Case report

Glucagonoma syndrome demonstrating giant duodenal villi

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SUMMARY A 39 year old man developed an itchy bullous rash in the perineum and on the extremities. Six years later, after giant intestinal villi had been noted at endoscopy, a diagnosis of the glucagonoma syndrome was made. Investigation revealed a large tumour of the pancreatic body and tail. The molecular species of glucagon secreted by the tumour were characterised using the combined purification procedures of immunoaffinity chromatography followed by gel filtration.

A necrolytic migratory erythematous skin rash, anaemia, angular stomatitis with or without diabetes mellitus are recognised features of the pancreatic glucagonoma syndrome.¹ The syndrome is associated with a pancreatic islet cell tumour producing glucagon.¹ Removal of the tumour in some cases has resulted in curing of the symptoms and signs of the syndrome.² Giant intestinal villi have been found in a patient with a renal tumour producing enteroglucagon.³

A patient with features of both conditions – that is, skin rash, anaemia, angular stomatitis, diabetes mellitus, a pancreatic tumour and giant duodenal villi is reported.

Case history

A previously healthy male agricultural worker first developed an itchy bullous skin rash in the perineum, feet and hands in April 1969, at the age of 39 years. Over the next six years the skin lesions were variously diagnosed as contact dermatitis, chronic mucocutaneous candidiasis or seborrhoeic dermatitis. The skin lesions responded to large quantities of topical steroids or systemic steroids. Diabetes mellitus diagnosed in April 1969, originally was treated with tolbutamide. In December 1970 the tolbutamide was withdrawn and the diabetes controlled with 10kJ (2400 cal) diet. Pulmonary and

renal tuberculosis was diagnosed in December 1970 responded to treatment with streptomycin, isoniazid, and ethambutol. Biopsy of a concurrent anal fistula was negative for *Mycobacterium tuberculosis*.

Minor relapses of the skin rash over the next three years responded to topical steroids with nystatin. From 1973 to 1975 the periods of remission became shorter and the relapses more widespread, painful, and difficult to control. Skin scrapings for the tinea were negative, but because of pedal interdigital fissuring, griseofulvin and topical miconazole nitrate were started without beneficial effect. Tolbutamide was reintroduced in May 1975.

In October 1975, the patient had developed recurrent diarrhoea, weight loss and a mild normochromic, normocytic anaemia (Hb 11.4 g/dl). A barium meal and follow through examination showed distorted antral mucosa, widening of the duodenal loop and dilation of the small intestinal lumen, these radiological features being suggestive of a tumour of the head of the pancreas with malabsorption secondary to exocrine pancreatic insufficiency. The patient was referred for upper gastrointestinal endoscopy.

A gastro-duodenoscopy showed no abnormality in the stomach nor any tumour invasion into the wall of the duodenum. Giant villi, however, were noted throughout the proximal duodenum and the possibility of a glucagonoma was first considered. The number of villi per endoscopic field is about one quarter that seen in controls – that is, the patient's

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villi are about four times the cross-sectional area of control villi (Fig. 1). Endoscopic biopsy showed some elongated villi; mean villous height, patient 733 μm ; controls 336 μm , SD 50-65 μm (n=6). Pancreatic juice collected *via* a Dreiling tube contained no malignant cells but on examination the gastric aspirate was found to contain large numbers of mycobacteria tuberculosis. The patient was referred for a further course of antituberculous therapy. At this time glucagon assay was not readily available on specimens from Galway.

Over the next year the skin lesions became almost constant and associated with severe burning pedal pain and oedema. Relapses of the skin lesions were accompanied by diarrhoea. Sigmoidoscopy revealed no abnormality in the rectum.

In November 1976, he was referred back to the Gastroenterology Department. Fasting blood drawn for glucagon assay showed massive hyperglucagonaemia (details of the assay will be given later). The patient was readmitted in December 1976 for

further investigation.

EXAMINATION

The rash had recurred. The lesions varied in character having either a central necrolytic bullous area of a dry scaly area surrounded by erythema and a figurate outline. The lesions were sited around the mouth and nose (Fig. 2), antecubital and popliteal fossae, groins and natal cleft and over pressure areas, ischial tuberosities and lateral surfaces of the legs. Acute lesions on the feet related to the zippers on his slippers were accompanied by extensive erythema and oedema, and healed lesions were demarcated by pigmented areas. Fissures were noted between the toes and on the soles of his feet. The nails were thickened and opalescent with longitudinal ridging, pitting and distal subungual hyperkeratosis. The buccal mucosa was normal although angular stomatitis was present. The tongue was shiny, red and fissured.

The patient was pale and emaciated, with no

Fig 1 Endoscopic photographs of duodenal mucosa of patient BB (A and B) and normal subject (C and D). Photographs were taken through an Olympus GIF-D₂ panendoscope. Figures B and D after spraying the mucosal surface with 0.4% indigocarmine.

