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Carcinoid Syndrome: Overview and Clinical Approach

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Abstract

Carcinoid syndrome is a rare condition associated with neuroendocrine tumors (NETs), particularly those in the gastrointestinal or bronchial systems. It results from releasing vasoactive substances, such as serotonin, into the bloodstream, leading to symptoms like flushing, diarrhea, and heart valve damage. Diagnosis involves clinical evaluation, biochemical tests, and imaging studies. Treatment includes somatostatin analogs, surgery, and other approaches. Potential complications include carcinoid crisis and carcinoid heart disease. Despite its rarity, increased awareness and research enhance the management of carcinoid syndrome and associated NETs. This review article aims to provide an overview of carcinoid syndrome and its clinical approach. Increased awareness, a better understanding of pathogenesis, and the development of new treatment modalities are contributing to improved care for individuals with carcinoid syndrome.

Keywords: Carcinoid syndrome; Carcinoid tumors; Neuroendocrine tumors; Serotonin; Vasoactive substances; Paraneoplastic syndrome; Carcinoid crisis; Carcinoid heart disease

Abbreviations: CS - Carcinoid Syndrome; NET - Neuroendocrine Tumors; GI – Gastrointestinal; 5-HIAA - 5-hydroxy indole acetic acid; CT - Computed Tomography; TR - Tricuspid Regurgitation; TS - Tricuspid Stenosis; PR - Pulmonary Regurgitation; PS - Pulmonary Stenosis; TTE - Transthoracic Echocardiography; 2D - 2-dimensional; 3D - 3-dimensional; MDCT - Multidetector CT; MRI - Magnetic Resonance Imaging; Ga-68 - Gallium-68; In-111 - Indium-111; INF-a - Interferon alpha; TNF - Tumor necrosis factor; IL-12 - Interleukin-12

Introduction

Carcinoid syndrome is a rare condition that occurs as a result of carcinoid tumors, which are slow-growing neuroendocrine tumors typically originating in the gastrointestinal tract or bronchial system [1,2]. Epidemiologically, in the USA, the incidence of carcinoid syndrome is estimated to be around 0.05 to 0.5 cases per 100,000 individuals. Although it is considered a rare disease, its prevalence may be underestimated due to its indolent nature, often leading to delayed diagnosis [2]. The pathogenesis of carcinoid syndrome involves the secretion of biologically active substances, such as serotonin, by the carcinoid tumor cells. These substances are released into the bloodstream and can cause various symptoms. Most carcinoid tumors express serotonin receptors, leading to excessive serotonin production, triggering the characteristic symptoms seen in carcinoid syndrome [1-4]. Clinical presentation of carcinoid syndrome can vary, but common manifestations include flushing, diarrhea, bronchoconstriction, and right-sided heart valve damage. These symptoms occur due

to the release of vasoactive substances like serotonin, which affect blood vessels and various organs, leading to a diverse range of clinical features.

Carcinoid syndrome diagnosis involves clinical evaluation, biochemical testing, and imaging studies [4,5]. Measuring urinary 5-hydroxy indole acetic acid (5-HIAA), a serotonin metabolite, is a valuable diagnostic tool. Imaging techniques like CT scans or somatostatin receptor scintigraphy can help localize the tumor. Endoscopy and biopsy are often necessary to confirm the presence of carcinoid tumors [6,7]. The primary goal of this review article is to provide a comprehensive overview of carcinoid syndrome, covering its epidemiology, pathogenesis, clinical presentation, diagnosis, and treatment options. It aims to synthesize current knowledge and research findings on the condition, offering a valuable resource to better understand this rare but clinically significant syndrome.

Epidemiology

The epidemiology of neuroendocrine tumors (NET), including carcinoid syndrome, has been changing over the years, with increasing incidence and awareness of the condition. Carcinoid syndrome is associated with neuroendocrine tumors and has distinct epidemiological characteristics [7]. The incidence of carcinoid syndrome has been reported to be relatively rare where an estimate of 10% of neuroendocrine tumors lead to this syndrome [8], with varying figures depending on the region. In the United States, the incidence is estimated to be around 0.05 to 0.5 cases per 100,000 individuals affecting both males and females in equal numbers, African Americans are more affected than other ethnic groups and being more common in patients > 65 yrs [9]. NET usually originates from the GI tract at 70% followed by respiratory tract with 25%.

