Case report

Hypertrophic gastritis associated with increased gastric mucosal prostaglandin E₂ concentrations in a patient with the carcinoid syndrome

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SUMMARY A case of a 69 year old man in whom hypertrophic gastritis was associated with the carcinoid syndrome is reported. Concentrations of prostaglandin E₂ were increased in plasma, gastric juice, gastric mucosa and urine. He had marked hypochlorhydria in response to pentagastrin stimulation (Peak acid output (PAO) pg:0.2 mmol/h). After successful hepatic arterial embolisation of the metastases (as indicated by an 85% decrease in 24 h urinary 5-HIAA) the concentrations of prostaglandin E₂ decreased in the plasma, gastric juice and gastric mucosa. The gastric mucosal hypertrophy regressed and secretion of acid in response to pentagastrin returned (PAO pg:9.0 mmol/h). These findings suggest that the carcinoid tumour was producing a substance which stimulated increased local synthesis of prostaglandin E₂ in the gastric mucosa, with concomitant gastric mucosal hypertrophy and inhibition of gastric acid secretion.

Increased circulating concentrations of prostaglandins (PGs) have been reported in patients with the carcinoid syndrome, and have been considered to contribute to the diarrhoea which occurs in that syndrome.¹⁻³ It is uncertain whether the tumour itself produces these PGs or stimulates PG synthesis in other tissues by a humoral mediator. Oral and parenteral PGs cause hypertrophy of the gastric mucosa in rats^{4,5} and increased local PG synthesis has been postulated to be involved in the pathogenesis of hypertrophic gastritis in man.⁶ We report a patient in whom the carcinoid syndrome was associated with hypertrophic gastritis and marked hypochlorhydria, and who had raised concentrations of prostaglandin E₂ (PGE₂) in the serum, gastric juice, gastric mucosa, and urine. After successful embolisation of the hepatic metastases the concentrations of PGE₂ decreased to near normal concentrations, the gastric mucosal hypertrophy regressed, and gastric secretion in response to pentagastrin returned.

Case history

The patient, a 62 year old man, presented in 1979 with dyspepsia. A barium meal showed giant gastric rugal folds and these appearances were confirmed at endoscopy. Biopsy showed the changes of chronic gastritis. At that time there was no diarrhoea, and other investigations were normal. The patient had a good symptomatic response to antacids. In 1985 he returned to the hospital with a history of diarrhoea for 18 months, and of excessive sweating and itching for 10 months. He had lost 3 kg in weight. On examination he had a cyanotic flush and there was nodular hepatomegaly extending 10 cm below the costal margin.

The diagnosis of the carcinoid syndrome was made on the basis of raised 24 hour urinary 5-hydroxy-indole acetic acid (5-HIAA) excretion on three successive occasions (1251 µmol, 1790 µmol, and 1533 µmol respectively; normal range: 10 to 45 µmol/24 h) and by the finding on percutaneous liver biopsy of typical small uniform tumour cells which were argentaffin positive. Hepatic ultrasonography, computerised tomography and magnetic resonance

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imaging showed that 70 to 80% of the liver was replaced with metastatic tumour.

A barium meal again showed gastric mucosal hypertrophy (Fig. 1a). A small bowel series and barium enema failed to show a primary tumour. Endoscopy with four snare biopsies of the antral gastric mucosa showed striking foveolar hyperplasia with associated smooth muscle fibres evident in the lamina propria – recognised changes seen in hypertrophic gastropathies (Fig. 2a). In addition there was evidence of severe active chronic gastritis with focal ulceration, luminal pus, and areas of intestinal metaplasia. Gastric secretory studies showed marked hypochlorhydria in response to pentagastrin stimulation (PAO_{pg} : 0.2/mmol/h). Basal serum gastrin measurements were within the normal range (0 to 100 ng/l) (Fig. 3).

Serum alkaline phosphatase and γ -glutamyl transpeptidase were raised at 344 U/l and 216 U/l respectively (normal ranges: 35–150 U/l and 5–50 U/l). Other investigations were either normal or negative, and included: full blood count, clotting profile, thyroid function tests, plasma cortisol, plasma catecholamines and urinary normetadrenaline excretion, meta-iodobenzoyl-glutamine scan, gastric parietal

cell and intrinsic factor antibodies, Schilling test and ^{51}Cr -human serum albumin studies for increased protein loss from the gastrointestinal tract.

The patient received treatment with pizotifen 2 mg daily, codeine phosphate 120 mg daily, cyproheptidine 12 mg daily, and indomethacin 150 mg daily, without clinical benefit. A temporary therapeutic response was obtained during treatment with prednisolone 20 mg daily.

In March 1986 the patient was readmitted to hospital with worsening symptoms of diarrhoea, further weight loss of 4 kg, and peripheral oedema. Urinary 5-HIAA excretion had increased to 2673 $\mu\text{mol}/24\text{ h}$ (Fig. 3). In view of the deterioration we undertook hepatic arterial embolisation using the Hammersmith Hospital protocol.⁷ Embolisation of the right hepatic artery was performed in March 1986, but for technical reasons it was not possible to embolise the left hepatic artery at the same time. Selective left hepatic arterial occlusion was performed in April 1986, when complete occlusion of the right hepatic artery was noted and a good therapeutic result was achieved as indicated by an 85% reduction in urinary 5-HIAA excretion (Fig. 3).

