

CASE REPORT

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A 17-year-old male with a Small Bowel Neuroendocrine Tumor: flushing differential diagnosis

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Abstract

Background: Neuroendocrine tumors (NETs) are heterogeneous neoplasms that originate from cells with a secretory function. Small bowel NETs (SB-NETs) are related to serotonin hypersecretion which causes: flushing, diarrhea, abdominal pain, bronchoconstriction and heart involvement, also known as carcinoid syndrome (CS). CS can be confused with an allergic reaction and thus should be considered as a differential diagnosis in the allergy consult. We present the case of a pediatric patient initially referred under the suspicion of food allergies.

Case presentation: We present the case of a 17-year-old male with evanescent non-pruriginous erythematous lesions- flushing that appeared with food consumption, associated with conjunctival injection, warmth and diaphoresis after the lesions disappeared. He denied abdominal pain, diarrhea, cough or wheezing. The 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion was elevated. The CT scan showed thickening of the distal ileum and multiple lesions on both hepatic lobules and the colonoscopy revealed a tumor in the ileocecal valve. Hepatic and intestinal biopsies reported a well-differentiated NET of the ileocecal valve with hepatic metastasis. He was started on octreotide and underwent a wide hepatectomy and right hemicolectomy with improvement of symptoms.

Conclusions: NETs can present as carcinoid syndrome (flushing, diarrhea, abdominal pain, wheezing), which constitutes vague symptomatology and represents a challenging diagnosis for physicians. They can be confused with an allergic reaction and the allergist should consider it as a differential diagnosis. Accurate diagnostic tests will help to diagnose NETs earlier and potentially prevent carcinoid heart disease, bowel obstruction, and improve quality of life and mortality in these patients.

Keywords: Flushing, Neuroendocrine tumors, Carcinoid syndrome, Food allergies, Carcinoid tumor

Background

NETs are heterogeneous malignant neoplasms, which originate from cells with a secretory function within the neuroendocrine system [1]. The median age of diagnosis is 66 years-old [2] and it tends to be more common in females [3–6]. NETs are uncommon in the pediatric population with an incidence around 0.995 cases per 100,000 in patients under 20 years old [3]. There is an under diagnose of this pathology related to a low index of suspicion and relatively non-specific symptoms [7].

Nonetheless, the incidence rate has increased over the last few decades [8, 9] given the increased detection of this pathology [10]. Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) shows NETs constitute a relevant cancer threat despite their low incidence rate [11]. One of the largest case series of NETs in kids [12] describes the difference between the pediatric population and adults. For instance, in children NETs develop more frequently in the appendix, with a more indolent course, as the majority does not have metastasis. The study shows evidence about the lack of standardized care as even the most common NET in kids, appendiceal [3, 6, 13], does not have proper guidelines for surgical treatment [12].

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SB-NETs occur more often during the sixth and seventh decade of life [14, 15]. The annual age-adjusted incidence in the United States was 1.05 per 100,000 persons in 2012 [9]. They are extremely rare in children and up to 30% of these tumors present in multiple sites [15–17]. SB-NETs grow slowly and tend to metastasize to the mesenteric root nodes and the liver. Approximately 80% of the mortality of these tumors is due to liver failure and 16% is due to bowel obstruction [18]. The overall survival (OS) depends on many factors, such as the stage or the extent of the tumor, histology (grade), depth of the tumor invasion, gender, race and age. In general, the OS reported for 5 years is 83% [19]. Localized disease has a median survival of 14 years, while distant metastases have 5.83 years [9]. In the case of loco-regional disease the 5-year survival is 65%. In well to moderately differentiated SB-NETs the 5-year and 10-year OS rates according to the extent were: 65% and 49% for localized disease; 71% and 46% for regional metastasis; 54% and 30% for distant metastasis [20, 21]. Finally, poorly differentiated SB-NETs have a 30 to 33 months OS [9]. Taking these numbers into account, it is evident the impact this disease has on mortality and the importance of early diagnosis.

The diagnosis of SB-NETs at an early stage is often difficult because the primary tumors tend to be small and generally do not lead to symptoms [22]. Upon diagnosis, 29% of SB-NETs cases are at a localized stage, 41% are in a loco-regional stage and 30% already have metastases [2, 15]. The metastasis rate in tumors smaller than 1 cm to the lymph nodes is 12% while distant metastasis is 5%. For tumors greater than 2 cm these rates are 85 and 47%, respectively [14]. In primary SB-NETs peritoneal carcinomatosis may be present in up to 30% of the patients [23]. SB-NETs are usually diagnosed at an advanced stage and their discovery is related to the manifestation of a local complication of the tumor [24]. Maglente et al. explored the reasons behind the delayed diagnosis of these malignancies. They found that different circumstances contributed to the diagnostic delay. For instance, if the patient failed to report the symptoms, there was less than a 2-month delay in the diagnosis; if the physicians did not order the appropriate tests, the delay was 8.2 months and if the radiologist failed to make the diagnosis there was a 12-month delay [25].