More commonly, carcinoid tumors arise from the midgut (the distal ileum or appendix) and being atypical sites foregut and hindgut where we get an order of prevalence of 35% for the appendix, 28% ileum, 13% rectum and other 13% for the bronchi. Gallbladder, pancreas, larynx, ovaries, liver and testicles have an incidence of 1%; however, these organs tend to metastasize more frequently through portal vein and mesenteric lymph nodes [10]. Carcinoid syndrome is rare, but its prevalence may be underestimated due to its indolent nature and often delayed diagnosis [11,12]. Prevalence data are challenging to ascertain, but it is believed to be increasing. While carcinoid tumors generally have a better prognosis than many other cancers, some cases can be associated with poor outcomes, especially if metastases are extensive. Mortality rates vary depending on tumor location and stage at diagnosis [8]. The prognosis for carcinoid syndrome is influenced by factors such as tumor size, location, stage, and the presence of metastases. Early diagnosis and intervention can lead to better outcomes. Many patients have a good prognosis with appropriate treatment [7,11].

Pathogenesis

Carcinoid Syndrome (CS) is a paraneoplastic syndrome that occurs due to the secretion of approximately 40 vasoactive hormones, predominantly 5-hydroxytryptamine (5-HT), into the systemic circulation after escaping first-pass hepatic metabolism [13,14]. Neuroendocrine Tumors (NETs) are a group of heterogeneous malignancies that arise in the gastrointestinal tract. These can be classified based on embryonic divisions of the GI tract, such as foregut, midgut, and hindgut [15]. NETs can also be found in the lungs and pancreas and rarely in other organs such as the breast, ovary, prostate, thymus, and skin [16]. Vasoactive hormones secreted by NETs, predominantly serotonin, histamine, tachykinins, kallikrein, and prostaglandins, are normally inactivated in the liver [17]. CS occurs when there is NET metastasis to the liver that results in vasoactive hormones directly entering the systemic location or are not inactivated due to impaired liver function due to the metastatic disease [18]. CS can also result in the absence of hepatic metastasis, such as gut tumors with locoregional disease or tumors that directly release vasoactive hormones into circulation, such as bronchial or ovarian carcinoid tumors [19].

The majority of carcinoid tumors express serotonin receptors, particularly the 5-HT2A receptor. This receptor activation by serotonin results in vasodilation and the release of various vasoactive substances, including bradykinin and histamine, which play a role in the pathogenesis of carcinoid syndrome symptoms. These vasoactive substances affect blood vessels and organs, leading to diverse clinical features. The liver typically plays a crucial role in metabolizing and deactivating biologically active substances like serotonin [16]. However, in cases where carcinoid tumors have metastasized to the liver or there is a hepatic compromise, these substances bypass hepatic metabolism, leading to their systemic circulation and the development of carcinoid syndrome. Carcinoid tumors can also produce other bioactive compounds, such as chromogranin A and neuron-specific enolase, which serve as biomarkers for tumor activity and can contribute to the overall pathogenesis of the syndrome [17-19]. The tumor's location and the extent of metastasis can influence the severity of symptoms and the pathogenesis of carcinoid syndrome. Understanding the pathogenesis of carcinoid syndrome is essential for its diagnosis and management. Biochemical testing, such as measuring urinary 5-HIAA (a serotonin metabolite), is a valuable diagnostic tool, helping to identify and quantify excess serotonin production. Imaging studies are also crucial for locating and assessing the extent of the tumors. Endoscopy and biopsy are often necessary for confirming the presence of carcinoid tumors and their pathogenic role in carcinoid syndrome.

