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Review Article

Unveiling the Rarity: A Comprehensive Review of Carcinoid Syndrome Symptoms in Individuals Aged 38 and Younger

Martin D Tanhaei MS[1,2,3,*], Talieh Norouzi MD[4], Caleb Sedam[1] and Marlon Rodriguez[1]

[1]*School of Medicine, St. George's University, True Blue, GRD*

[2]*Biomedical Engineering, University of California, Irvine, CA, USA*

[3]*Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA*

[4]*Fasa University of Medical Sciences, IRN*

***Corresponding author:** Martin D Tanhaei, MS, Biomedical Engineering, University of California, Irvine, USA; Johns Hopkins University, Baltimore, USA; School of Medicine, St. George's University School of Medicine, True Blue, GRD

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Abstract

Carcinoid syndrome, primarily caused by neuroendocrine tumors in the gastrointestinal and bronchopulmonary systems, manifests with symptoms like flushing, diarrhea, and wheezing due to excessive serotonin secretion. Because it is rare, especially in individuals 38 years and younger, diagnosis can be challenging but missing it can lead to severe clinical outcomes. This review delves into the presentation and management of carcinoid syndrome in this younger demographic, highlighting the need for increased clinical awareness and thorough investigation. By analyzing recent literature and case studies, we reveal the diagnostic complexities faced by physicians when younger adults present with symptoms mimicking conditions such as asthma or gastrointestinal disorders. The review emphasizes the importance of early diagnosis and customized management strategies to improve outcomes in this population, and it showcases the critical nature of distinguishing carcinoid syndrome from more common ailments.

Keywords: Carcinoid syndrome; Neuroendocrine Tumors; Younger Adults; Diagnostic Complexities; Symptom Mimicry (Asthma, Gastrointestinal Disorders); Flushing; Diarrhea; Wheezing

Introduction

Carcinoid tumors embody a distinctive subset of neuroendocrine malignancies predominantly arising within the gastrointestinal tract and, to a lesser degree, within the bronchopulmonary system. Carcinoid syndrome is a condition characterized by a distinct set of symptoms including flushing, diarrhea, and wheezing due to excessive serotonin hormone production **(Figure 1)** [1]. Despite their noted slow growth and relative rarity, these tumors present significant clinical conundrums, notably when afflicting younger populations (aged 38 and younger).

Focusing on individuals aged 38 and younger highlights the rare but unique characteristics of this disease among a younger demographic. This age range allows us to identify potential early-onset factors and improve our understanding of the disease's progression in younger adults, which can influence diagnosis and treatment.

A case that epitomizes the clinical challenges of diagnosing carcinoid syndrome in young adults involved a 36-year-old female presenting with symptoms initially indicative of recurrent asthmatic attacks. This patient's journey, marked by recurrent emergency room visits and an array of nonspecific symptoms, eventually led to the diagnosis of intestinal carcinoid syndrome, thereby highlighting the deceptive and complex nature of this condition in younger individuals. Such instances underscore the critical necessity for astute clinical vigilance and a comprehensive investigative approach in patients presenting with atypical symptoms across different systems **(Figure 1)** [1].

The incidence of appendiceal carcinoids, recognized as the most prevalent neuroendocrine tumors within the appendix, remains exceedingly low, found in only 0.3–0.9% of appendiceal specimens [2]. However, their clinical significance cannot be understated, particularly among the younger demographic, due to potential metastatic behavior and the necessity for precise surgical intervention dictated by tumor dimensions and invasion depth [2].

Although the manifestation of carcinoid syndrome from such tumors remains rare, its occurrence underscores the need for early identification and comprehensive management strategies [1].