After embolisation there was clinical improve-

Fig. 1 Barium meal appearances before (a) and after (b) hepatic arterial embolisation, showing resolution of gastric mucosal hypertrophy.

ment, with weight gain, and resolution of the diarrhoea, cyanosis, and peripheral oedema. Repeat endoscopy and upper gastrointestinal barium studies in May 1986 showed that the previously noted gastric mucosal hypertrophy had reverted to normal (Fig. 1b). Histological examination of four antral biopsy specimens obtained with standard biopsy forceps showed minimal persistence of intestinal metaplasia and complete resolution of the foveolar hyperplasia (Fig. 2b). Further gastric secretory studies showed an increased gastric secretory response to pentagastrin with the PAO_{pg} being 9.0 mmol/h and 7.0 mmol/h, four and seven weeks respectively after the second embolisation (Fig. 3).

In an attempt to relate the gastric abnormalities to the carcinoid tumour, we measured prostaglandin E_2 concentrations in plasma, gastric juice, urine, and gastric mucosa. Before embolisation of the hepatic metastases body fluid and tissue concentrations of PGE_2 ranged from 2 to 140 times those measured in simultaneously studied controls (Table 1). After embolisation concentrations were markedly reduced from pretreatment levels but remained raised compared with simultaneously studied controls.

PROSTAGLANDIN ASSAYS

Prostaglandin concentrations in plasma, urine, gastric juice and gastric mucosal biopsies were measured on samples obtained in December 1985 (before hepatic arterial embolisation and before starting a therapeutic trial of indomethacin), and again after embolisation in May 1986 when indomethacin had been withdrawn for several weeks. Prostaglandin concentrations in plasma were measured after taking 10 ml of blood into a lithium heparin tube containing 0.3 ml indomethacin solution (0.2 mg/ml in ethanol) at 4°C and immediately separating the plasma by centrifugation at 4°C. Plasma was used for PGE_2 measurements because because blood coagulation may liberate prostaglandins⁸ and indomethacin was added to the tubes to prevent PGE_2 synthesis during storage.⁹ Urine samples and fasting gastric juice samples (obtained at endoscopy) were immediately transferred into tubes containing 0.3 ml indomethacin solution. Samples of gastric mucosa obtained by endoscopic biopsy were immediately placed in tubes containing 5 ml indomethacin solution. All samples were stored at -20°C until assayed for PGE_2 . On each occasion that samples were taken from the patient for measurement of PGE_2 concentrations, similar samples were obtained from two other patients

also undergoing endoscopy in whom no endoscopic abnormality was present and who were not receiving drugs affecting prostaglandin synthesis. These samples were treated identically to those of the patient, and were used as controls for the assay. Concentrations of PGE_2 were measured in duplicate by a competitive radioimmunoassay with a sensitivity of 15 pg/ml.¹⁰

GASTRIC SECRETORY STUDIES

Gastric secretory studies were done after an overnight fast. The stomach was intubated with a vented 14FG tube and gastric secretion stimulated by an intramuscular injection of pentagastrin (6 µg/kg). Gastric juice was aspirated continuously in 4×15 minute batches. Peak acid output (PAO_{pg}) in mmol/h was calculated by summing the outputs during the two highest 15 minute collection periods and multiplying the result by two.¹¹

Discussion

In the patient we describe it seems likely that the hepatic tumour was causally related to the raised gastric mucosal concentrations of PGE_2 , and that the gastric mucosal hypertrophy and secretory inhibition were attributable to the high local concentrations of PGE_2 .

Prostaglandins appear to be involved in a variety of paraneoplastic syndromes, and it has been proposed that PGs may mediate the features of the carcinoid syndrome in some patients.³ In one reported study, 18 of 22 patients with the carcinoid syndrome had increased plasma concentrations of PGE_2 with a median increase of five times that of the reference range.¹ When plasma PG concentrations have been raised in patients with the carcinoid syndrome it has been uncertain whether PGs were being secreted by the tumour, or were the result of increased tissue PG synthesis in response to a circulating factor. Carcinoid tumour tissue concentrations of PG have been reported as being low,¹² but, conversely, in two small intestinal carcinoids high concentrations of an unidentified eicosanoid were detected which was probably a PG although its structure could not be determined.¹³ In the majority of patients with the carcinoid syndrome who have had increased circulating concentrations of PGs there is, therefore, scant evidence that these derive from the tumour itself.

In our patient it seems likely for two reasons that the increased concentrations of PGE_2 in the gastric

Fig. 2(a) Full thickness biopsy appearances of the gastric mucosa before embolisation. Note the marked foveolar hyperplasia associated with occasional smooth muscle fibres in the lamina propria. Part of the muscularis mucosae can be seen at the foot of this photomicrograph. (H&E.) (b) Gastric mucosal biopsy appearances after embolisation. Foveolar hyperplasia has now completely resolved. (H&E.)

