

Review of Treatment Options of Psychiatric Symptoms in a Case of Functional Neuroendocrine Tumor

Prajjita Sarma Bardoloi*

Department of Psychiatry, Queen Elizabeth II Hospital, Grande Prairie, Alberta T8V 2E8, Canada

*Corresponding author: Prajjita Sarma Bardoloi, Department of Psychiatry, Queen Elizabeth II Hospital, Grande Prairie, Alberta T8V 2E8, Canada, Tel: 17805387252; E-mail: bardoloi@ualberta.ca

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Abstract

Neuroendocrine tumors (NET) are tumors arising from neuroendocrine cells in the body and are found in the gastrointestinal tract, and less commonly pancreas, lungs, thymus and thyroid C-cells. There has been a recent increase in the prevalence of the NETs, which is attributed to better diagnostic procedures. NETs were thought to be slow growing benign tumors in the past but almost all NETs are now considered to have malignant potential. These tumors cause systemic symptoms by releasing vasoactive substances to the bloodstream and are often associated with psychiatric symptoms like depression, anxiety or psychosis. Treating such individuals would require multidisciplinary team approach due to the complexity of the illness. The purpose of this article is to review the various aspects of this illness and challenges of treating the associated psychiatric symptoms.

Introduction

NETs are tumors arising from the diffuse neuroendocrine cells in the body.

They are often classified by their site of origin and their symptoms seem to vary according to various sites [1-6].

- Foregut lungs, thymus, C-cells of thyroid, bronchi and stomach tumors present with tumor cells with more neural like cells and also behave similarly. They are low in serotonin and other vasoactive substances [1].
- Midgut Small intestine, appendix and proximal part of large intestine tumors show epithelial like qualities and are endocrinal in nature. They are high in serotonin and other active substances [1].
- Hindgut distal part of the large intestine, rectum tumors do not have any vasoactive chemicals [1].

Sixty-seven percent NETs are found in the gastrointestinal tract, out of which 29% are found in small intestine, 19% in appendix and 13% in the rectum [5].

Epidemiology: Incidence of NET has increased over last few decades [6-8]. Incidence over last 10 years was found to be in between 2.47 to 4.48% [6]. The increase was found to be four-fold between 1973 and 2004.

Symptoms: NETs can remain non-functioning and asymptomatic for many years before they are diagnosed; due to symptoms secondary to the release of the active products to the blood stream, or physical effect of the tumor e.g., pressure effect from enlarged lymph nodes, intestinal obstruction or bleeding. The average delay in diagnosis of these tumors is at least 7 years [9].

As stated above, the NETs arising from midgut are endocrinal in nature and produce large amounts of biogenic amines, peptides and lipids e.g., serotonin, bradykinins, tachykinins, prostaglandins and histamine [10,11]. These products are usually metabolized by the liver [12].

Symptoms secondary to the vasoactive products are seen when the tumor metastasizes to the liver or erodes a blood vessel that bypasses the liver [13].

About 30% of the NETs become functionally active due to release of such substances to the blood stream, giving rise to a cluster of symptoms also known as carcinoid syndrome (**Table 1**).

Psychiatric symptoms: In metastatic carcinoid tumor, prevalence of depression is about 50% [14] and anxiety about 35% (**Table 2**) [15].

Presence of psychotic symptoms with carcinoid tumor was reported in two studies [16]. Two article reviews reported presence of cognitive symptoms in cases of carcinoid tumor [17].

The psychiatric symptoms may be due to multiple causes including the release of biogenic amines. Prevalence of psychiatric symptoms in cancer is high in general but studies

have reported that symptoms of anxiety and depression relatively higher in carcinoid tumor.

Table 1 Carcinoid Syndrome.

Physical distress and fatigue	Commonest
Dry flushing without sweating	70%
Diarrhea	50%
Intermittent abdominal pain	40%
Bronchospasm	-
Lacrimation and rhinorrhea	-

Table 2 Psychiatric Symptoms [18,19].

Psychiatric symptoms associated with NETs
Anxiety
Depression
Psychosis
Cognitive symptoms

Serotonin: Serotonin is one of the biogenic amines secreted by the carcinoid tumors that play an important role in producing the symptoms of carcinoid crisis [20].

