

Case Report

Synchronous Gastric Carcinoid and Gastric Adenocarcinoma with Plummer-Vinson Syndrome: A Case Report and Literature Review

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SUMMARY

Synchronous gastric tumours, though considered rare are now being increasingly reported in literature. They can grow separately within the stomach or merge with each other (*collision tumor*) or can form a mixed (*composite*) type of tumor. We present here an unusual case of synchronous gastric carcinoid and adenocarcinoma on the background of chronic atrophic gastritis with associated postcricoid oesophageal web. Upper gastrointestinal (GI) endoscopy of this 60-year-old female, who was a known case of hypertension with ischemic heart disease, showed a postcricoid web and a polypoidal, nodular mass along with 2 to 3 separate small nodular lesions in the distal gastric body. Histopathology and immunohistochemistry of the biopsies from the mass and nodular lesions confirmed moderately differentiated adenocarcinoma and carcinoid tumor respectively, with evidence of chronic atrophic gastritis and intestinal metaplasia. *H.pylori* was negative. Serum gastrin levels were elevated and anti-parietal cell antibodies were positive. Laboratory investigations revealed iron deficiency anaemia. There was no lymphadenopathy or distant metastasis on CT abdomen and no symptoms suggestive of carcinoid syndrome. She underwent

a total gastrectomy with local lymphadenectomy. Plummer-Vinson syndrome has been described with gastric tumors, but not with the synchronous ones. This might be the first case where it has occurred along with synchronous gastric tumors or might be just a chance occurrence.

Key words: Gastric carcinoid, Gastric adenocarcinoma, Iron deficiency anaemia, Postcricoid oesophageal web, Plummer-Vinson syndrome

INTRODUCTION

Gastric carcinoids account for 0.3% of gastric neoplasms and 11-41 % of all gastrointestinal carcinoid tumors.^{1,2} They are classified into three types depending on clinical and histological characteristics. Type I is associated with chronic atrophic gastritis (CAG), achlorhydria, hypergastrinemia and enterochromaffin like (ECL) cell hyperplasia, with or without pernicious anaemia.^{1,2} Type II is associated with Zollinger-Ellison (ZE) syndrome and multiple endocrine neoplasia type- I (MEN- I) syndrome.^{1,2} Type III tumors are sporadic, not associated with hypergastrinemia or CAG-A, and are invasive, large and solitary tumors.^{1,2}

Though adenocarcinoma is the most common malignancy of the stomach, a gastric carcinoid is relatively uncommon, and the coexistence of these two tumor is rare.³

Plummer-Vinson syndrome is characterised by dysphagia (due to an upper oesophageal or hypopharyngeal web) and iron deficiency anaemia. It is considered as a premalignant lesion associated with cancers of upper digestive tract.⁴ There are few anecdotal reports of this syndrome

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occurring concurrently with gastric cancers.⁵ But the occurrence with a synchronous type of gastric cancer or gastric carcinoid has not yet been reported.

CASE REPORT

A 60-year-old female presented with dysphagia localized to the upper part of neck and, epigastric pain of five months duration, associated with generalized weakness, anorexia and weight loss. There was no history of vomiting, hematemesis or malena. She was a known case of hypertension with anterior wall myocardial infarction on medications. Her family history was not contributory. On examination she was pale. Vitals signs were normal with a systolic blood pressure of 150 mm Hg. Laboratory findings revealed, iron deficiency anaemia with hemoglobin 82 g/L, hematocrit 24.8%, MCV 73fL, MCH 23.4pg, MCHC 28.2 g/dl, RDW 28%, platelets $380 \times 10^3/\text{mm}^3$, reticulocyte count 2%, serum iron 42 $\mu\text{g}/\text{dl}$, total iron binding capacity (TIBC) 462 $\mu\text{g}/\text{dl}$, and serum ferritin 10 ng/ml. She had a decreased ejection fraction of 40% with diastolic dysfunction on 2D-echocardiography. Rest of the routine laboratory tests were normal.

Upper GI- endoscopy showed a post cricoid web which ruptured as scope passed across it [Figure-1]. A lobulated, polypoidal mass (3cm x 3cm) was seen in the distal gastric body along the greater curvature, with two to three nodular lesions in the vicinity [Figure-2]. Mucosa was pale with decreased mucosal folds.

Histopathology of the biopsies from the mass and the nodules revealed a moderately differentiated adenocar-

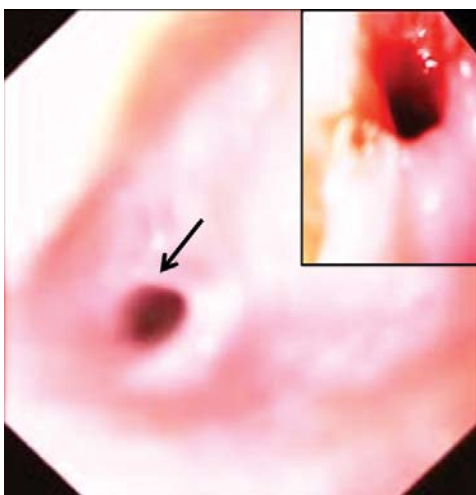


Figure 1. Postcricoid web (*arrow*) seen at endoscopy. It got ruptured as the scope passed across it (smaller picture in inset).

