Beyond IBS: Recognizing Carcinoid Syndrome and Unmasking Diagnostic Overlaps

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Abstract:

Introduction and aim of the study

Irritable bowel syndrome (IBS) and carcinoid syndrome are distinct conditions, functional and neoplastic respectively, yet they often present with similar gastrointestinal symptoms such as diarrhea, bloating and abdominal pain. This clinical overlap can lead to misdiagnosis and delayed identification of neuroendocrine tumors (NETs). This study compares IBS and carcinoid syndrome in terms of pathophysiology, clinical presentation, diagnostic approaches and therapeutic strategies. Emphasis is placed on diagnostic errors and the importance of timely recognition of NETs.

Materials and methods

A literature review was conducted focusing on diagnostic criteria such as Rome IV, biochemical markers including 5-HIAA and chromogranin A, and imaging modalities like CT, MRI and PET. Publications from 2009 to 2025 were analyzed, with the majority from 2020 to 2024. A total of 24 original research articles were included.

Results

Although both conditions share gastrointestinal complaints, features such as facial flushing, valvular heart disease and failure to improve with dietary changes are more suggestive of carcinoid syndrome. IBS is diagnosed based on symptoms alone, while NETs require biochemical and radiological confirmation.

Conclusions

Accurate differentiation between IBS and NETs is essential. In patients with persistent, atypical or treatment-resistant symptoms, appropriate testing significantly improves prognosis and may be life-saving. Increased clinical awareness can reduce diagnostic delay and enhance patient outcomes.

Keywords: Irritable Bowel Syndrome; Carcinoid Tumor; Neuroendocrine Tumors; Differential Diagnosis; Gastrointestinal Diseases;

1. Introduction

NETs are characterized by their slow progression and the insidious onset of nonspecific symptoms, which often leads to significant diagnostic delays. In a landmark study conducted in the United States (N = 758), the average time from the onset of initial symptoms to a confirmed diagnosis was reported to be above 50 months [1,2,3].

Data from two large patient surveys (N = 2231) revealed that many individuals were initially misdiagnosed with conditions such as IBS (24%–49%), gastritis or dyspepsia (13%–46%), and psychiatric disorders, including anxiety or depression (4%–26%), before receiving a correct diagnosis of NET. These findings highlight the diagnostic challenges associated with NETs

and underscore the need for increased clinical awareness, particularly in patients with persistent and unexplained gastrointestinal symptoms [4,5].

These findings highlight the importance of considering NETs earlier in the diagnostic process for patients with persistent, unexplained gastrointestinal symptoms. The high rate of misdiagnosis underscores the need for heightened clinical suspicion, particularly when standard therapies prove ineffective. Greater awareness and earlier use of specific diagnostic tests may lead to faster detection and significantly improve patient outcomes.

Early detection and resection of rectal neuroendocrine tumors (r-NETs) are strongly associated with improved patient outcomes.

According to recent data, the 5-year survival rate reaches 94%–100% in cases of localized disease, while it significantly decreases to 71%–88% with regional metastasis and drops further to 14%–33% in the presence of distant metastases. These findings underscore the critical importance of timely diagnosis and intervention in optimizing long-term survival in patients with r-NETs [5,6].

These data clearly demonstrate that the prognosis of r-NETs is highly dependent on the stage at diagnosis. Early detection not only increases the likelihood of curative resection but also dramatically improves long-term survival. Therefore, prompt recognition and intervention should be a priority in the clinical management of patients with suspected r-NETs.

2. Definition and the subtypes of IBS

IBS is a widespread, chronic gastrointestinal disorder based on the interaction between the brain and gut. IBS is characterized by recurrent abdominal discomfort and altered bowel habits, occurring without identifiable structural or biochemical abnormalities [7, 8]. The Rome IV criteria allow for the classification of IBS into four subtypes: IBS with predominant constipation (IBS–C), IBS with predominant diarrhoea (IBS-D), IBS with mixed bowel habits (IBS-M), unclassified IBS (IBS–U) [1, 8, 10].

Assessment is focused on the presence of recurrent abdominal pain occurring at least once a week, changes in stool frequency, stool form and also pain associated with bowel movements [8, 13].