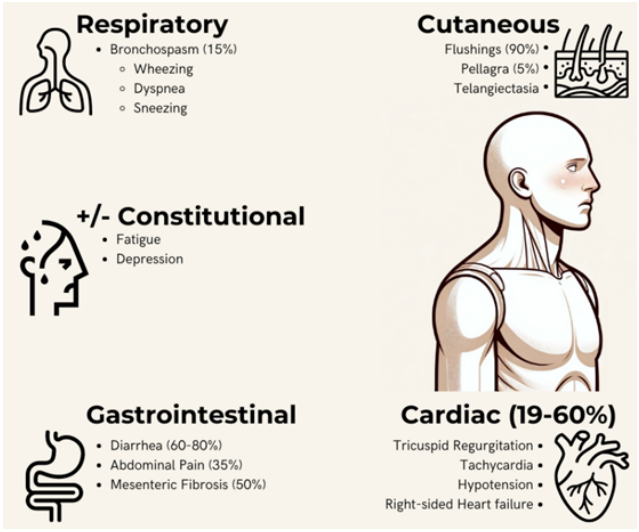

Figure 1: Carcinoid syndrome symptoms (% frequency in symptomatic population). Data adapted from [1].

Bronchopulmonary carcinoid tumors further contribute their share of diagnostic dilemmas, accounting for less than 2% of all lung neoplasms [3]. Their often asymptomatic or non-specific presentation leads to frequent misdiagnosis, especially in the young, where typical symptoms associated with these tumors may not be evident. The importance of early and accurate diagnosis is thereby underscored, with surgical excision serving as the critical determinant of prognosis.

This review aims to delve into the peculiarities of carcinoid syndrome among younger individuals, drawing insights from documented instances within both gastrointestinal and bronchopulmonary contexts. By examining cases from our compiled reports, including appendiceal and duodenal carcinoid manifestations in younger individuals, this paper is dedicated to unraveling the clinical manifestations posed by these elusive tumors. Our objective is to furnish an overview of the symptom-based analysis of carcinoid syndrome in this demographic, emphasizing the urgency of recognizing this rare entity and the necessity of implementing timely, definitive therapeutic interventions.

Survey Methodology

In our survey on carcinoid syndrome in younger adults, we conducted a systematic literature search using PubMed, Google Scholar, and Scopus databases with terms like "carcinoid syndrome in young adults," "neuroendocrine tumors in adolescents," and more specific phrases such as "appendiceal carcinoid presentation in young patients." We focused on reports with patients 38 years old and younger. We refined our search to include diagnostics and presentations of carcinoid syndrome, applying no initial restrictions on language or publication date but prioritizing articles from the last decade. Screening was conducted through title and abstract evaluation, followed by full-text reviews for relevance and depth, including cross-referencing within selected papers to ensure a comprehensive and unbiased collection of pertinent literature.

Review

Respiratory Symptoms

Carcinoid syndrome, a constellation of symptoms resulting from hormonally active metastatic neuroendocrine tumors, often presents with complex, multi-system manifestations. Among its diverse symptoms, respiratory issues such as chronic cough, wheezing, hemoptysis, and respiratory distress are significant, especially in younger patients. These respiratory symptoms can mimic common conditions, like asthma, leading to misdiagnosis and resource waste. Moreover, misdiagnosis may delay proper treatment. This section explores case studies illustrating the respiratory manifestations of carcinoid syndrome in younger patients, which underscore the importance of considering carcinoid syndrome in the differential diagnosis of persistent, treatment-resistant atypical respiratory symptoms.

Chronic cough and wheezing are symptoms frequently associated with asthma or chronic bronchitis, leading to potential misdiagnosis in patients with carcinoid tumors. A notable case involves a 14-year-old female who presented with fatigue lasting 6-8 months and a chronic cough for 2-3 months [5]. Initially considered to be asthmatic, further investigation revealed an endobronchial carcinoid tumor, highlighting the necessity of considering carcinoid syndrome in young patients with unexplained respiratory symptoms.

Severe respiratory symptoms such as hemoptysis and respiratory distress may also be pivotal in the discovery of carcinoid tumors. The case series "Pediatric Bronchial Carcinoid Tumors" presents 5 patients aged 9 to 16 years, where hemoptysis and respiratory distress were key symptoms leading to the diagnosis of carcinoid tumors (Table 1) [6]. For instance, an 11-year-old male, initially treated for recurrent pneumonia, was eventually found to have a carcinoid tumor after presenting with hemoptysis, illustrating the critical need for an expansive differential diagnosis in persistent respiratory conditions.