Fig. 3 Time course of changes in urinary 5-HIAA excretion, plasma gastrin concentrations, and gastric acid secretion in relation to sampling for tissue and body fluid PGE₂ concentrations (P) and hepatic arterial embolisations (E).

mucosa resulted from increased local PG synthesis rather than local accumulation of PGE₂ produced by the tumour. First, concentrations of PGE₂ in the gastric mucosa and juice were extremely high relative to those in the plasma, and this could not be attributed to local accumulation because the gastric mucosa has a high concentration of PG 15-OH-dehydrogenase and is one of the most catabolically active tissues in the body for PGs.^{14,15} Second, circulating PGs are not excreted by the kidney, so that increased PGE₂ concentrations in the urine indicate increased renal synthesis of PGE₂.¹⁶ The

marked reduction in PGE₂ concentrations after hepatic arterial embolisation indicates that the increased concentrations were dependent on the hepatic metastases.

Carcinoid tumours secrete a wide variety of humoral substances,¹⁷ some of which are candidate mediators of the increased synthesis of PGE₂ observed in our patient. For example, serotonin has been shown to increase arachidonic acid metabolism in the gastrointestinal mucosa, and the secretory and motor effects of 5-HT have been considered to be mediated by PGE₂.^{18,19} When serotonin concentrations and PG concentrations were measured in the plasma of patients with the carcinoid syndrome although eight of 10 patients had increased serotonin concentrations, only one had increased concentra-

Table 1 Relative tissue and body fluid concentrations of PGE₂ in patient compared with simultaneously studied controls before and after hepatic artery embolisation

	Patient	Controls
Before embolisation		
Plasma	13.3	1.0
Gastric mucosa	143.1	1.0
Gastric juice	63.4	1.0
Urine	2.7	1.0
After embolisation		
Plasma	2.4	1.0
Gastric mucosa	2.7	1.0
Gastric juice	1.5	1.0

On each occasion the average value from the two simultaneously studied control patients has been taken as 1.0 and the patient's results expressed as a multiple of this normalised value.

Table 2 Plasma concentrations of gastrointestinal hormones before hepatic arterial embolisation

Hormone	Concentration	Normal range
VIP	19 pmol/l	<30
HPP	419 pmol/l	<300
Glucagon	<6 pmol/l	<50
Neurotensin	10 pmol/l	<200
Somatostatin	15 pmol/l	<100
Neurone specific enolase	20 μg/l	<15
Substance P	60 pmol/l	<30
Secretin	10 ng/l	<50

tions of PGs. Conversely, in one further patient who had increased concentrations of PGE₂ in the plasma, serotonin concentrations were within the normal range.² It seems, therefore, that serotonin is unlikely to be a mediator of the increased synthesis of PGE₂ in the carcinoid syndrome.

Carcinoid tumours may produce bradykinin²⁰ or kallikrein.^{21,22} These substances have been detected in increased concentrations in the plasma of patients with the carcinoid syndrome, and may cause increased synthesis of PGs in other tissues.²³⁻²⁵

It is likely that the increased PG concentrations in the gastric mucosa were the cause of the hypertrophic gastritis and hypochlorhydria in our patient. Prostaglandins are trophic to the gastric mucosa^{4,5} and, in the rat, treatment with 16,16-dimethyl PGE₂ results in a dose dependent increase in cell turnover and hypertrophy of all gastrointestinal mucosae.²⁶ In addition, PGE₂ analogues may cause gastric mucosal injury including haemorrhagic gastritis in man,²⁷ and haemorrhagic gastritis and even gastric perforation at high doses in dogs.²⁸

Achlorhydria has long been recognised as a feature of the carcinoid syndrome.²⁹ Naturally occurring PGE₂ and its synthetic analogues when administered either orally or parenterally inhibit gastric secretion in response to all stimuli, in healthy subjects and duodenal ulcer patients.^{31,32} In addition, PGE analogues inhibit the release of gastrin in response to food^{32,33,34} and decrease the raised gastrin concentrations in patients who are achlorhydric in association with pernicious anaemia.³³ As plasma gastrin concentrations increased in our patient after hepatic arterial embolisation, although gastric secretion of acid had also increased, it seems likely that the fasting gastrin concentrations were inappropriately low for the degree of hypochlorhydria, and that there was inhibition of gastrin release attributable to the increased local concentration of PGE₂.

We have considered the possibility that other substances than PGE₂ may have been responsible for the inhibition of gastric acid secretion and gastrin release in our patient. Serotonin and its precursor 5-hydroxytryptophan inhibit gastric secretion in dogs, but because the secretory inhibition observed is weak and poorly sustained,^{34,35} and plasma concentrations of the inhibitory hormones somatostatin, secretin and VIP were within the normal ranges (Table 2), we conclude that the most likely explanation for the hypochlorhydria in our patient was the high local concentration of PGE₂. The concurrent active gastritis may have contributed to the secretory impairment.

In summary, in our patient we have observed hitherto undescribed features associated with the carcinoid syndrome, and which are probably attribut-

able to overproduction of PG as part of a new paraneoplastic syndrome.

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