2.1 Epidemiology

Recent data estimate the prevalence of IBS at approximately 12% of the general population. [5]. It should be acknowledged that a significant number of individuals experiencing IBS-related symptoms do not seek medical consultation. Scientific researches based on The Rome Foundation Global Epidemiological Study using Rome show that the prevalence rates in Europe and the United States were analogous, but in Asia and Australia were marginally lower. Egypt had the highest prevalence rate of internet surveyed countries [7, 12].

Women are more commonly impacted by this condition. Women frequently struggle with abdominal pain and constipation, while men mainly experience IBS with diarrhea. The prevalence of IBS decreases with age. There are also differences in the occurrence of specific subtypes between the United States and Europe. In the United States, these subtypes occur in equal proportions, while in Europe, IBS-C and IBS-M are more common [8].

2.2 Pathophysiology

The gut-brain axis is recognized as a key factor in the development of gastrointestinal disorders. Our emotions have a significant impact on intestinal function, including motility, mucosal secretion, and barrier integrity. It is ultimately the brain that modulates the perception of abdominal pain and feelings of discomfort in the digestive system. Based on this, it can be concluded that traumatic events may significantly influence the onset of IBS symptoms as well as their exacerbation [7, 9, 11, 15].

2.3 Visceral Hyperalgesia

Some patients with increased intestinal permeability and hypersensitivity to both somatic and visceral stimuli exhibit a lowered pain threshold. A likely mechanism underlying the altered pain perception and the emergence of visceral pain is the sensitization of nociceptive pathways in the gut [7, 11, 12].

2.4 Other Factors Associated with IBS

A potential trigger for gastrointestinal symptoms is intestinal dysmotility, which is linked to abnormal serotonin secretion. Additionally, changes in the gut microbiota, food intolerances, antibiotic use, and intestinal infections are increasingly recognized as contributing factors in the pathogenesis of IBS [7, 10, 11, 15].

2.5 Symptoms

Clinical manifestations include diarrhea, abdominal pain, constipation, bloating, fatigue, defecation disturbances – changes in stool frequency and form, mucus in stool, relief after defecation [7, 14].

2.6 Diagnosis and Practical Use of the Rome IV Criteria

A thorough patient history plays a crucial role in the diagnosis of IBS. In clinical interviews, the use of the Rome criteria is particularly helpful for formulating diagnostic questions [7, 11, 12].

The Rome IV criteria are guidelines for the diagnosis and treatment of disorders related to gut-brain interaction. To diagnose IBS, a patient must experience recurrent abdominal pain on average at least one day per week in the last three months and this pain must be associated with at least two of the following three criteria: related to defecation, associated with a change in stool frequency, associated with a change in stool form [7, 11, 12, 13].

It is especially important to conduct more in-depth diagnostic evaluations in patients aged 50 and older. If a patient presents with atypical symptoms for IBS, alarming symptoms or has a significant family history, further investigations should be conducted to rule out malignancies, inflammatory bowel diseases, celiac disease, food intolerances and *Clostridium difficile* infection [7, 10, 14].

3. Definition of NETs

NETs are rare types of cancer that can arise in almost any organ of the body. These tumors are known for their ability to produce and release substances typical of both nerve and endocrine (hormonal) cells, such as chromogranin A and somatostatin receptors [18, 19].

NETs are part of a broader category called neuroendocrine neoplasms (NENs). This group also includes neuroendocrine carcinomas (NECs), which are poorly differentiated and therefore more aggressive and harder to treat than NETs. Well-differentiated NETs are often clearly defined and, in the case of pancreatic NETs, may even be encapsulated. At the time of diagnosis, these tumors frequently show deep infiltration into surrounding tissues, such as the intestinal wall, and may already have metastasized. Macroscopically, they can be difficult to detect. Histologically, they are composed of uniform cells with round or oval nuclei and granular chromatin, giving them a characteristic “salt and pepper” appearance under the microscope [16].

3.1 Location

NENs can occur in almost any part of the body. The most common sites are the gastrointestinal tract (about 60% of all NENs and 70% of NETs) and the lungs (approximately 20% of NENs and 25% of NETs). Less common locations (accounting for around 5% of NETs) include the head and neck region, thymus, thyroid, breast, skin, and the genitourinary system [16, 17, 18].