Another article discussed a 22-year-old female with a history of intermittent productive cough with bloody sputum and wheezing. She was initially managed as bronchial asthma, but was later diagnosed with a bronchial carcinoid tumor following a detailed investigation [2]. This case underscores the importance of considering carcinoid syndrome in young patients with unexplained hemoptysis and wheezing, particularly when

Table 1. Summary table of patient presentation aged 9 to 15 years with respiratory manifestations of carcinoid syndrome. Data adapted from [5,6].

Age/Sex	Presenting Pulmonary Symptom	Location in Pulmonary System
9/F	Respiratory distress, wheezing	Left main stem bronchus
11/M	Hemoptysis	Right main stem bronchus
12/M	Persistent pneumonia	Right lower lobe
13/F	Tachypnea, and pneumonia	Left main stem bronchus
14/F	Chronic Cough	
15/F	Respiratory distress	Right bronchus intermedius
16/M	Recurrent pneumonia	Right bronchus intermedius
22/F	Intermittent Productive Cough, Hemoptysis, Wheezing	

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symptoms persist despite standard asthma treatments.

Gastrointestinal Symptoms

Abdominal Pain, Vomiting, and Anorexia

Carcinoid tumors can mimic several common gastrointestinal conditions, including appendicitis, which often leads to their incidental discovery during surgical procedures intended for other presumed conditions. A notable example is drawn from the case of a 16-year-old female who presented with severe right lower quadrant pain, nausea, and vomiting. The clinical presentation suggested appendicitis, but during surgical intervention, an appendiceal carcinoid tumor was discovered [2]. Another instance involved a 13-year-old female with similar symptoms—abdominal pain in the right lower quadrant and decreased appetite over two days, leading to the incidental finding of a carcinoid tumor during appendectomy [7].

In the realm of chronic gastrointestinal symptoms, carcinoid syndrome can manifest as persistent diarrhea and malabsorption, which are often mistaken for more common digestive disorders. For example, a 26-year-old male presented with chronic symptoms, including increased appetite and weight gain, accompanied by proximal muscle weakness and purple striae on his abdomen. Although the initial focus was on the gastrointestinal and endocrine symptoms, further investigation revealed an ectopic ACTH-producing carcinoid tumor, which highlighted the underlying carcinoid syndrome [8]. These cases emphasize the importance of considering carcinoid syndrome in the differential diagnosis when young patients exhibit unexplained chronic gastrointestinal symptoms, potentially leading to earlier detection and appropriate interventions.

Finally, we can see gastrointestinal manifestations in the case of a 26-year-old female suffering from constant and worsening right lower abdominal pain for the previous six months, while also experiencing anorexia, nausea, and constipation. Further workup found the cause to be a carcinoid tumor manifesting from the patient's right ovary [9]. While the gastrointestinal symptoms associated with carcinoid syndrome, such as abdominal pain, vomiting, and persistent diarrhea, are well-documented, their prevalence among younger patients remains understudied. However, available data suggest that while these symptoms may appear similar to more common conditions like appendicitis or irritable bowel syndrome, they often have a disproportionate impact on the quality of life in younger individuals. Early recognition and appropriate intervention are critical, as the misdiagnosis rates in this demographic are notably higher, underscoring the need for greater awareness and specificity in clinical evaluations.

Dermatological and Cutaneous Features

Flushing

Flushing is a hallmark sign of carcinoid syndrome, characterized by transient episodes of reddening of the skin, typically triggered by stress, certain foods, or alcohol. This subsection reviews specific cases to differentiate carcinoid-related flushing from other conditions with similar presentations, such as menopause or rosacea. For instance, a 35-year-old female with a late-stage diagnosis of carcinoid heart disease reported prolonged episodes of flushing, initially overlooked as a benign skin condition [10]. In another case, a 38-year-old male with untreated depression and a history of nonspecific fatigue experienced flushing alongside other systemic symptoms, which was later attributed to an underlying carcinoid tumor after a series of diagnostic evaluations [11]. These cases illustrate the importance of recognizing the unique characteristics of carcinoid-induced flushing, such as its sudden onset and association with other symptoms of the syndrome.

