

CASE REPORT



## An unusual case of proton pump inhibitor induced hyperchromograninemia

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### ABSTRACT

**Objective:** To describe an unusual case of symptomatic hyperchromograninemia associated with proton pump inhibitor (PPI) use.

**Case Summary:** A 55-year-old man with stage 1 follicular lymphoma and GERD on omeprazole presented with symptoms suggesting carcinoid syndrome. The only positive finding on workup was a markedly elevated level of chromogranin A and no carcinoid tumor was identified. Omeprazole was discontinued, following which his symptoms resolved and chromogranin A levels returned to normal. To the best of our knowledge, no symptoms have been previously reported in association with PPI-induced hyperchromograninemia.

**Discussion:** The reliability of chromogranin A as a marker for neuroendocrine tumors is of growing concern. The reasons for the associated symptomatology in this case are unclear but could involve physiologic effects of chromogranin A breakdown products. The role of pharmacogenomics in PPI metabolism is discussed as a potential explanation for the significant hyperchromograninemia.

**Conclusion:** The phenomenon of PPI-induced hyperchromograninemia is highlighted for providers especially in the context of neuroendocrine tumor diagnosis and surveillance. The need for more research into chromogranins is proposed.

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Chromogranin A; carcinoid; neuroendocrine neoplasm; proton pump inhibitor; biomarker

## 1. Introduction

Carcinoid tumors are well-differentiated neuroendocrine tumors which occur in the gastrointestinal (GI) tract and less commonly in the pulmonary epithelium and gonads. They secrete a variety of vasoactive peptides including serotonin, histamine, kinins and prostaglandins. Common manifestations of carcinoid syndrome include skin flushing and diarrhea and less commonly right-sided cardiac fibrosis and bronchospasm.



The chromogranins are a family of ubiquitous proteins found in secretory granules of some endocrine and neuroendocrine cells. Their exact physiologic significance is unclear. Chromogranin A (CgA) is the most well studied of these and is a primary marker in the diagnosis and surveillance of neuroendocrine tumors (NET) [1–4]. Its reliability in this role is of growing concern. Published literature has identified other causes of elevated CgA (hyperchromograninemia) in the absence of a NET which may lead to diagnostic challenges and confusion. This list includes chronic gastric acid suppression with PPIs, and to a smaller extent with H<sub>2</sub> Receptor blockers [1–5]. Notable among these reports of isolated hyperchromograninemia is the absence of any clinical manifestations suggesting active neuroendocrine tumor activity. This is because isolated

hyperchromograninemia is not known to cause any symptoms.

We present the case of a 55-year-old man who had marked hyperchromograninemia with symptoms suggestive of carcinoid syndrome. After further evaluation and imaging, he was found to have no evidence of a carcinoid or other neuroendocrine tumor. His long-standing use of omeprazole was discontinued after which his chromogranin A levels returned to normal and all his symptoms resolved. This case illustrates the diagnostic dilemma such a scenario initially posed, and also highlights growing concerns about the reliability of chromogranin A as a marker for neuroendocrine tumors as well as the need for more research in this regard. This also appears to be the highest reported level of isolated chromogranin A elevation in the absence of a neuroendocrine tumor.

## 2. Case report

A 55-year-old man with a history of chronic kidney disease stage 3, gastroesophageal reflux disease (GERD) and stage 1 follicular lymphoma on a routine outpatient office visit reported a few months' history of episodic flushing, diarrhea and pre-syncope symptoms. Flushing involved a feeling of warmth and mild redness affecting his face and upper torso and lasted from a few

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minutes to half an hour. These flushing episodes occurred up to three times a week and were sometimes associated with mild disequilibrium and presyncopal symptoms.