Clinical Features

There is a wide range of clinical manifestations associated with carcinoid tumors. Primordial manifestations such as

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diarrhea, hyperemia, pain, asthma, wheezing, and pellagra vary in percentage depending on the stage of development (initial or during disease), getting 32-93% on initial development and a 68-100% during disease for diarrhea, 23-100% on initial development and a 45-96% during disease for hyperemia, 10% and 34% respectively for pain and a minor percentage for asthma, wheezing and pellagra [20]. Diarrhea is known to be aqueous, with approximately <1L a day in 60% of patients. It is accompanied by abdominal pain and hyperemia in 85% of cases, with an estimated duration of 2 or 5 minutes or hours in an advanced stage. Hyperemia is predominantly observed in metastatic NET of the midgut, whereas in cases of bronchial NET, the duration is higher, reaching days. And 67% of patients manifest steatorrhea as an initial sign [21,22].

During the syndrome development, cardiac manifestations could happen in 11-40% of cases. This is due to the formation of fibrotic plaques localized in the endocardium, which could end up in carcinoid heart disease (CHD) where it is observed in patients with tricuspid insufficiency (90-100%), tricuspid stenosis (43-59%), pulmonary insufficiency (50-81%), pulmonary stenosis (25-59%) and lesion on the left half of the heart (11%) who in the future might develop cardiac insufficiency [20-23]. However, these numbers are decreasing in intensity and frequency, and a hypothesis is due to the use of somatostatin analogs. In addition, there are dermatological (pellagryform skin lesions), respiratory (wheezing), neurological manifestations (cognitive decrease), Peyronie's disease, and occlusion of mesenteric veins or arteries [20].

Diagnostic approach

Carcinoid syndrome has various biomarkers available to make the correct diagnosis. Even though clinical diagnosis is vital, biochemical analysis is imperative. The biochemical analyses available are 24-hour urinary excretion of 5- HIAA (5- hydroxy indole acetic acid), Chromogranin A, and increased serotonin serum levels [24]. Measuring the levels of 5-HIAA is the initial laboratory test of choice. 5-HIAA is a degradation product of serotonin metabolism. Therefore, in carcinoid syndrome, it will be elevated. This test should be done in a 24-hour urine sample; it has a sensitivity of 73% and a specificity of 100%. However, false positives have been described, specifically in patients who eat foods rich in tryptophan. Consequently, the patient should avoid these tryptophan-rich foods 72 hours prior [24]. Chromogranin is a secretory protein produced by neuroendocrine cells and is used as a biomarker for these tumors. Chromogranin A is used not as a diagnostic test but as a test to assess disease progression, response to therapy, or recurrence in carcinoid syndrome and tumors. Elevations of Chromogranin A have been described primarily on metastatic midgut lesions. Plasma Chromogranin A levels are sensitive but not specific, as they are also elevated in liver failure, renal impairment, atrophic gastritis, and IBD. Therefore, plasma chromogranin A is more preferred as a screening test than its diagnostic ability [25]. Plasma 5-HIAA can also be used as a diagnostic test. It can and should be used as a diagnostic and for monitoring patients with carcinoid tumors [25]. Imaging studies can and should be used to assess the location of the leading site of the carcinoid tumor. X-ray is a simple tool and can be used when the tumor's location is considered pulmonary [25]. Somatostatin receptor scintigraphy is the preferred imaging test to locate the lesion, based on the principle that these tumors have high concentrations of somatostatin receptors [24]. The radionuclides used in this test are indium-111 octreotide and indium-111 pentetreotide. The degree of uptake is directly proportional to the density of the receptors [25].

Treatment Strategies

Treatment of carcinoid syndrome focuses on reducing the hormone levels or tumor load to reduce symptoms, especially those produced due to increased serotonin serum levels, such as skin flushing and diarrhea [26,29]. While surgery remains the mainstay of many gastroenteropancreatic NETs, somatostatin analogs, such as octreotide LAR and lanreotide, have revolutionized the management of these tumors [31]. Long-acting somatostatin analogs are considered cornerstones in treating carcinoid syndrome [29].