The most commonly involved type of cells in SB-NETs are the enterochromaffin (EC) cells, which are in charge of producing and storing 5-HT (serotonin). This substance is released from EC cells by different stimuli like mechanical stimulation, nutrients and chemical stimulators such as acetylcholine (ACh) [26]. In the case of SB-NETs, hypersecretion of 5-HT can cause allergy-like symptoms such as diarrhea, flushes, bronchoconstriction and heart involvement, in the form of plaque-like deposits

in the heart valves [2, 22, 26]. These symptoms are known as carcinoid syndrome (CS), which is usually related to metastasis [15, 27]. In cancer registries 3–19% of patients with a SB-NET have CS, but in specialized centers the incidence has been reported as high as 71% [28–31]. CS constitutes an unusual presentation [4, 27, 32], especially in the pediatric population, as they usually have a localized disease [1, 11, 13].

To better understand CS, it is important to define flushing. It is the changes in cutaneous blood flow accompanied by reddening of the skin; it can be divided into episodic and persistent. Flushing tends to favor face, neck and upper torso, because of the relative increased volume of visible superficial cutaneous vasculature in these zones [33]. Differential diagnosis of flushing encompasses a wide spectrum of benign and malignant entities. Because of this, it is important that clinicians look for associated symptoms in order to discern the etiology. Nonetheless, the majority of conditions that present with flushing do have overlapping symptoms [33]. The flush characteristics in NETs can help to establish the location of the tumor. Midgut tumors present with a rapid cyanotic flushing, lasting for less than a minute and are often associated with a mild burning sensation. On the other hand, foregut tumors cause pruritic wheals over the entire body [33]. Again, it is important to take into account that these symptoms usually relate to the spread of the tumor.

NETs are challenging due to their unspecific symptoms [11, 34, 35]. CS components can be confused with an allergic reaction and should be considered as a differential diagnosis in the allergy consult. They are also challenging given their unpredictable behavior. After all, most of the patients with small bowel NETs tend to have distant tumor spread but with a low-grade disease, which makes precise prognostication and management quite complex [34]. We present the case and diagnostic approach of a pediatric patient initially referred to the allergy specialist under the suspicion of food allergies.

Case presentation

A 17-year-old male was remitted to the allergist because he presented evanescent, erythematous lesions with any food consumption. He had been seen by other specialists because of this symptomatology and given the relation between the occurrence of symptoms and food ingestion there was the suspicion of food allergies. Along with these lesions he also presented conjunctival injection, warmth and diaphoresis after the lesions disappeared. He stated circumstances like standing for a long time, valsalva and strong emotions also triggered the symptoms. He denied abdominal pain, diarrhea, coughing or wheezing.

The initial physical exam was normal; no lesions were observed. While in consult we decided to trigger the symptoms. The patient was asked to eat; the first time he

had coffee and a piece of chocolate cake. Nine minutes after the ingestion he presented an evanescent erythematous rash on the face, trunk and extremities (Fig. 1), which lasted 12 min and resolved spontaneously. The lesions were flat, non-pruriginous, nor painful and didn't leave any bruising after disappearing. Given the characteristics of the lesions, the diagnosis of urticaria was discarded. In order to dismiss the suspicion of a food allergy, we asked him to drink only water and once again the rash appeared. We consequently established there was no correlation with any specific food. Based on the characteristics of the rash, we determined it corresponded to a flushing, with an atypical presentation, as it was present in lower extremities and hands.

As the patient only presented flushing, we considered carcinoid syndrome an unlikely differential diagnosis, because it usually includes abdominal pain, diarrhea, wheezing or bronchoconstriction. Also, carcinoid syndrome is related to the release of serotonin in NETs, which is an improbable pathology in a teenager. Nonetheless, during his workup the 24-h urinary sample of 5-hydroxyindoleacetic acid, a metabolite of serotonin, was 42.6 mg, reference value is less than 10 mg/24 h and serum chromogranin A was normal. It was unusually high taking into account the patient, as part of the preparation for this test, was avoiding drugs and foods with high serotonin levels such as avocado, walnuts, banana, pineapple, among others [2, 36]. Therefore, the flushing observed was somehow associated to endogenous serotonin hypersecretion. There was a high suspicion of a NET and thus we ordered a CT scan. The CT scan showed thickening of the distal ileum and multiple lesions on both hepatic lobules (Fig. 2). To further