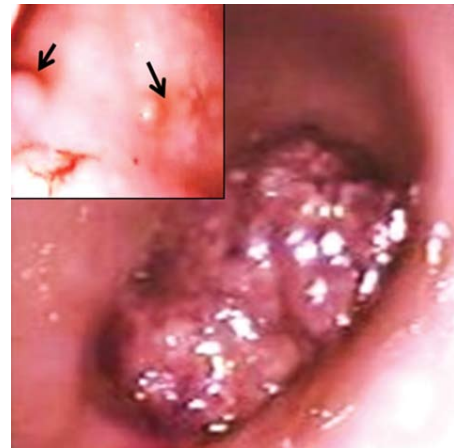


Figure 2. A 3cmx3cm polypoidal, lobulated, nodular mass visualised at endoscopy in the distal part of the gastric body. Two to three small nodular lesions were seen near the tumor mass (smaller picture with *arrows*).

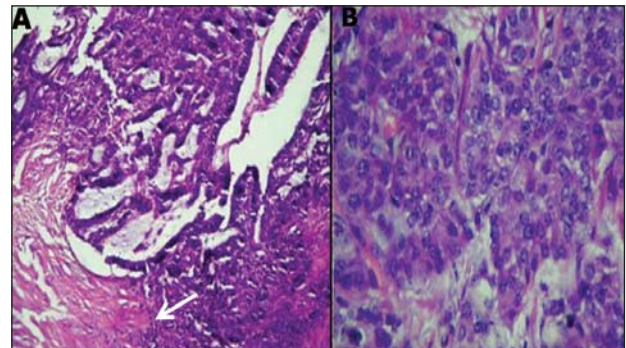


Figure 3. A-H&E staining of the biopsy from the mass in the body showing moderately differentiated adenocarcinoma with breaching of the muscularis mucosa (*white arrow*) (10X). B-Tumor cells at higher magnification (40X).

cinoma [Figure-3], and an intramucosal carcinoid tumor [Figure-4], respectively with tumor cells infiltrating the muscularis mucosa in both. There were also changes of chronic atrophic gastritis with foci of intestinal metaplasia. The nodular biopsy stained positive for synaptophysin. Results of *H.pylori* were negative on biopsy and rapid urease test. Fasting serum gastrin levels were elevated 940 ng/L and 24 h urinary 5-hydroxyindole acetic acid levels were normal-3.19mg (N: 2-6mg). Antiparietal cell antibody was positive. Vitamin B12 levels, serum calcium, serum phosphorus and calcitonin levels were normal. Abdominal CT scan showed no evidence of lymphadenopathy or organ metastasis. CT-neck and thorax showed normal thyroid and parathyroid glands. Indium¹¹¹-octreotide scan was not available to us. Diagnosis

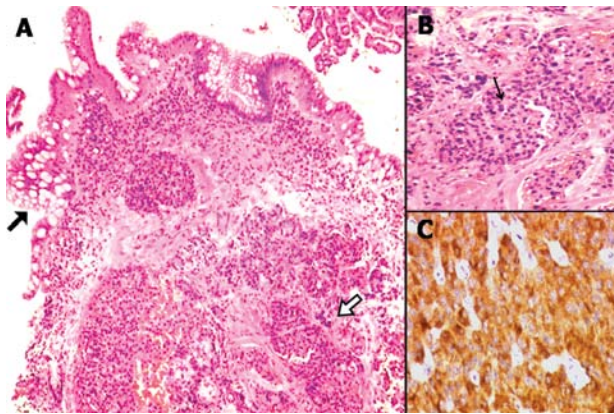


Figure 4. A-H&E staining of the biopsy from the nodular region showing changes of chronic atrophic gastritis with foci of intestinal metaplasia (increased number of goblet cells and lymphocytic infiltration in lamina propria) (black arrow). Carcinoid tumor cells are seen arranged in nested pattern in deep submucosa with breaching of muscularis mucosa (white arrow) [10X]. B- Carcinoid tumor cells seen at higher magnification (40X). C-Positive immuno-staining with synaptophysin.

of multiple type-I gastric carcinoids with gastric adenocarcinoma was made.

A total gastrectomy with local lymphadenectomy was performed. Patient is under regular follow up with iron and vitamin B12 supplements for the past six months. There is no recurrence of tumor or metastasis.