Pharmacological Treatment

Somatostatin analogs have been extensively studied in patients with CS and are considered the central pillar when treating the clinical disease. Somatostatin, secreted by the pancreas, is known to bind somatostatin receptors, which are expressed in most (80%) carcinoid tumors [26]. Octreotide and lanreotide both target the somatostatin receptor subtype 2 and have even been proven to inhibit tumor growth in clinical trials [27,28]. Both drugs are available for injection: Octreotide at a dose of 20 to 30mg, intramuscularly, once a month, and Lanreotide subcutaneously, at 120 mg every month [28]. Somatostatin analogs inhibit gallstone contractility. Therefore, prophylactic cholecystectomy is sometimes recommended [26]. Serotonin is synthesized from tryptophan through the action of tryptophan hydroxylase. The FDA has recently approved telotristat in the US, an oral tryptophan hydroxylase inhibitor, to be used with somatostatin analog therapy, mainly to control the diarrhea associated with CS [26].

It has been proven to considerably decrease the serum levels of 5-HIAA, which poses a promising option for treatment to prevent or delay the onset of carcinoid heart disease (CHD) [28]. When diarrhea and flushing are refractory to the action of somatostatin analogs, interferon alfa has been proven to provide relief in 40 to 50% of cases [28]. It also may produce antitumor effects via T-cell stimulation, although objective responses are scarce [26,28]. However, tolerability may be low, given that fatigue, fever, and flu-

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like symptoms occur in most patients [27]. Chemotherapy is not usually helpful in decreasing symptoms of carcinoid syndrome secondary to well-differentiated neuroendocrine tumors but is used as first-line treatment to treat malignant, high-grade, poorly differentiated neuroendocrine tumors of the pancreas and stomach, especially if Ki67 antibody levels are over 10% [26]. Used combinations of chemotherapeutic agents include streptozotocin, 5-fluorouracil, platinum compounds, and methotrexate [26,27]. Although not considered chemotherapy, everolimus is registered as an antiproliferative treatment option for progressive NETs [27].

Non-pharmacological Treatment

Cytoreductive surgery is the mainstay in the surgical treatment of carcinoid syndrome. Surgery is reserved for patients with 90% of the tumor bulk can be removed without diffuse bi-lobar involvement, compromised liver function, or widespread extrahepatic metastases. Hepatic resection can control the symptoms of carcinoid syndrome [26]. Patients with carcinoid syndrome received a continuous infusion of octreotide (2000 μg/day) at least 12 hours before, during, and at least 24 hours after surgery to prevent perioperative carcinoid syndrome [30]. Embolization is a therapy to treat liver tumors by blocking their blood supply. Because liver tumors thrive or highly oxygenated blood from the hepatic artery, blocking that supply may kill it. Embolization of the entire liver can be undertaken for patients with bilobar disease. Bland embolization uses only microparticles, whereas chemoembolization, also known as transarterial chemoembolization (TACE), uses chemotherapy in addition to microparticles. Patients undergoing HAE should also receive pre- and post-embolization octreotide to prevent a carcinoid crisis. Radiofrequency ablation delivers heat through a needle to the metastatic cells in the liver, causing cell death. Microwave ablation destroys liver tumors using the heat generated by microwave energy. Radioembolization using yttrium-90 (90Y)-labeled resin or glass microspheres is growing [26].

Complications: Carcinoid crisis

Carcinoid Crisis (CC) is generally described as a sudden onset of hemodynamic instability (prolonged hypertension or severe hypotension, unresponsive to standard practices), sometimes accompanied by characteristics of carcinoid syndrome, such as prolonged flushing, wheezing, and hyperthermia. The underlying mechanism of CC is still unknown. However, some Authors first hypothesized that CC could represent an extreme complication of Carcinoid Syndrome caused by a sudden and massive release of tumor hormones that may be triggered by tumor manipulation or anesthesia [32]. CC is mainly associated with foregut (respiratory tract, thymus, stomach, duodenum, and pancreas) and midgut (small intestine, appendix, and right colon) NETs. Although theoretically, every kind of tumor stress can cause CC, it typically occurs during invasive procedures, such as surgery and liver embolization, but it can also arise during clinical examination [33]. An excessive amount of serotonin in the bloodstream, the principal amine responsible for CS, could cause CC due to increased tryptophan intake in the diet or, less likely, a release after spontaneous tumor necrosis [34]. In CC, the most implicated compounds seem to be vasoactive peptides, such as serotonin, histamine, bradykinin, tachykinins, and kallikrein. In particular, patients with carcinoid flushing exhibit elevated levels of bradykinin and kallikrein in the bloodstream, which are considered the most probably responsible for flushing rather than serotonin [35]. Current guidelines, such as the European ENETS and the American NANETS, continue to recommend the administration of octreotide to prevent and manage CC onset [36].