He denied skin irritation or other cardiorespiratory symptoms and there was no skin rash. This had been witnessed on occasion by his wife and work colleagues. Diarrheal stools were non-bloody, without any associated pain and averaged about three times a day. A review of systems was otherwise unremarkable. None of his symptoms was associated with exertion or food or alcohol intake. His home medications included omeprazole, aspirin, calcium carbonate and rituximab. Physical examination in the office was completely unremarkable. Laboratory testing noted normal complete blood count, complete metabolic panel (except for a creatinine level of 1.3 mg/dl, which was at baseline), and normal thyroid function tests. Carcinoid syndrome was suspected. Plasma CgA checked returned markedly elevated at 3210ng/ml (Normal range: <93ng/ml). CgA was repeated a month later and was even higher at 5120 ng/ml by the same reference lab and symptoms persisted. Plasma free metanephrines, urine 5-Hydroxyindoleacetic acid (5-HIAA) and serum serotonin all returned normal. A whole-body PET/CT showed stable follicular lymphoma with no evidence of any neuroendocrine tumor. Omeprazole was discontinued and 4 weeks later, his CgA level was down to 250ng/ml with all his symptoms drastically improved. At a subsequent 6-month follow-up visit, chromogranin A level had normalized at 61 ng/ml, the patient had no new complaints and all symptoms including flushing, diarrhea and pre-syncopal symptoms had completely resolved.

### 3. Discussion

Carcinoid tumors are rare slow-growing neuroendocrine tumors first described in 1907 by Siegfried Oberndorfer. The original term translates; ‘carcinoma-like’ to describe the unique feature of behaving like a benign tumor despite having a malignant appearance microscopically [6]. They arise from enterochromaffin and enterochromaffin-like (ECL) cells mostly in the GI tract. Less commonly they may be found in the pulmonary epithelium as well as other areas such as the thymus, ovary, kidney, skin, and breast. Many vasoactive peptides produced by these tumors include 5-Hydroxytryptamine (5-HT or serotonin), histamine, tachykinins, and prostaglandins which when released into systemic circulation cause the constellation of symptoms termed carcinoid syndrome [7]. The features of carcinoid syndrome include facial flushing (with or without hypotension and tachycardia), secretory diarrhea, bronchospasm, venous telangiectasias, mesenteric and retroperitoneal fibrosis and carcinoid heart disease [8]. Carcinoid

syndrome occurs in up to 40% of patients with well-differentiated neuroendocrine tumors [9].

CgA is known to be the best general marker for neuroendocrine tumors including carcinoid tumors with highest levels (up to several thousand ng/ml) reported in metastatic carcinoid tumors with a good correlation with disease burden, prognostication and for disease surveillance [1,10,11].

CgA may also be modestly elevated in several other disease processes including prostate and breast cancer, congestive heart failure, liver and renal failure, inflammatory bowel disease, chronic atrophic gastritis, as well as by drugs that suppress gastric acid production such as PPIs and to a lesser extent H<sub>2</sub> receptor blockers [1–5]. For these causes of CgA elevation not related to NETs, the most common culprit is the use of PPIs [3,5]. Hyperchromograninemia resulting from PPI use is typically moderate with no associated symptoms reported, and with chromogranin levels returning to normal after discontinuation of PPI [1–3,5,11,12].

PPIs cause gastric acid suppression by irreversibly blocking the gastric parietal cell Hydrogen/potassium adenosine triphosphate enzyme system (H<sup>+</sup>/K<sup>+</sup> ATPase) [13]. The resultant hypochlorhydria stimulates gastrin production by the gastric antral ‘G’ cells which has a trophic effect on the CgA-producing gastric enterochromaffin-like cells (ECL) [14–16]. Thus, hypergastrinemia from use of PPI, and to a smaller extent from H<sub>2</sub> receptor blocker use induces chromogranin A release from the gastric ECL cells. During long-term gastric acid suppression, serum CgA levels reflect the presence and severity of gastric fundic ECL cell hyperplasia [14]. This phenomenon of PPI-induced hyperchromograninemia has been described all PPIs, including Omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole [1–3,5,11,12]. To the best of our knowledge, this case represents the highest reported level of apparently artifactual hyperchromograninemia from any other cause in the absence of a demonstrable neuroendocrine tumor.

The reason for our patient’s symptoms in the absence of a detectable carcinoid tumor is unclear. We are not aware of a previous report of such associated symptomatology with isolated hyperchromograninemia. Chromogranins can act as precursor hormones giving rise to some bioactive peptides (e.g., Vasostatin I and II, chromostatin and catestatin) which in vitro have been demonstrated to have some vasoactive effects and may modulate catecholamine release in the sympathoadrenal system [1,17,18]. However, research into the clinical relevance of these bioactive peptides from chromogranin is sparse and their exact physiological role is not well understood. In the setting of such high CgA levels, it is not known if systemic symptoms could be attributed to increased circulating levels of some of these breakdown products.