Fig 2 Patient BB, with typical rash involving middle third of face.

subcutaneous fat. There was no jaundice or lymphadenopathy. The abdomen was distended but soft. No hepatosplenomegaly, renal masses, other masses or ascites were detected. Bowel sounds were active. Generalised muscle weakness and wasting was noted. Hyperaesthesia was found in a 'glove and stocking distribution'. Reflexes were brisk, with flexor plantar responses. His mental status was volatile, at times he was uncooperative and at other times docile.

The patient repeatedly refused surgery in Galway and eventually a laparotomy was performed elsewhere. At operation, the presence of a large tumour of the pancreas (12×18 cm) was confirmed. Excision was impossible because of extension of the tumour around the superior mesenteric axis, the portal vein, and extending into the porta hepatis and retroperitoneal space. Biopsy revealed an islet cell carcinoma of the α cell type. Tissue was not available to extract glucagon-like immunoreactive species for comparison with the peripheral blood species. The patient died postoperatively.

Investigation

HAEMATOLOGY

Haemoglobin 11.1 g/dl, platelets 379 000, ESR 16 mm/l. Red cells were mildly anisocytic, poikilocytic, and macrocytic. No Howell Jolly bodies were detected. Serum iron, folate, and vitamin B12 normal.

BIOCHEMISTRY

Routine biochemical screen showed abnormalities of gamma glutamyl transferase 34 U/l (normal range (NR) 5–25 U/l). Cholesterol 3.36 mmol/l (NR 3.37–7.0 mmol/l). Urinary 5 hydroxyindole acetic acid (four collections) mean 106 mol/24 h (NR<52 mol/24 h). Plasma and urinary aminograms showed severe generalised hypoaminoacidaemia with the presence of ethanolamine (Table 1) and very low lysine and glutamine/glutamic acid excretion. Serum zinc 15.3 mmol/l (NR 12.25–16.8 mmol/l).

INTESTINAL INVESTIGATIONS

Faecal fat excretion 8 mmol/24 h (NR<18 mmol/24 h), vitamin B12 absorption 28.1% (NR 11–28%). Excretion of ingested radio-opaque markers started within 24–36 hours on three separate occasions, but the patient would not cooperate with the assessment of mean transit time. Barium meal and selenomethionine (Se^{75}) pancreatic scan and abdominal ultrasound examinations indicated the presence of a mass 8–10 cm in diameter in the body and tail of the pancreas. The ^{99m}Tc sulphur colloid liver and spleen scan was normal.

Table 1 Plasma aminogram

Amino acids	BB mol/l	Normal range mol/l
Taurine	166	102–222
Hydroxy-proline	0	9–31
Threonine	33	124–168
Serine/glutamine	150	672–846
Glutamic acid	46	44–76
Citrulline	6	26–46
Proline	27	169–309
Glycine	104	194–287
Alanine	110	330–508
Valine	86	215–289
Cystine	21	101–135
Methionine	17	26–38
Isoleucine	26	66–102
Leucine	61	133–187
Tyrosine	16	57–87
Phenylalanine	56	56–74
Ornithine	9	47–83
Lysine	85	167–229
Histidine	50	78–100
Arginine	72	63–115
Ethanolamine*	29	0

* Not normally seen in adults.

METABOLIC STUDIES OF THE GLUCAGONOMA

Blood samples for hormone analysis were drawn into ice cool heparin tubes, centrifuged at 4°C, the plasma separated into aprotinin (Trasylol) 1000 KIU per ml plasma and stored at –20°C until assayed. All hormones were measured by radioimmunoassay using a standard dextran coated charcoal separation method. Details of the assay methods and the specificity of the antibodies used are reported elsewhere; insulin,⁴ gastrin,⁵ secretin^{6–8} and vasoactive intestinal polypeptide.^{9 10}

Glucagon was assayed using two antisera of different specificity.¹¹ Firstly an N-terminal reactive antibody (YY57) which measures all known species of glucagon-like immunoreactivity extractable from the pancreas and gut. The materials assayed by antibody YY57 are referred to as N-GLI. The other antibody, a C-terminal reactive antibody (YY89), is more specific for pancreatic glucagon but shows 2% cross reactivity with intestinal extracts.¹² The materials assayed by antibody YY89 are referred to as C-GLI.