Complications: Carcinoid Heart Disease

Carcinoid heart disease (CHD), once considered an enigma, has dramatically improved its diagnosis and treatment over the last two decades [37,38,45]. Despite being a rare presentation of carcinoid syndrome, it eventually manifests in about 50% of the patients and is a significant contributor to morbidity and mortality [39,40]. Carcinoid heart disease is commonly a paraneoplastic manifestation of carcinoid tumors mediated by serotonin, histamine, tachykinins, prostaglandins, and kallikrein secretion [39,40]. Under normal circumstances, these substances cannot cross the hepatic first-pass metabolism and thus cannot enter the systemic circulation and reach the right side of the heart. Additionally, the left side of the heart is protected from these substances by monoamine oxidase in the pulmonary capillaries, which degrades serotonin [39]. Therefore, for CHD to occur, liver metastases should sufficiently compromise hepatic function [39,40]. Exceptions include ovarian carcinoids, which can bypass portal circulation, and midgut carcinoids with retroperitoneal lymph node metastases, whose drainage is into the thoracic duct [41,42]. CHD has an insidious onset, usually between 50-70 years, with most patients being asymptomatic and incidentally detected [39,45]. The most common presentation of CHD is fatigue and mild dyspnea on exertion [3]. CHD can be classified into the following clinical phenotypes:

Valvular disease

The right-sided valves are involved more commonly with tricuspid valve disease, seen in 97% of the cases, and pulmonary valve disease, in 88% of the cases. Regurgitant lesions were found to be more common than stenosis lesions in both of the right-sided valves. Clinical findings include a pan systolic murmur which increases on inspiration (Tricuspid regurgitation TR), elevated jugular venous pulse with prominent a-waves (Tricuspid stenosis TS) and prominent v-waves (TR) and, less commonly, a mid-diastolic murmur (TS). Pulmonary valve disease can result in the findings of an early diastolic murmur (Pulmonary regurgitation PR) and, less commonly, ejection systolic murmur (Pulmonary stenosis PS) [39].

Right-heart failure can complicate this, which presents with pedal edema, ascites, and hepatomegaly [39]. Left-sided valvular

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involvement is seen in only 1 out of 10 cases and is usually either due to a patent foramen ovale, lung carcinoids, or extensive liver involvement [40]. Murmurs can be present in such cases due to aortic or mitral valve disease [39]. Serotonin is implicated as the chief culprit behind CHD. It stimulates fibroblastic growth and leads to fibrosis of the cardiac valves, similar to that produced by fenfluramine or ergotamines [39]. Transforming growth factor-beta (TGF-beta) also contributed to fibrosis, especially TGF-beta1 and TGF-beta3 isotopes [44]. Increased levels of TGF-beta latency-associated peptide and latent binding protein have been found in valve specimens of CHD patients, both stimulating fibrosis [39,44]. This leads to the deposition of fibrous plaques on the valve leaflets and cusps, chordae tendinae, papillary muscles, ventricular walls, and pulmonary artery intima. These plaques lead to commissural fusion and chordae contractures, causing the valvular manifestations of CHD [39]. Histopathological examination of these plaques shows the deposition of an extracellular matrix and myofibroblasts lined by an endothelial cell layer. They also show lymphocytic and mast cell infiltration. The underlying valvular structure is intact [39].