- About 95% of body's serotonin is found in the enterochromaffin cells in the GI tract and the remaining 5% in the platelet and the brain. The platelets do not produce serotonin, they uptake the serotonin produced by the enterochromaffin cells. In the brain, serotonin is secreted by the serotonergic neurons.
- Serotonin is produced from its precursor tryptophan which is also a precursor of Niacin. In carcinoid syndrome, excessive production of serotonin causes depletion of tryptophan and decreased production of niacin as a result. This leads to niacin deficiency symptoms, namely pellagra, which can also contribute to the psychiatric symptoms.
- In the brain, serotonin production is dependent on the availability of tryptophan. As only L- tryptophan or free-tryptophan [unbound to albumin] can enter the brain by crossing the blood brain barrier; it affects serotonin biosynthesis by the neurons. L- tryptophan level is also reduced by substances like cortisol, the level of which is high in cases of depression, which can further reduce brain serotonin production.
- Half-life of serotonin is about 5 days in the platelet, same as the life of platelet, whereas in the brain it is only few minutes and is quickly deactivated by the monoamine oxidase enzymes.
- Peripheral effects of serotonin are local vasoconstriction where it is released and also vasodilatation and increased capillary permeability; constriction of veins and induction of venous thrombosis and promotion of platelet aggregation.

- Serotonin has positive chronotropic effect on the heart through 5HT₄ receptors and can cause cardiac rhythm disorders.
- Excessive serotonin gives rise to debilitating diarrhea affecting the quality of life of patients with carcinoid syndrome.
- Prolonged exposure to high level of serotonin can cause fibrosis of heart valves, more commonly on the right side, causing valvular heart disease [21]. Excessive serotonin is also linked to fibrosis of uterus, skin (scleroderma), pulmonary and retroperitoneal fibrosis in the long run, causing multiple complications (**Table 3**) [22].

Table 3 Long term complications of NETs [4-6,8,14].

Carcinoid heart disease
Mesenteric or retroperitoneal fibrosis,
Desmosis
Niacin deficiency or Pellagra

Diagnosis of NET: Diagnosis should be made based on clinical symptoms, measurement of biomarkers, imaging studies, histological studies (**Table 4**) [16,17,22].

Table 4 Diagnostic tests to detect NETs.

Biochemical tests	Imaging
Chromogranin A (CgA)	CT scan
Urinary 5HIAA	MRI
Neurokinin	Scintigraphy (octreoscan)
Pancreatic polypeptide	Endoscopic ultrasound
	PET

Treatment of NET: Focused on removal of the primary tumor and symptoms associated to the vasoactive products, as well as other associated symptoms (**Table 5**) [22-25].

Table 5 Treatment of NETs.

Surgical and radiological treatments
Medical treatment
Somatostatin analogues
Interferon
Peptide receptor radionuclide therapy
Traditional chemotherapy
Treatment of comorbid illnesses

Treatment of psychiatric symptoms: Treatment of psychiatric symptoms in functional NET patients has been found to be utterly challenging. As the active products like serotonin can itself produce psychiatric symptoms, especially anxiety and mood symptoms, antidepressants like SSRIs-Selective serotonin reuptake inhibitors can sometimes worsen

the symptoms of the illness; and there are case reports of patients with worsening diarrhea and flushing. Cases were reported about unmasking functional NET by SSRIs [28-30].

On the contrary, there are other case reports of treating psychiatric symptoms in functional NET patients successfully with SSRIs.

Besides medications, it is important to incorporate psychotherapeutic and other supportive measures.

Case Presentation

A 50-year-old female who was presented in the emergency department, was referred for psychiatric consultation due to worsening anxiety and depression with suicidal ideations. She had low mood, poor sleep, poor appetite/energy, and suicidal ideations with a plan to overdose on her prescription medications. She had very high anxiety and was experiencing frequent panic attacks. She did not have any psychotic or manic symptoms. There was no history of alcohol or street drug abuse, but there was some concern about overusing prescription opioids. She was on paroxetine 40 mg and lorazepam 1 mg thrice daily at the time of presentation to the hospital. She also had diarrhea and flushing.

Past psychiatric history was positive for depression, anxiety and borderline personality disorder with multiple suicide attempts. She was tried on several antidepressant medications in the past with partial benefit.

Past medical history was significant for the followings:

- Irritable bowel syndrome since teen age
- Fibromyalgia
- Hypothyroidism
- Abdominal pain for several years
- Cholecystectomy and tubal ligation many years ago.
- Laparoscopy and D&C- for abdominopelvic pain and menorrhagia ten years ago, some adhesion found, otherwise normal findings.
- Small bowel obstruction with internal hernia; underwent surgery with adhesion lysis five years ago. No abnormal growth or lymph nodes were found at that time.
- Choledocholithiasis with jaundice, treated with ERCP and sphincterotomy.
- Continued to have abdominal pain and recurrent jaundice despite all surgical procedures.
- Developed recurrent diarrhea, flushing and GI bleeding two years ago.
- Dyspnea and tachycardia two years ago. Echocardiogram showed aortic and mitral regurgitation with stable congestive heart failure. Patient reported that she may have had rheumatic fever when she was young but did not have any cardiac symptoms in the past.
- Abdominal CT scan at that time showed a mesenteric mass of about 3 cm in widest dimension. NET was then suspected and investigation along that line, were done. She was negative for 5HIAA and octreotide scan at that time but 5HIAA became positive when repeated in few months.