Fasting levels of gastroentero-pancreatic (GEP) hormones in the patient and the normal range are shown in Table 2. Where several fasting results from the patient were available the range, mean and number of samples are shown. There were rises of N-GLI 25 000 ng/l (NR 0–288 ng/l) and C-GLI 26 000 ng/l (NR 0–188 ng/l). The fasting insulin was mildly raised 22 mU/l (NR 0–15 mU/l). All other GEP hormones studied were within the normal

Table 2 Fasting plasma gastroentero-pancreatic hormone concentrations

	Patient			Normal fasting range
	n	Range	Mean	
Gastrin (ng/l)	6	40–85	55	0–83
Secretin (ng/l)	4	0–20	10	0–63
Insulin (mU/l)	10	12–44	22	0–15
VIP (ng/l)	3	40–60	50	0–133
N-GLI (ng/l)	15	18 000–43 000	25 000	0–288
C-GLI (ng/l)	15	10 000–42 500	26 600	0–188

range.

Several tests known to provoke the release of glucagon were performed to study the production of the hormone by the tumour and to permit further biochemical analysis of the molecular form/forms of glucagon secreted. During the studies blood was drawn through an indwelling IV cannula kept open by a slow 0.9% saline infusion. During two of these studies arginine infusion and tolbutamide injection, the patient experienced severe upper abdominal pain radiating through to his back.

1 Glucose tolerance test

A 50 g oral glucose tolerance test showed a normal fasting plasma glucose concentration but the peak level and that at 120 minutes were above the normal range, confirming the diagnosis of diabetes mellitus (Fig. 3). An initially high fasting insulin level was found without the expected rapid rise after the glucose load. The fasting levels of N-GLI and C-GLI were markedly raised, however, following the glucose test there was a transient rise in C-GLI without any concomitant significant rise in N-GLI. In controls no significant rise in either N-GLI or C-GLI was seen after the glucose load. In the majority of patients with pancreatic glucagonoma syndrome an oral glucose tolerance test resulted in a rapid secretion of glucagon,¹³ although a few tumours did not react in this way.¹⁴

2 L-arginine infusion

A 30 minute infusion of 30 g L-arginine monohydrochloride (McCarthy's Ltd, Romford, Essex) produced a biphasic outpouring of N-GLI and C-GLI (Fig. 4). Again there was a much greater secretion of C-GLI than N-GLI. In controls there was a biphasic outpouring of glucagon-like immunoreactivities with the major peak 10 minutes after commencement of the infusion and the minor peak 30 minutes later. A greater rise was noted in C-GLI (95 ng/l to 499 ng/l) than N-GLI (115 ng/l to 255 ng/l) in controls. In the majority of patients with pancreatic glucagonoma syndrome, arginine

Fig 3 50 g oral glucose tolerance test, (//// or —) indicate control range.

infusion produces a marked increase in plasma glucagon with a less marked rise in insulin level.¹³ In our patient there was an early doubling of the insulin level, although in controls the secretion of insulin was biphasic with a high late peak.

3 IV Tolbutamide

One gram intravenous tolbutamide (Hoechst Pharmaceuticals) resulted in a rapid biphasic production of N-GLI and C-GLI with a peak N-GLI of 175 000 ng/l after two minutes, the highest level recorded in the patient (Fig. 5). During this test higher levels of N-GLI than C-GLI were recorded, whereas during the glucose tolerance test and arginine infusion higher levels of C-GLI than N-GLI were noted. The explanation for this phenomenon is not known. In the pancreatic glucagonoma syndrome a rapid rise in glucagon has been noted in many cases,¹³ whereas in controls a fall occurred. The rapid plasma insulin response in our patient was typical of the pancreatic glucagonoma syndrome and was similar to that seen in controls as was the fall in blood glucose. Four hours after the intravenous tolbutamide the lowest glucagon levels recorded in

Fig 4 30 g iv L-arginine infusion study, (////// or —) indicate control range.

Fig 5 1 g iv tolbutamide study, (////// or —) indicate control range.

the patient were obtained (N-GLI 12 000 ng/l and C-GLI 10 500 ng/l).

Affinity and gel chromatography were performed on peripheral blood drawn during a fast and after arginine infusion. These procedures allowed separation, purification and estimations of molecular size of the glucagon-like immunoreactivities secreted by the tumour.

AFFINITY CHROMATOGRAPHY

All procedures were performed at 4°C. Plasma samples (2 ml) diluted in an equal volume of 0.04 M PO_4 (pH 7.4) were allowed to flow first through a C-terminal reactive glucagon antibody (YY89) Sepharose conjugate and then through an N-terminal reactive glucagon (YY57) Sepharose conjugate connected in series. This resulted in the separation of glucagon-like immunoreactivity absorbed onto the YY89 or C-terminal reactive column (C-GLI) and that absorbed onto the YY57 or N-terminal reactive column (N-GLI). The