Vasospastic disease

Patients with CHD can present with symptoms suggestive of acute coronary syndrome and are found to have coronary vasospasm, especially those with nonocclusive coronary artery disease. In patients with atherosclerosis, there is a downregulation of vasodilatory 5-HT1 receptors and an upregulation of the vasoconstrictor 5-HT2 receptors in the vascular endothelium. Thus, serotonin can cause coronary vasospasm in patients with CHD. In the presence of a patent foramen ovale, serotonin can lead to stent thrombosis in the coronary arteries through platelet activation [39,45].

Arrhythmias

Although uncommon, serotonin release in carcinoid syndrome is associated with ventricular tachyarrhythmias and atrial arrhythmias. The mechanism proposed is cardiac stimulation by increased sympathetic impulses induced by a vasoactive amine [39,45].

Direct myocardial disease

Rarely, CHD can be caused by metastases to the cardiac muscle, the most common site being the ventricular septum [43]. It is usually asymptomatic when it presents as a single atrial mass, while ventricular septal metastases can present with outflow tract obstruction. They are associated with a higher tumor burden [45].

Diagnosis of CHD involves a combination of biomarkers and radiological tests. Urinary levels of 5-HIAA and chromogranin A are used to evaluate disease progression and cardiac involvement. NT-proBNP is found to have diagnostic value in CHD with sensitivity and specificity rates of 92% and 91%, respectively. It is also used for prognostication, with higher levels pointing to higher mortality prospects [39,45]. The primary diagnostic tool for CHD is a 2-dimensional (2D) transthoracic echocardiography (TTE). It is helpful in evaluating valvular disease and cardiac function and can also identify intracranial metastases. 3-dimensional (3D) TTE is preferred over its 2D counterpart, especially in aortic valve disease in CHD. Speckle-tracking TTE can be used for prognostic stratification of risk in CHD. Multidetector CT (MDCT) and cardiac MRI can be alternatives when TTE images are suboptimal or cardiac metastases need to be evaluated [45]. The presence of somatostatin receptors on the tumor cells has enabled the use of radiotracer modalities in the diagnosis of cardiac metastases in CHD. Ga-68 octreotide, In-111 octreotide, and F-dihydroxyphenylalanine can be used for this purpose. Newer tracers, such as iobenguane I-123, can also be used [45].

The management of CHD involves medical and surgical techniques. Heart failure is managed medically as per the standard of care. However, volume-depleting agents such as diuretics should be used cautiously in patients with right ventricular failure and valvular disease as they can reduce cardiac output. While somatostatin analogs such as octreotide, pasireotide, and lanreotide can lower serotonin levels and provide symptomatic improvement in carcinoid syndrome, they cannot reverse cardiac disease progression or reduce mortality rates. They may be used preoperatively to prevent hemodynamic instability [45]. In cases resistant to somatostatin analogs, Interferon-alpha can be given. Several drugs are currently being evaluated for their efficacy in CHD, such as the paclitaxel-trastuzumab-Interleukin12 combination and a peripheral serotonin synthesis inhibitor, telotristat etiprate [45]. Surgical treatment includes valve replacement for right heart dysfunction and symptomatic valvular heart disease. Biological and mechanical valves can be implanted. However, both come with their set of shortcomings. Biological valves have a higher risk of early degeneration due to their susceptibility to carcinoid-induced fibrosis and graft failure. In contrast, mechanical valves require long-term anticoagulant ions following implantation, which can increase the bleeding risk and reoperation need [45].

Conclusion

Carcinoid syndrome is a rare condition associated with carcinoid tumors, typically slow-growing neuroendocrine tumors in the gastrointestinal tract or bronchial system. The syndrome is characterized by releasing biologically active substances, including serotonin, into the bloodstream, leading to symptoms such as flushing, diarrhea, bronchoconstriction, and heart valve damage. Diagnosing carcinoid syndrome involves clinical evaluation, biochemical testing (including urinary 5-HIAA measurement), and imaging studies such as CT scans and somatostatin receptor scintigraphy. Endoscopy and biopsy may be necessary for confirmation. The treatment of carcinoid syndrome includes somatostatin analogs, surgery, and other pharmacological and non-pharmacological approaches, depending on the specific case. Carcinoid heart disease and carcinoid crisis are potential

