine tumor cells and is detectable in plasma [15]. Its measurement has been reported to be useful in the detection of Carcinoid tumors as it does not rely on serotonin secretion and can be detected in both functioning and non-functioning tumors [13]. Plasma levels seem to correlate well with tumor burden and treatment response, with a level of >5000 μg/L being associated with a poor prognosis [1]. However, levels can be falsely elevated with other neuroendocrine tumors such as that of pancreatic type [22].

Routine laboratory tests and radiological imaging often do not demonstrate the primary lesion [14]. Standard imaging techniques like computed tomography (CT) and barium contrast series rarely identify the tumor. Detection on CT can be improved by using intraluminal water, instead of barium, or rapid intravenous contrast medium administration and multiplanar reconstructions [23]. In the early stages, the tumor is small and confined to the bowel wall therefore small bowel series and enteroclysis may be more sensitive than CT or magnetic resonance imaging. CT is an excellent technique to show metastatic disease extensions, liver metastases and also useful in monitoring treatment response. The tumor appears as an ill-defined mesenteric mass containing calcification in up to 70%. As Carcinoid liver metastases are usually hypervascular, administration of intravenous contrast may make it isodense relative to the liver [24].

Transabdominal ultrasound is only useful in identifying a small proportion of small bowel Carcinoids and up to two thirds of liver metastases. It is more commonly used to guide needle biopsy to establish diagnosis in equivocal cases [25]. Endoscopic ultrasound is reported to be highly sensitive in detecting primary tumors of the stomach, duodenum, pancreas and rectum, as well as local nodal involvement. A few other investigatory tools used are endoscopy, which is valuable in diagnosing rectal as well as gastric Carcinoids. Angiography may be helpful in showing irregularity of the mesenteric and intestinal arcade branches, with stellate arrangements of the arteries, lack of identifiable venous drainage, and minimal tumor stain [24].

The unique metabolic features of the neuroendocrine allow for nuclear medicine molecular imaging techniques to be used with great sensitivity and specificity. These include single photon emission computed tomography (SPECT) and positron emission tomography (PET). PET scan is able to produce better image quality, therefore is more accurate in detecting small tumor foci [25]. The conventional use of 18F-fluorodeoxyglucose is less useful due to the low glycolytic rate of neuroendocrine tumor cells. Hence other techniques using tracers such as 5-hydroxytryptophan or iodine-123- labeled octreotide are helpful in diagnosing and locating Carcinoid tumors and identifying metastases [26]. Scintigraphy with radio-labelled octreotide has also been successfully used to localize previously undetected primary or metastatic lesions, with a sensitivity of 80-90%. It is more sensitive for extrahepatic than hepatic lesions due to the heterogeneous octreotide uptake in normal liver. Furthermore, octreotide scans may have a role in predicting the clinical response to somatostatin analogues treatment. Lastly, I^{123}-labelled MIBG scan has a reported sensitivity of 55-70% and maybe useful in negative octreotide scan cases or patients on long acting octreotide [27].

Prognosis of Carcinoid Tumors

Prognosis varies depending on multiple factors including location, histological subtype, residual disease post resection and metastasis. In addition, some studies have reported the levels of 5-HIAA, plasma chromagranin A, weight loss and tumor size to be important factors. Complete removal of a small tumor is associated with a 90% 5-year survival [28]. The 5-year survival rate of appendiceal Carcinoid tumor is 76%, whereas that of ileal Carcinoid is 47-65% and 70% for Carcinoid tumors of other GIT sites. In general, the likelihood of metastasis is related to tumor size. However, the size of the tumor does not influence the prognosis and is an unreliable predictor of metastasis. Appendiceal tumors are usually < 2cm in > 95% of cases and about 30% of tumors> 2cm have metastasized at the time of diagnosis. The overall 5-year survival rate is 76%, 94% for those with local disease, 85% for those with regional metastases and 34% for those with distant metastases [29]. The average survival from time of diagnosis of ileal Carcinoid tumor is 8.1 years. The 5-year survival rate is 73% for localized disease while it is approximately 60% for those with regional metastases [30]. Rectal Carcinoids have an overall five-year survival of 81% in patients with local disease, 47% for regional metastases and 18% for distant metastases, with metastasis commonly to local lymph nodes and the liver [2].