DISCUSSION

Type I and Type II tumors occurs in the setting of hypergastrinemia which causes ECL-cells hyperplasia. They develop through a sequence of “hyperplasia-dysplasia-neoplasia”, and ECL-cell hyperplasia and dysplasia are identified as the precancerous lesions of ECL-cell carcinoid.⁶ In Type I tumors, associated CAG causes achlorhydria through destruction of the parietal cells in the fundus and the body. The resultant chronic hypergastrinemia (due to uninterrupted stimulation of antral G-cells) causes ECL cell hyperplasia.² CAG also causes intestinal metaplasia, a well recognized risk factor for gastric carcinomas. *H. pylori* also has been implicated in the development of carcinoid tumors through the same mechanism of hypergastrinemia in animal models and rarely in humans.² Only a minority of patients with type I tumors are symptomatic, experiencing dyspepsia, pain, unexplained weight loss or gastrointestinal bleeding.^{2,7} These tumors are often multifocal, found in the fundus

or body and are less than 2 cm in diameter. Nodal and liver metastasis occurs in 2%, without causing tumor-related deaths.^{2,7} Endoscopic polypectomy is curative in tumors less than 1 cm.^{2,7} For multiple tumors larger than 1 cm, and with abdominal symptoms, antrectomy or subtotal gastrectomy (including the antrum) is recommended.^{2,7}

Type II tumors are the least common variety (5-10% of all gastric carcinoid tumors).^{1,2} Hypergastrinemia in these tumors is due to ZE syndrome associated with MEN-I syndrome^[1,2]. They are multicentric, variable in size and are prone for local nodal metastasis. However tumor-related death or carcinoid syndrome is rare. Various treatment modalities have been used including endoscopic polypectomy, partial or total gastrectomy, or medical management with somatostatin analogues.⁸

Type III tumors are sporadic, invasive, large and solitary tumors without associated hypergastrinemia or CAG^[1,2]. They account for 13% of all gastric carcinoid tumors.^{1,2} The invasiveness is thought to arise from the overexpression of mutated p53 gene protein, which regulates cellular apoptosis.² Metastasis occurs in 66% of patients, when tumor size is more than 3cm, but in only 10% when tumor is solitary and less than 1cm.⁷ Carcinoid syndrome occurs in those with liver metastasis. Prognosis is poor with 5-year survival rate of about 20%.^{2,8} Radical or extended radical gastrectomy with loco-regional lymphadenectomy is recommended in absence of liver or distant metastasis.^{1,8} Those with liver metastasis can be treated with a multidisciplinary approach, including a combination of treatments with somatostatin analogs, hepatic artery embolisation or chemoembolisation, surgical debulking, adjuvant receptor targeted therapy and even orthotopic liver transplantation.⁹

Though considered rare many cases of synchronous gastric carcinoid and adenocarcinoma are now being reported.^{3,6,10} Both gastric carcinoid and adenocarcinoma can be associated with other neoplasms and can grow separately, merge together creating a “collision tumor” or can form a “mixed” or “composite” tumor.^{3,6,10} Sometimes distinguishing between collision and composite tumor may be difficult.¹⁰

There are many hypotheses to explain the simultaneous occurrence of gastric carcinoid and gastric carcinoma. CAG (either autoimmune or due to *H. pylori*) has been implicated in the development of gastric carcinoids and also causes intestinal metaplasia which is a risk factor for development of gastric adenocarcinoma. Genetic

mutations and DNA microsatellite instability can explain the tumor multiplicity.¹¹ Furlan *et al*, by using microallelotyping, has demonstrated that mixed tumors are monoclonal in origin whereas collision tumors have two different cell lines of origin with different histogenesis and tumorigenic pathways.¹² Another study found that carcinoids and adenocarcinomas, appear to arise from a common multipotent epithelial stem cell.¹⁰ However despite these studies, no definite conclusion can be stated regarding their aetiopathogenesis. Nevertheless upcoming reports of these rare synchronous gastric tumors of distinct histotypes may bring new insight into understanding their biological behaviour.

Plummer-Vinson syndrome is known to be a risk factor for upper digestive tract cancers. Squamous cell carcinoma of hypopharynx, oral cavity or oesophagus is reported in 10% of these patients with 3–15% incidence rate of upper oesophageal cancer.⁴ There are anecdotal reports of gastric cancers occurring with this syndrome.⁵ However associated synchronous gastric adenocarcinoma and gastric carcinoid has never been reported so far. The cause for its association with gastric malignancies is not clear. However it is well accepted that atrophic mucosal changes of the alimentary tract due to iron deficiency anaemia may render hypopharynx and upper oesophagus more prone for malignancy.⁵

Therefore a careful endoscopic evaluation of upper gastrointestinal tract is of utmost importance in Plummer-Vinson syndrome to rule out associated malignancy.

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