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complications associated with this syndrome. Carcinoid syndrome is relatively rare but associated with significant morbidity and mortality. Patients may present with relatively fewer symptoms even in the advent of a severe disease. Causes of carcinoid syndrome are hitherto unrecognized. Multiple treatment options are available, including surgery. Various complications are associated with this rare paraneoplastic syndrome. Hence, interprofessional management is required for improved outcomes. Epidemiological studies are increasing awareness of pathogenesis, diagnosis and prognostic factors, and various new treatment modalities. It carries a pretty good prognosis if diagnosed and managed in time. However, more multi-center trials involving new treatment modalities and primarily focusing on carcinoid tumors should be done.

References

1. Modlin IM, Lye KD, Kidd M (2003) A 5-decade analysis of 13,715 carcinoid tumors. Cancer 97(4): 934-959.
2. Oberg K (2012) Neuroendocrine tumors of the digestive tract: impact of new classifications and new agents on therapeutic approaches. Curr Opin Oncol 24(4): 433-440.
3. Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, et al. (2015) Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol 26(8): 1604-1620.
4. Strosberg J, El-Haddad G, Wolin E, Hendifar Andrew, Yao James, et al. (2017) Phase 3 trial of 177Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med 376(2): 125-135.
5. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, et al. (2016) ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 103(2): 172-185.
6. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, et al. (2012) Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 61(1): 6-32.
7. Pandit S, Annamaraju P, Bhusal K (2023) Carcinoid Syndrome. [Updated 2023 Feb 13] In: StatPearls [Internet] Treasure Island (FL) StatPearls Publishing.
8. Olariu E, Douthit N, Gade Ajay K (2020) Carcinoid Syndrome: A review. Cureus 12(3): e7186.
9. Santacroce L, Espat J Malignant Carcinoid Syndrome. Medscape.
10. Öberg K, Eriksson B (2005) Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 19(5): 753-781.
11. Zemlíková H (2005) Carcinoid syndrome: A statistical evaluation of 748 reported cases. J Exp Clin Cancer Res 18(2): 133-41.
12. Wilke A, Rudolf A, Rinke Anja, Mayer Christina, Herbert Peter, et al. (2008) Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. Clin Gastroenterol Hepatol 6(7): 820-827.
13. Lye KD, Kidd M, Modlin Irvin M (2003) A 5-decade analysis of 13,715 carcinoid tumors. Cancer 97(4): 934-959.
14. WILLIAMS E D, Sandler M (1963) The Classification of Carcinoid Tum Ours. Lancet 1(7275): 238-239.
15. Raphael MJ, Chan DL, Law C (2017) Singh S Principles of Diagnosis and Management of Neuroendocrine Tumours. CMAJ 189(10): E398-E404.
16. Oronsky B, Ma PC, Morgensztern D, Carter CA (2017) Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. Neoplasia 19(12) 991-1002.
17. Pandit S, Annamaraju P, Bhusal K (2003) Carcinoid Syndrome StatPearls Publishing.
18. Aluri V, Dillon JS (2017) Biochemical Testing in Neuroendocrine Tumors. Endocrinol Metab Clin North Am 46(3): 669-677.
19. Jensen R (2019) Tumores endocrinos del tubo digestivo y páncreas. Harrison principios de la medicina interna 20a ed. México: McGraw-Hill p. 601-604.
20. Iams WT, Koehler Kenna (2023) Carcinoid tumors outside the abdomen. Cancer Med 2(7): 7893-7903.
21. Kulke MH, Glickman JN, Swanson RS, Ashley SW, Raut Chandrajit P (2006) Carcinoid tumors. Curr Probl Surg 43(6): 383-450.
22. Prónai L, Németh AM, Tulassay Z (2002) Carcinoid tumorok [Carcinoid tumors]. Orv Hetil 143(19 Suppl):1087-92.
23. Johanna M Zuetenhorst, Babs G Taal (2005) Metastatic Carcinoid Tumors: A Clinical Review the Oncologist 10(2): 123-131.
24. Gade AK, Olariu E, Douthit NT (2020) Carcinoid Syndrome: A Review. Cureus 12(3): e7186.
25. J Hofland, Herrera-Martínez D, Zandee T Wouter, Herder de (2019) Management of carcinoid syndrome: a systematic review and meta-analysis. Society of Endocrinology 26(3): R145-R156.
26. Ferrari AC, Glasberg J, Riechelmann RP (2018) Carcinoid syndrome: update on the pathophysiology and treatment. Clinics. 73(suppl 1): e490s.
27. Clement D, Ramage J, Srirajaskanthan R (2020) Update on Pathophysiology, Treatment, and Complications of Carcinoid Syndrome. J Oncol 2020: 8341426.
28. Pasquer A, Walter T, Milot L, Hervieu V, Poncet G, et al. (2021) Principles of Surgical Management of Small Intestinal NET. Cancers 13(21): 5473.
29. Artale S, Barzaghi S, Grillo N, Maggi C, Lepori S, et al. (2022) Role of Diet in Managing Carcinoid Syndrome: Clinical Recommendations for Nutrition in Patients with Neuroendocrine Tumors. Nutrition and Cancer 74(1): 2-11.
30. Sjoerdsma A, Weissbach H, Udenfriend SA (1956) clinical, physiologic and biochemical study of patients with malignant carcinoid (argentaffinoma). Am J Med 20(4): 520-532.
31. Kahil ME, Brown H, Fred HL (1964) The carcinoid crisis. Arch. Intern. Med. 114: 26-28.
32. Zhou W, Fann P, Yen Y (2010) Carcinoid crisis 24 h after bland embolization: A case report. Biosci Trends 4(3): 143-144.
33. Bardasi C, Benatti S, Luppi G, Garajovà I, Piacentini F, et al. (2022) Carcinoid Crisis: A Misunderstood and Unrecognized Oncological Emergency. Cancers (Basel) 14(3): 662.
34. Oates J, Sjoerdsma KMA, Gillespie L, Mason D, Melmon K, (1964) Release of a kinin peptide in the carcinoid syndrome. Lancet 1: 514-517.
35. Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, et al. (2017) The surgical management of small bowel neuroendocrine tumors: Consensus guidelines of the north American neuroendocrine tumor society. Pancreas 46(6): 715-731.