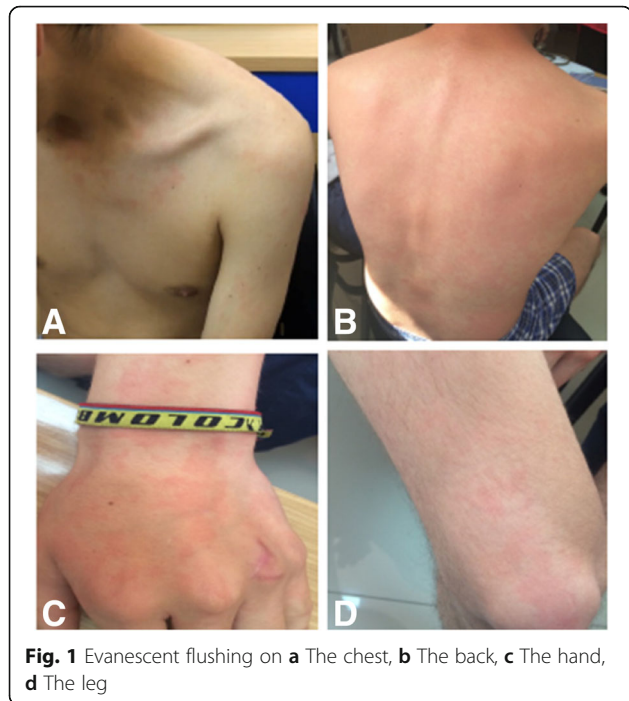


Fig. 1 Evanescent flushing on **a** The chest, **b** The back, **c** The hand, **d** The leg

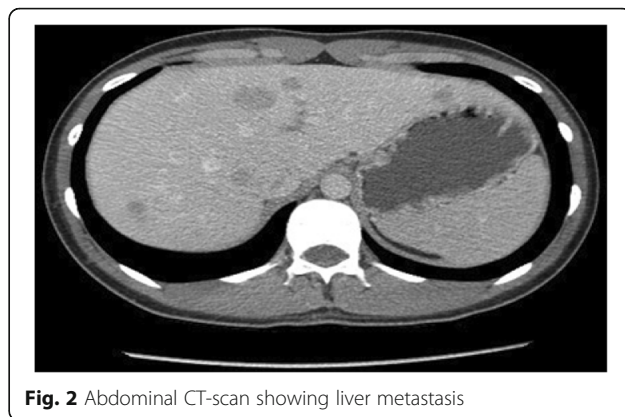


Fig. 2 Abdominal CT-scan showing liver metastasis

evaluate these lesions, a colonoscopy was done which revealed (Fig. 3) a prominent ileocecal valve with a mammillated and eroded lesion. The hepatic and intestinal biopsies identified a well-differentiated grade 2 primary NET (Fig. 4) of the ileocecal valve with hepatic metastasis. Treatment was established; he was started on octreotide LAR 30 mg intramuscular monthly and underwent a wide hepatectomy and right hemicolectomy, with initial improvement of the symptoms.

Two years later the follow up visits showed evidence the patient had tumor progression in his liver. This suggests that the octreotide was not sufficient to block the effect of the neuroamines produced by the tumor. Everolimus 10 mg p.o. daily was started in combination with octreotide LAR in an attempt to control symptoms and tumor progression. Also, with the evident progression of hepatic lesions, the patient has so far been taken to four radiofrequency ablations in order to counteract its growth. The Endocrine Service continues to follow this patient and based on current disease evolution, more interventions will most likely be needed.

Discussion and conclusion

This case shows a differential diagnostic for flushing not usually considered by allergists, CS symptoms are vague