Treatment of Carcinoid Tumors

Treatment can either be surgical, medical or radiological and this section shall illustrate these various options. The presence of intra-abdominal or hepatic metastases warrants a combined medical, surgical and radio therapeutic approach to control the symptom and the size of the tumor [6]. There are still significant uncertainties regarding the management options for patients with metastatic

disease. In general, the more aggressive and poorly differentiated tumors are treated with chemotherapy, whilst the well differentiated tumors may be treated with a variety of biotherapeutic regimens [31].

Surgical Treatment

Surgical removal of the primary tumor is the mainstay of treatment [2]. The patients will have either localized surgically curable disease or metastatic incurable disease [32]. The goal is to obtain tissue for diagnosis, document the extent of disease, remove tumor for potential cure, alleviate symptoms and to prolong survival. The success depends on the site, size and presence of metastases. While generally success of surgery is related to the size of the primary tumor, this does not pertain to the small intestine [33].

Carcinoid tumors of the small intestine often presents as small bowel obstruction and is treated with resection of the involved segments and mesentery, wide enough to ensure negative margins and removal of the involved lymph nodes. This may benefit even patients with extensive liver or lymph node metastases. Duodenal lesions ≤ 1cm can be excised via endoscopic approach. However, as the lesions are generally submucosal, it is usually not possible to completely excise them [34]. Hence lesions ≥ 2cm generally requires a pancreaticoduodenectomy or segmental resection. Furthermore, there could be synchronous or metachronous tumor, therefore, the entire bowel must be examined carefully. About two thirds of the appendiceal Carcinoids arise in the tip, whereas less than 10% arise in the base. Simple appendectomy of a tumor< 1cm in diameter, which is usually 99% of the occurrence is curative. For tumors 1-2 cm, appendectomy is adequate unless there is evidence of local mesenteric invasion or presence of tumor at the base of the appendix. In the latter and those ≥ 2cm standard right hemicolectomy is recommended [35].

In the colon, the tumors are usually seen in the caecum due to the greater concentration of Kulchitsky cells there and are treated with a right hemicolectomy whereas sigmoid Carcinoids are treated by anterior resection and unresectable lesions by colostomy. Rectal lesions between 1-2 cm without evidence of invasion can be locally excised and regular examination will be sufficient treatment as less than 5% of tumors< 1cm metastasize [36]. Rectal lesions > 2cm require low anterior resection or abdominoperineal resection as metastasis occurs in 18-20% of the cases. However, in the latter group, retrospective studies have shown that these procedures do not appear to extend the survival beyond that observed with local excision. Therefore, one should take into account the patient's age and co-morbidities as the approach for larger rectal Carcinoid tumors [34].

Medical Treatment

Patients with metastatic Carcinoid tumor should be treated medically unless they have intestinal obstruction, ischemia, or are refractory to medical therapy. The aim of treatment is for symptomatic relief by reducing hormone levels and tumor growth, and to improve quality of life as tumor load may not be significantly altered [37]. There is no clear evidence that the particular treatment is able to reduce tumor size in the majority of patients, therefore, it should be chosen as a function of adverse effects, long term efficacy and possibility of repetition of treatment [34].

Chemotherapy: The response rate of conventional chemotherapy has been reported to be 10-30%. Clear therapeutic advantage has not been demonstrated and due to this questionable efficacy and associated toxicity, chemotherapy should be reserved for those who have not responded to other therapies. When used individually, symptomatic remission is only transient, lasting a few months and no positive result is found in relation to the tumor size [38]. The response rate has been reported to be 10- 33% and this is increased with combination therapy. Combination therapy, especially the four drug regimen of 5-fluorouracil, streptozotocin, doxorubicin and cyclophosphamide has been reported to be superior to single therapy. Combination of streptozocin and 5-fluorouracil has been shown to have an overall response rate of 29-33%, with median survival of 28 months in patients with primary small bowel Carcinoid tumors [39].