3.2 Epidemiology

Carcinoid tumors (a term often used for NETs) are considered rare, but their diagnosis is becoming more frequent. This is largely due to the increased use of medical imaging for other conditions, which can lead to incidental findings. In the small intestine, NETs are most often found in the ileum. In the large intestine, they are commonly located in the cecum, while rectal NETs tend to occur sporadically. Colorectal NETs are diagnosed more frequently in Asia, whereas small intestinal and gastric carcinoids are more common in Europe. Gastrointestinal NETs most often occur in the seventh decade of life [6].

3.3 Pathogenesis

Carcinoid tumors develop from specialized neuroendocrine cells known as enterochromaffin cells, also referred to as Kulchitsky cells. One of the most frequently mutated genes in carcinoid tumors is MEN1. Somatic mutations in this gene have been identified in approximately 11–22% of cases. NETs can secrete a wide range of biologically active substances, including serotonin, histamine, tachykinins, kallikrein, and prostaglandins. When these substances enter the bloodstream, they may cause systemic effects, most notably carcinoid syndrome [6, 21].

3.4 Clinical Symptoms

The clinical presentation of NETs varies widely. NETs that secrete hormones into the bloodstream may cause carcinoid syndrome - a specific group of symptoms caused by the tumor's secretions. It is important to remember that not every carcinoma causes this syndrome [6, 20].

The most common clinical features of carcinoid syndrome include: flushing – This is the most frequently reported symptom. It typically affects the face, neck, and upper chest, and is caused by the release of histamine. Episodes last from 30 seconds to 30 minutes and may occur spontaneously or be triggered by factors such as alcohol, stress, anesthesia, or palpation of the liver [6, 22, 23]. Diarrhea – Affects approximately 80% of patients. It is typically chronic, watery and non-bloody with patients sometimes experiencing up to 30 bowel movements per day [21, 22]. Cardiac involvement – Occurs in 60% to 70% of patients and is caused by fibrotic plaque-like deposits on the endocardium, valves, and other cardiac structures, e.g., the pulmonary and aortic arteries. The right side of the heart is most commonly affected, leading to valvular disease and signs of right-sided heart failure [22, 23]. Bronchospasm – A less frequent symptom, also related to histamine release. It often occurs together with flushing and is characterized by shortness of breath and wheezing [6, 22, 23]. Other rare symptoms – These may include pellagra, resulting from a deficiency of niacin (vitamin B3), which occurs due to excessive conversion of tryptophan to serotonin. Additional complications may include muscle wasting and ureteral obstruction secondary to retroperitoneal fibrosis [22].

The presence of carcinoid syndrome is considered a negative prognostic factor, typically indicating advanced or metastatic disease [23].

3.5 Diagnosis

Diagnosing NETs can be challenging and often requires a high index of clinical suspicion, especially in patients with unexplained gastrointestinal symptoms. The diagnostic process generally includes the following components:

Biochemical testing - In healthy individuals, only a small fraction (about 1%) of tryptophan is converted to serotonin. In patients with carcinoma syndrome, most of this amino acid is

metabolised to serotonin, whose metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is excreted in the urine. The urinary 5-HIAA test has high sensitivity and specificity (approximately 90%). False-positive results may occur due to the consumption of serotonin-rich foods or certain drugs [6].

Imaging studies - After biochemical confirmation, imaging is used to localize the tumor and assess the extent of disease. Available imaging modalities include: CT (Computed Tomography), MRI (Magnetic Resonance Imaging), radiolabeled nuclear scans such as octreotide scan or Gallium-68 DOTATATE PET scan.

Triphasic CT is commonly used due to its widespread availability but has limitations, including moderate sensitivity (around 50%), difficulty detecting tumors smaller than 1 cm, and challenges in differentiating colorectal adenocarcinoma from NETs. MRI is considered more sensitive for detecting liver metastases.