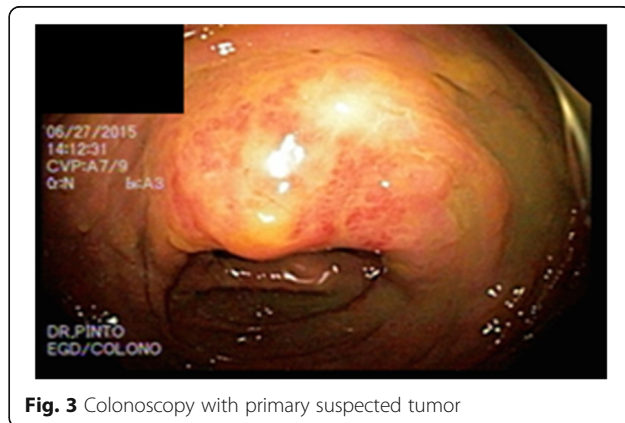


Fig. 3 Colonoscopy with primary suspected tumor

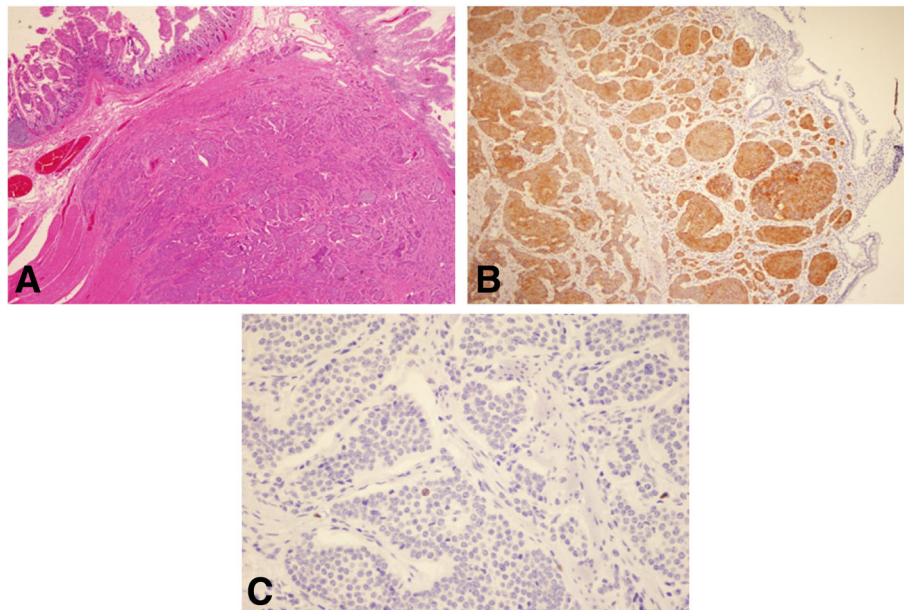


Fig. 4 Ileocecal valve mucosa biopsy showing a grade 2, well-differentiated NET **a** Hematoxylin and eosin (H&E) staining **b** Intense reactivity to chromogranin staining **c** Ki 67 staining determined a 1% proliferation cellular index

and can delay the diagnosis [5, 36]. Given the similar symptoms between NETs and allergic reactions, Pfanzagl et al. created an experimental model of EC cells to better understand these tumors. The model showed that EC cells had an increased response to Ach, which promotes intestinal secretion and motility, in the presence of histamine (HA) acting on H4Rs and H3Rs. This suggests that EC cells might play a role in the intestinal symptoms of diseases related to increased mast cell numbers like food allergies [26]. This shows that the same substances overlap in NETs and allergic reactions. Reason why, it is imperative for doctors to be able to separate benign entities from life-threatening conditions associated with flushing. After all, an early diagnosis helps to initiate an effective treatment to prevent carcinoid heart disease, prevent bowel obstruction, and improve quality of life and mortality.

Flushing of typical CS often involves the face, neck and upper chest [33]. This case had an atypical presentation because the patient had a flush not only in his face, thorax and abdomen but also in the distal part of his upper extremities (Fig. 1c). On the other hand, the duration was longer than expected in midgut tumors, less than one minute [33]. Moreover, he had no other associated symptoms like hepatomegaly or abdominal pain [35], making the diagnosis rather troublesome. This case is also one of the few reports of CS in children associated with high 5-HIAA levels [3, 27, 36]. He had a very advanced disease at the time of diagnosis, in concordance with Navalkele et al., in which less than half of the children and young adults were diagnosed before regional and distant spread of the disease [11].

Finally, it is important to emphasize the fact that SB-NETs are extremely rare in children and because of this, they are seldom considered among the differential diagnosis of allergy-like symptoms, such as flushing. This report will help to expand the limited literature and promote the use of the available tools in the adult world within the context of young children [37]. All this, in order to tackle the lack of standardized care of a rare but treatable disease [7, 11, 12, 36]. After all, an early diagnosis and surgical resection is probably the only curative therapy for NET [21].

Abbreviations

5-HIAA: 5-hydroxyindoleacetic acid; CS: Carcinoid Syndrome; CT: Computed tomography; NETs: Neuroendocrine tumors; SB-NETs: Small Bowel Neuroendocrine tumors

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Availability of data and materials

We do not have new software or database or tools as part of the case report.

Authors' contributions

MAFM, EG, DGD performed the diagnosis, DGD established clinical treatment. RGD and AV carry out the surgery. MAFM was a major contributor in writing the manuscript. EG, DGD, MAFM, RGD and AV read and approved the final manuscript.

Ethics approval and consent to participate

The present study complied with the ethical requirements (in accordance with Law 8430 of 1993) established by Colombian law, and was approved by

the Ethics Committee from the Hospital Universitario Fundación Santa Fe de Bogotá Colombia.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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