Serotonin Antagonists: There are multiple agents which inhibit 5HT synthesis and peripheral 5HT antagonists many of which are poorly tolerated due to their side effects and have fallen out of favour. In addition, they are rarely associated with tumor regression [40]. Parachlorphenylalanine is an inhibitor of tryptophan hydroxylase which prevents the conversion of tryptophan to 5HT. It relieves flushing and diarrhea in 50-60-% of patients and reduces urinary 5-HIAA excretion in up to 80% of patients. Unfortunately, there is significant incidence of psychiatric symptoms like confusion and depression, and may cause significant sedation and hypersensitivity reaction. P-chlorophenylalanine reduces 5HT synthesis, and is reported to reduce diarrhea, flushing and 5-HIAA excretion by 50-90%. However, it causes hypersensitivity reactions and psychiatric disturbances [34].

Cyproheptadine is considered as an antagonist to serotonin and histamine receptors. It has only been shown to be useful in reducing diarrhea in 60% of patients and flushing in 47% of patients, but has a mean duration of response of 8 months and has no effect on the tumor size and may exacerbate other complications of Carcinoid syndrome like heart disease [37].

Methysergide has been found to provide some symptomatic relieve. Ketanserin had been shown to reduce the frequency and severity of flushing by 70% and diarrhea by 30% [41]. However due to their significant side effects like dizziness, sedation, nausea and

hypotension, they are not used routinely [42]. Ondansetron has been reported to provide immediate and sustained symptomatic relief. However, it has no advantage in terms of reducing tumor growth and tachyphylaxis is often encountered [43].

Interferon-A: The recombinant form is thought to be a cytotoxic agent, acting selectively on tumor cells to inhibit cell division by prolonging the cell cycle [44]. Interferon α is found to significantly decrease the tumor markers in 40-55% of patients and reduce tumor size in 10-20% of the patients. Stable disease is reported in 78% of patients and this is thought to be due to its cytostatic effect [37].

Somatostatin Analogue: It is considered as the first line treatment for patients with low grade tumors and Carcinoid syndrome, acting to inhibit the neuropeptide release and therefore the gut endocrine and exocrine function. This is effective in controlling symptoms like diarrhea, flushing and halves urinary 5-HIAA in more than 70% of patients [45].

Octreotide is particularly effective in abolishing flushing and has been reported to improve Carcinoid syndrome in up to 88% of the patients. It needs to be administered three times daily subcutaneously due to its short half-life of 90-120 minutes, but new slow release analogues and depot preparations have been developed that can be given every 2-4 weeks [46]. The median duration of response is 12 months, and the mean remission time has been reported to be 9 months. Whilst the tumor growth is reported to be lower during treatment, there is no advantage in terms of tumor size reduction. Also, it is effective in preventing Carcinoid crisis associated with surgical removal of the tumor [47]. Combination therapy of interferon α and octreotide has been shown to be effective and better tolerated than monotherapy. Up to 77% of patients had a biochemical response, but no significant tumor regression was reported [48].

Radiotherapy

This form of treatment has not been extensively studied. It may be effective in palliation of bone or central nervous system metastases [49]. The role of percutaneous radiotherapy in Carcinoid tumors is controversial because the tumors are highly resistant to radiation. However, adjuvant mediastinal radiotherapy can be considered if lymph nodes are involved. Furthermore, local radiotherapy can be used if the tumor is inoperable to alleviate symptoms and improve survival of patients [50].

Conclusion

The aim of treatment of Carcinoid tumors is to achieve cure and or improve quality of life by palliating symptoms and prolong survival. The recent WHO classification scheme may be helpful with diagnosis, prognosis as well as choice of the appropriate treatment regimen. There are various lines of treatment of Carcinoid tumors though choice of treatment and their applications can be quite complex. Prognosis usually depends on the site and size of the primary tumor together with the presence and extent of distant metastasis.

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