Another possible explanation for the significantly elevated CgA examines the role of pharmacogenomics in PPI metabolism in the liver by the cytochrome P450 isoenzyme 2C19 (CYP2C19). This enzyme plays important roles in the metabolism of 5–10% of drugs in the current use including PPIs (especially omeprazole). CYP2C19 exhibits such a wide variation in genetic polymorphism such that a person may phenotypically be a slow metabolizer or an extensive metabolizer affecting circulating drug/metabolite levels [19–21]. In the event that our patient happened to be a poor metabolizer of omeprazole, he could have higher than normal circulating levels of the omeprazole with standard dosing. This would be expected to correlate with much higher CgA elevation, with an associated increase in circulating CgA breakdown products. Genetic testing for CYP2C19 polymorphism was not pursued in our patient. Considering cost implications and until more research is available, routine checking of CgA levels or CYP2C19 polymorphism in all otherwise asymptomatic patients on chronic PPIs may not be justified. This case, however, suggests the need to consider these on a case-by-case basis in the appropriate clinical or investigational context.

Could an actual carcinoid tumor be indeed present in our patient? Enterochromaffin-like cell hyperplasia is noted to be a predisposing factor for carcinoid tumors of the stomach [5]. Some animal studies have shown gastric carcinoid tumors of ECL origin to develop in rats treated with high doses of PPIs [22,23]. The possibility of chronic PPI use as a cause of gastric or intestinal tract neoplasms has been postulated for humans also, but not been conclusively proven and is the subject of ongoing research [24,25]. It is plausible to think that an early precursor stage to actual carcinoid tumor development may have been present in our patient which rapidly regressed upon withdrawal of PPI. The resolution of hyperchromograninemia and all his symptoms after discontinuation of PPI would argue against the presence of an established carcinoid tumor. His level of chromogranin A elevation would typically correlate with a heavy carcinoid tumor disease burden which we do not expect to have been missed on PET/CT scan.

It has been reported that carcinoid syndrome may be associated with normal circulating levels, individually of either serotonin, histamine or 5-HIAA [26]. However, normal levels of all the afore-mentioned markers in carcinoid syndrome are not known. Because all other biochemical markers for carcinoid syndrome were absent in our patient, there was no justification to pursue further workup for a carcinoid tumor with an octreotide scan so this was deferred.

Outside of PPI and H2receptor blocker use, no other classes of drugs have been reported to cause hyperchromograninemia to the best of our knowledge. Discontinuing his omeprazole was the only change made prior to the resolution of his symptoms and a thorough medication history was assessed for any over-the-counter or alternative medication use. This makes the potential role of another culprit medication or underlying disease process unlikely. Awareness of the pitfalls in using chromogranin A as a marker for neuroendocrine diagnosis and surveillance may reduce the tendency to pursuing extensive, invasive and frequently costly workup in the appropriate clinical setting. Proton pump inhibitor use is widespread and often procured over-the-counter, which makes an accurate patient medication history always important. Clinicians need to be cognizant of the potential ramifications of long-term PPI use including hyperchromograninemia as well as the growing body of evidence which may point to an associated increased risk of neuroendocrine and non-neuroendocrine gastric neoplasms.

#### 4. Conclusion

Proton pump inhibitors which are commonly used can cause elevation of chromogranin A in the absence of a neuroendocrine tumor and providers need to be aware of this phenomenon. This potentially affects the utility of CgA as a reliable marker for diagnosis, prognostication and surveillance in NETs. Our patient had an unusually high level of chromogranin A with associated symptoms but otherwise no clear evidence of an underlying carcinoid tumor. This may be the first report of any clinical symptoms associated with apparently isolated PPI-associated hyperchromograninemia. Clinicians should regularly review the appropriateness of continued PPI use in patients. There is a need for additional research on CgA and its exact physiologic role.

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#### Author Contributions

Kwabena Adu-Gyamfi: Did the literature review and wrote the manuscript.

Richmond Gyamfi: Assisted with literature review, manuscript writing and editing of the manuscript.

Sandeep Patri, MD: Assisted with literature review, manuscript writing and editing of the manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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