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36. Dobson R, Burgess MI, Pritchard DM, Cuthbertson DJ (2014) The clinical presentation and management of carcinoid heart disease. Int J Cardiol 173(1): 29-32.

37. Hart EA, Meijs TA, Meijer RC, Dreijerink KM, Tesselaar ME, et al. (2017) Carcinoid heart disease: a guide for screening and timing of surgical intervention. Neth Heart J 25(9): 471-478.

38. Chengyue Jin, Ajay Nair S, Balasingam Thevakumar, Muhammad Majid, Shahad Al C, et al. (2021) Carcinoid Heart Disease: Pathophysiology, Pathology, Clinical Manifestations, and Management. Cardiology 146(1): 65–73.

39. For DJ, Khattar RS (2004) Carcinoid heart disease: presentation, diagnosis, and management. Heart 90(10): 1224-1228.

40. Bernheim AM, Connolly HM, Pellikka PA (2007) Carcinoid heart disease in patients without hepatic metastases. Am J Cardiol 99(2): 292-294.

41. Requilé A, Van De Bruaene A, Reenaers V, Dendale P (2014) A case of carcinoid heart disease with desaturation and no liver metastases. Echocardiography 31(10): E307-E309.

42. Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, et al. (2010) Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging 3(1): 103-111.

43. Waltenberger J, Lundin L, Oberg K, Wilander E, Miyazono K, et al. (1993) Involvement of transforming growth factor-beta in the formation of fibrotic lesions in carcinoid heart disease. Am J Pathol 142(1): 71-78.

44. Ram P, Penalver JL, Lo KBU, Rangaswami J, Pressman GS (2019) Carcinoid Heart Disease: Review of Current Knowledge. Tex Heart Inst J 46(1): 21-27.

45. Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC, et al. (1993) Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation 87(4):1188-1196.

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