As another example, a 17-year-old male with suspected food allergies who experienced flushing, and conjunctival injections, upon consumption of foods and liquids, including water, was eventually found to have a primary carcinoid tumor in his colon that had subsequently metastasized to the liver [12].

Skin Lesions

Skin lesions are less common but significant dermatological manifestations of carcinoid tumors, often prompting further investigative procedures. This subsection highlights cases where these features played a critical role in the diagnostic process. A 13-year-old female with tachypnea and pneumonia also displayed facial acne, hirsutism, and skin stretch marks, which raised suspicions of an underlying neuroendocrine tumor, later confirmed through imaging and histopathological studies [6]. These examples underscore the importance of thorough skin examinations for patients presenting with unusual dermatological signs, as they may be indicative of more complex systemic diseases like carcinoid syndrome.

The dermatological manifestations of carcinoid syndrome, including flushing and skin lesions, pose diagnostic challenges due to their similarity to symptoms of more common conditions like rosacea or allergic reactions. To differentiate these from carcinoid-related features, clinicians must consider associated systemic symptoms and the context of their presentation. For example, carcinoid-related flushing is typically episodic and may coincide with other carcinoid syndrome symptoms like diarrhea or wheezing, which are not typical of dermatological conditions. A thorough patient history and consideration of additional symptoms can help guide the differential diagnosis more effectively.

Cardiac Involvement, Endocrine and Hormonal Effects, and Other Unique Manifestations in Carcinoid Tumors

Carcinoid Heart Disease

Carcinoid heart disease, though rare in young patients, can present with distinct cardiovascular symptoms that complicate the diagnostic process. An illustrative case is a 35-year-old Hispanic woman from South Texas who suffered from undiagnosed carcinoid syndrome for over a decade, which eventually progressed to severe carcinoid heart disease. Initially, her symptoms were misattributed to more common cardiac conditions, delaying appropriate treatment [9]. This case highlights the necessity for cardiologists to consider carcinoid syndrome in patients presenting with unusual cardiac symptoms like tricuspid regurgitation or right-sided heart failure, particularly when accompanied by systemic symptoms like flushing or diarrhea.

Ectopic ACTH Syndrome

The ectopic ACTH syndrome is a condition where tumors outside the pituitary gland produce adrenocorticotropic hormone (ACTH), often leading to features reminiscent of Cushing's syndrome. A notable case involved a 26-year-old male who exhibited increased weight, appetite, proximal muscle weakness, easy bruising, and the appearance of purple striae on his abdomen. His symptoms were initially managed as typical Cushing's syndrome until further investigations revealed an ectopic

ACTH-producing carcinoid tumor [8]. This case underscores the importance of endocrinologists considering ectopic sources of ACTH production in young patients presenting with signs of Cushing's syndrome, particularly when typical pituitary imaging is inconclusive.

Rare and Atypical Symptoms

Carcinoid syndrome can also present with less typical symptoms that vary widely among patients. For example, a 38-year-old male with carcinoid syndrome experienced nonspecific fatigue and weakness, which were initially dismissed as symptoms of his untreated depression. Only upon detailed evaluation were these symptoms linked to his underlying neuroendocrine condition [11]. Such cases demonstrate the diverse and often misleading presentation of carcinoid syndrome, emphasizing the need for a comprehensive assessment of patients with unexplained systemic symptoms.

Conclusion

Carcinoid syndrome in younger individuals often presents unique diagnostic challenges due to its rarity and the atypical presentation of symptoms compared to those seen in adults **(Figure 2)**. This comprehensive review underscored several critical points. Firstly, respiratory symptoms are a common manifestation but are frequently nonspecific. Young patients may experience wheezing (10.3%), chronic cough (6.9%), and hemoptysis (6.9%), which are often initially misdiagnosed as