- Patient underwent abdominal surgery, and the mesenteric lesion, part of small intestine and few enlarged lymph nodes were removed. The mesenteric lesion and the lymph nodes were positive for NET, during histopathological test.
- Patient also underwent cardiac valve replacement surgery soon after that.
- Patient continued to have diarrhea and flushing despite removal of the abdominal lesions, and these symptoms responded to octreotide injection.
- Abdominal MRI showed few hepatic lesions, but they were inactive on octreotide scans. It was concluded that these lesions could be metastatic and are secreting the vasoactive amines but possibly too small to be detected by octreotide scan.
- During all these years of her physical health issues, she continued to exhibit symptoms of anxiety and depression.

Family History was positive for NET with metastasis.

Social History was significant for social isolation with poor family support. Patient lived alone in a small city and struggled to go for her appointments. She also experienced childhood trauma and abuse, in other words, positive history of adverse childhood experiences (ACE).

This patient was on warfarin with weekly bloodwork, opioids, thyroid supplement and cardiac medication besides being on paroxetine and lorazepam.

Patient was admitted in psychiatric unit for stabilization and review of psychiatric medications.

Brainstorming

Evidently, this patient has been suffering for years. Like most of the patients with NET, she too was diagnosed only after developing the carcinoid syndrome. She was admitted under psychiatry for her psychiatric symptoms but those would not improve without attending to the rest of her body. So, she is a perfect example where a holistic/biopsychosocial approach was much needed.

Management plan

Therapeutic alliance and building trust: This was the first step as she lost faith in the system and also felt ignored due to possibly the stigma attached with her previous diagnosis of borderline personality disorder.

Biological aspect

Question: Were her anxiety and depression her primary problem, secondary to the vasoactive amines or due to SSRIs, or due to the stress related to her chronic illness and poor social support?

- Patient was weaned off of paroxetine and was started with bupropion.
- Received her regular dose of Sandostatin octreotide.
- Her pain issues were addressed.

- Tried on pregabalin for anxiety and pain but discontinued due to adverse effects. So benzodiazepine was continued.
- Referred to dietician for specific low serotonin diet.

Psychological aspect

- Supportive psychotherapy, instillation of hope and providing support.
- Teaching coping skills and grounding techniques using mindfulness-based training.
- Getting connected with social worker and therapist.

Social and community aspect

- Discharge planning meeting involving multidisciplinary team.
- Assignment of outreach worker to continue with the supportive work.
- Outpatient mental health follow up appointments.
- Pain clinic referral.
- Continuation with follow up with cancer clinic, cardiologist and other specialists follow ups.
- Follow up with her family doctor, Social worker and dietician.

Outcome

Patient was much more optimistic following the procedures. Anxiety and depressive symptoms were partially improved. Symptoms related to carcinoid syndrome also improved.

Discussion

This patient came to us with symptoms related to carcinoid syndrome and worsening anxiety and depression.

Looking at this case predisposing factor, she had positive family history of NET. Her health issues had a chronological pattern indicating followings:

- Anxiety and depression
- IBS, fibromyalgia, chronic abdominal pain.
- Adhesions, fibrosis and complications related to those – herniation and intestinal obstruction.
- Valvular heart disease.
- GI bleeding, diarrhea and flushing
- Enlarged mesenteric lymph nodes
- Liver metastasis

Although patient's psychiatric symptoms predate the diagnosis of NET, it is important to consider the full picture and treat the person as a whole rather than focusing on the psychiatric aspect only.

The exacerbation of psychiatric symptoms could be a result of carcinoid syndrome rather than isolated symptoms and addressing those accordingly helps patient recover faster.

As we are learning more about psychiatric illnesses, looking at them as an illness of the brain and having a holistic, mind body approach helps understand the patient better.

Finally, remembering team approach and biopsychosocial approach is a crucial part of management [18].

Conclusion

Each case in medical science can be a learning opportunity. I would like to use few words of mindfulness to help us understand those cases more, to see each case with a beginner's mind, exploring each and every possibility, and being empathic and non-judgmental.

Drawbacks: Discussion about diagnosis and treatment were limited and beyond scope for this article.

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