Octreotide scans are particularly useful for detecting tumors outside the abdominal cavity. Today, they are often combined with **PET (Positron Emission Tomography)** to significantly improve the sensitivity for identifying abnormal lesions within the abdomen. The diagnostic accuracy of these methods in asymptomatic patients with gastrointestinal NETs is estimated to range from 80% to 90% [6].

4. Similarities and differences in the clinical picture between IBS and carcinoid tumors

IBS and gastrointestinal carcinoid tumors, particularly those associated with carcinoid syndrome, share overlapping symptoms such as chronic diarrhea, abdominal pain, and bloating. However, their underlying mechanisms, clinical course, and response to treatment differ significantly, making accurate differential diagnosis essential.

IBS is a functional GI disorder linked to gut-brain axis dysregulation, visceral hypersensitivity, abnormal intestinal motility, and psychosocial factors. IBS-related diarrhea is typically intermittent and non-debilitating, often alternating with constipation. Abdominal pain is relieved by defecation, and systemic symptoms like weight loss or fever are absent [12]. In contrast, carcinoid tumors are NETs that can release vasoactive substances like serotonin, leading to carcinoid syndrome.More than 40 substances have been identified as potentially responsible for this syndrome [24,25]. Carcinoid syndrome is characterized by secretory diarrhea, facial flushing, and, in advanced cases, cardiac fibrosis. Diarrhea in carcinoid

syndrome is profuse and unresponsive to diet or stress. A distinguishing feature of carcinoid syndrome is episodic flushing, which results from vasodilation induced by circulating vasoactive amines. It typically lasts seconds to minutes and is triggered by stress, alcohol, or certain foods. Systemic signs such as tachycardia and hypotension may also be present [25, 26, 27].

Therapeutically, IBS responds to dietary changes, probiotics, and antispasmodic agents, while carcinoid syndrome requires somatostatin analogs and targeted therapies. Diagnostically, IBS is a diagnosis of exclusion, based on Rome IV criteria, whereas NETs are confirmed through biochemical markers such as elevated 24-hour urinary 5-HIAA and serum chromogranin A levels, alongside advanced imaging modalities like CT, MRI, and PET/CT using radiolabeled somatostatin analogs [28].

In conclusion, while IBS and carcinoid tumors share overlapping symptoms, their etiology, disease course, and treatment approaches differ significantly. Awareness of these differences, particularly the presence of systemic symptoms and the lack of response to IBS treatment, enables quicker and more accurate diagnosis, avoiding delays in cancer treatments.

Comparison of Clinical and Diagnostic Features: IBS vs Carcinoid Syndrome

Feature	**IBS**	**Carcinoid Syndrome**	**References**
Etiology	Functional disorder – dysregulation of the gut-brain axis	Secretion of bioactive amines by NETs	[6, 7, 9, 11, 21]
Main Symptoms	Abdominal pain, bloating, alternating diarrhea/constipation	Flushing, chronic diarrhea, wheezing	[6, 7, 8, 22, 23]
Type of Diarrhea	Intermittent, moderate	Profuse, watery, treatment-resistant	[7, 14, 21, 22]
Relief after Defecation	Yes	No	[7, 12, 24]

Systemic Symptoms	Absent	**Present (flushing, tachycardia, hypotension)**	[6, 12- 24]
Response to Diet	Often improves	No effect	[7, 14, 23]
Cardiac Involvement	Absent	Present (e.g., right-sided heart valve fibrosis)	[22- 24]
Diagnostic Criteria	Rome IV criteria + clinical interview	Biochemical markers (5-HIAA, Chromogranin A) + imaging	[6, 8, 13, 28]
Biochemical Markers	Not applicable	5-HIAA, Chromogranin A	[6, 22, 28]
Imaging Required	No	Yes (CT, MRI, PET/CT)	[6, 28]
Treatment	Diet modification, probiotics, antispasmodics	Somatostatin analogs, tumor resection, targeted therapies	[10, 20, 23, 36]

5. Risk of misdiagnosis - case examples

There are published reports describing cases in which carcinoid tumors were initially misdiagnosed as functional bowel disorders, leading to significant delays in proper diagnosis and management.