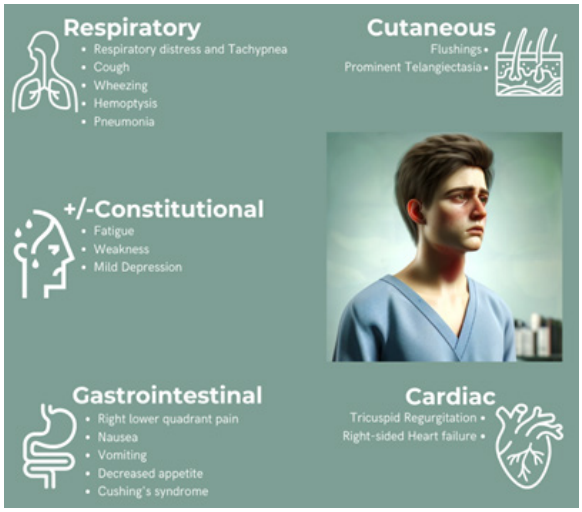

Figure 2: Carcinoid syndrome symptoms in aged 38 and younger - research summary.

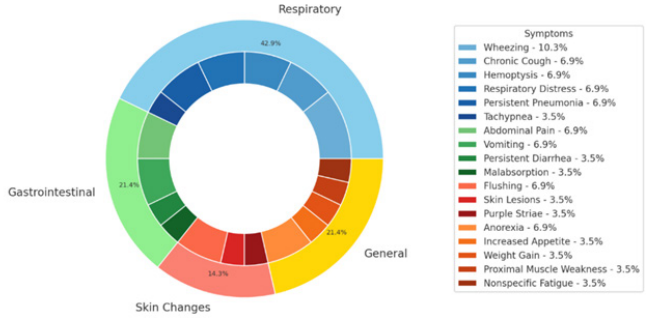

Figure 3. This nested ring pie chart categorizes and details the frequencies (%) of carcinoid syndrome symptoms among individuals aged 38 and younger, showcasing major categories in the outer ring and specific symptoms in the inner ring.

asthma or recurrent respiratory infections **(Figure 3)**.

Similarly, gastrointestinal symptoms in younger individuals can mimic more common conditions like appendicitis. This leads to many carcinoid tumors being incidentally discovered during surgical procedures that were initiated for entirely different conditions. Such findings highlight the deceptive nature of carcinoid syndrome's symptomatology in young adults, making it a complex clinical puzzle.

The review also draws attention to the importance of considering carcinoid syndrome in differential diagnoses, especially when young patients present with persistent and unexplained symptoms across multiple systems. The variability and subtlety of these symptoms can significantly delay accurate diagnosis and appropriate management, emphasizing the need for increased awareness among healthcare professionals.

Healthcare professionals are urged to adopt a heightened state of diagnostic vigilance when encountering young patients with unexplained, multisystem symptoms. Persistent respiratory problems such as coughing and wheezing, or gastrointestinal issues that do not respond to typical treatments, should raise the suspicion of carcinoid syndrome. Such symptoms, while often subtle, are indicative of potentially serious underlying conditions that require further investigative effort.

Interdisciplinary collaboration is also essential in the effective management of carcinoid syndrome. Given the complex and varied presentations of the syndrome, a team comprising gastroenterologists, oncologists, endocrinologists, and pulmonologists can provide a comprehensive evaluation to help pinpoint the source of the symptoms. This collaborative approach ensures that all possible aspects of the syndrome are thoroughly considered and addressed.

Additionally, continuous education on the evolving presentations and management strategies for carcinoid syndrome should be emphasized. Healthcare professionals, especially those in pediatrics and young adult care, should be updated regularly about the latest research and case studies that shed light on this condition. Understanding the nuances of carcinoid syndrome in younger populations will significantly enhance early diagnosis and improve treatment outcomes, ultimately leading to better patient care and prognosis.

Author Contributions

Concept and design: Martin D. Tanhaei, Talieh Norouzi

Acquisition, analysis, or interpretation of data: Martin D. Tanhaei, Talieh Norouzi, Marlon Rodriguez, Caleb Sedam

Drafting of the manuscript: Martin D. Tanhaei, Talieh Norouzi, Marlon Rodriguez, Caleb Sedam

Critical review of the manuscript for important intellectual content: Martin D. Tanhaei, Talieh Norouzi, Marlon Rodriguez, Caleb Sedam

Supervision: Martin D. Tanhaei, Talieh Norouzi

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