A clinical case described an 80-year-old woman who presented with a 14-year history of intermittent diffuse abdominal pain and alternating bowel habits. These symptoms were initially interpreted and managed as a functional gastrointestinal disorder, most likely irritable bowel syndrome. Despite ongoing treatment, her complaints including abdominal discomfort, weight loss, and fatigue persisted without improvement. Notably, typical features of carcinoid

syndrome such as secretory diarrhea or flushing were absent, which contributed to the prolonged misdiagnosis.

Further investigations were initiated only after her abdominal pain worsened and a palpable mass was detected in the left lower quadrant. Laboratory findings revealed elevated levels of chromogranin A and 5-hydroxyindoleacetic acid. Imaging studies including contrast-enhanced computed tomography and somatostatin receptor scintigraphy confirmed the presence of an ileal carcinoid tumor with mesenteric metastases and signs of subacute intestinal ischemia. Because of the extent of the disease and mesenteric involvement, surgical resection was no longer feasible. The patient was managed conservatively with somatostatin analog therapy and remained clinically stable for the following two years [29].

Similarly, a case published in *Cases Journal* in 2009 described a 74-year-old woman who had been experiencing recurrent abdominal pain, bloating, and irregular bowel movements for approximately four years. These symptoms were initially misdiagnosed as IBS, resulting in prolonged conservative treatment with no significant improvement. Only after the emergence of new symptoms nausea and frequent loose stools were further diagnostic investigations performed. Imaging revealed a tumor in the terminal ileum, which was surgically removed and histologically confirmed to be a neuroendocrine carcinoid tumor [30].

Conversely, in some cases, recurrence of carcinoid syndrome is initially suspected but later ruled out. For instance, in 2016, a case was published involving a 72-year-old man with a history of a small bowel NETs who presented with diarrhea and abdominal pain. A recurrence of carcinoid syndrome was initially suspected, but subsequent testing revealed an infection with multidrug-resistant *Campylobacter coli*. After appropriate antibiotic treatment, the patient's symptoms resolved [31].

These cases illustrate the importance of accurate and comprehensive diagnostic evaluation in patients presenting with nonspecific gastrointestinal symptoms. Carcinoid tumors can mimic various benign conditions, and early detection is key not only to avoid complications but also to prolong survival and improve quality of life.

6. Conclusion

Carcinoid syndrome, a clinical presentation of hormonally active NETs, remains a notable diagnostic challenge due to its often nonspecific gastrointestinal symptoms that closely resemble those of IBS. This symptomatic overlap often leads to misdiagnosis and delays in appropriate identification, resulting in many carcinoid tumors being diagnosed at an advanced stage. At this point, treatment options are significantly reduced and the overall prognosis is considerably poorer [29].

A meticulous clinical history and physical examination are crucial in differentiating organic causes of chronic diarrhea from functional gastrointestinal disorders. Given that symptoms of carcinoid syndrome may not occur or be nonspecific in early stages, and typically manifest as the disease progresses, NETs should be considered in patients with persistent, unexplained gastrointestinal complaints. Notably, the presence of alarming symptoms should prompt oncologists to consider the possibility of carcinoid syndrome. Early detection of carcinoid tumors is paramount to improving prognosis, enabling curative or palliative interventions at a more favorable stage of disease progression [1, 32].

Improving clinician awareness through targeted education and training on the rarer etiologies of chronic abdominal symptoms has the potential to significantly reduce diagnostic latency and enhance patient outcomes. Research findings suggest that individuals with NETs often seek care from family physicians as their first point of contact which may contribute to misdiagnosis if they are unaware of the possibility of such a tumor [29,30]. In the differential diagnosis between IBS and carcinoid tumors, a strong clinical intuition is crucial. Although the symptoms of both conditions can be similar, subtle differences require the physician's experience and attentiveness.

These findings highlight the importance of developing standardized diagnostic pathways and promoting interdisciplinary collaboration. Further research should focus on refining noninvasive biomarkers and advanced imaging techniques to improve accurate identification of NETs. Recent progress in oncological therapies has substantially widened the range of available treatment options for patients [33]. Improved awareness and diagnostic accuracy hold the potential to markedly reduce misdiagnosis rates, thereby enabling earlier detection and more tailored therapeutic strategies.

Disclosure

Author's contribution

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