immobilised antibodies were contained in 5 cm × 1 cm glass columns. The flow rate was 4 ml per hour. After application the columns were washed with 10 column volumes of 0.04 M PO_4 (pH 7.4), NH_4OH (pH 10.5) containing 0.15 M NaCl and distilled H_2O to desorb non-specifically bound materials. Elution of glucagon-like immunoreactivity was achieved with 4 M guanidine HCl.¹⁵ Fractions (0.5 ml) were collected and assayed for glucagon-like immunoreactivity. This revealed that only the C-terminal antibody conjugate had absorbed the glucagon-like immunoreactivity. No glucagon-like immunoreactivity was eluted from the N-terminal antibody conjugate nor was any found in plasma which had been exposed to and flowed through both columns. The glucagon-like immunoreactivity from the C-terminal column reacted with both N- and C-terminal antibodies in the radioimmunoassay but demonstrated an overreaction with the C-terminal antibody. Those fractions containing glucagon-like immunoreactivity were pooled and 0.5 ml aliquots

subjected to gel chromatography.

GEL CHROMATOGRAPHY

All procedures were performed at 4°C. Sephadex G-50 Superfine was equilibrated in 0.1 M NH_4HCO_3 (pH 8.8), and packed into a 1 m $\times$ 1 cm glass column. The column was calibrated with blue dextran, cytochrome-C, insulin, glucagon, and potassium chromate (K_2CrO_4). The flow rate was 5 ml per hour. One ml fractions were collected. 100 l ml aliquots from each fraction were assayed for N-GLI and C-GLI. The gel chromatography profile revealed three peaks of immunoreactivity of molecular size, molecular weight 20 000; 12 000 and 3500 approximately (Fig. 6). The major peak was in the 12 000 molecular weight region with the 20 000 molecular weight being the minor peak. In normal fasting subjects only two peaks are observed in the 3500 molecular weight region and the void volume (>30 000 MW) with the latter being the major peak.

Fig 6 Sephadex G-50 Superfine gel chromatography of fasting plasma previously purified by immunoaffinity chromatography on a C-terminal reactive glucagon antibody Sepharose conjugate. Eluates were assayed by an N-terminal antibody (— N-GLI) and a C-terminal antibody (.... C-GLI). (/) shows position of GLI peaks in control subjects. Column markers are shown, BD=blue dextran, cc=cytochrome C, I=insulin, G=glucagon, K_2CrO_4 =potassium chromate.

Fig 7 Sephadex G-50 Superfine gel chromatography of plasma during L-arginine infusion; plasma previously purified by immunoaffinity chromatography on a C-terminal reactive glucagon antibody Sepharose conjugate. Eluates were assayed by an N-terminal antibody (— N-GLI) and a C-terminal antibody (.... C-GLI). (/) shows position of GLI peaks in control subjects. Column markers are shown, BD=blue dextran, cc=cytochrome C, I=insulin, G=glucagon, K_2CrO_4 =potassium chromate.

During arginine infusion changes in the gel chromatographic profile occurred (Fig. 7). There was a marked increase in the 12 000 and 3500 molecular weight region immunoreactivity, the glucagon-like immunoreactivity in the 3500 molecular weight region showing a stronger reaction with the N-terminal antibody and the 12 000 molecular weight peak glucagon-like immunoreactivity showed stronger reaction with the C-terminal antibody. No peak was found in gel chromatography of either fasting specimen or the arginine infusion specimen which corresponded to the >30 000 molecular weight peak found in normal fasting subjects.

Discussion

The pancreatic glucagonoma syndrome, which is characterised by a typical skin rash, angular stomatitis, glossitis, weight loss, anaemia, diabetes mellitus, and glucagon-producing tumour of the pancreas has been repeatedly documented.^{1 13 14} The similarity of the rash to that seen in acrodermatitis enteropathica and its response to zinc supplements lead to the suggestion that the skin lesions and glossitis of the glucagonoma syndrome are related to sequestration of zinc by the actively secreting tumour.¹⁶ It has been suggested that fatty acid deficiency may produce the skin lesion but even in relapse the fasting serum lipids were normal in our patient apart from minimal depression of cholesterol. Spontaneous improvement in the skin rash on withdrawal of sulphonylureas was noted in a 38 year old man with a pancreatic glucagonoma.¹⁷ Soler *et al* suggested that the tolbutamide was provoking glucagon release from the tumour and thus a more severe skin rash.¹⁷ The relative remission of symptoms from 1971–1973 in our patient when diabetic control was by calorie restriction alone and subsequent relapse on re-introduction of tolbutamide support this theory.

Our patient not only had features of the pancreatic glucagonoma syndrome but also had large villi in the proximal duodenum. The enlarged villi, initially noted at endoscopy, were confirmed by morphometric measurement on biopsy material. Endoscopic biopsies are not ideal for this assessment because of their small size, paucity of villi, tendency to curl and problems of optimal orientation. Nevertheless, the mean villous height in controls (336 μm) was similar to that found by other authors (393 μm).¹⁹ The frequency of the occurrence of large villi in pancreatic glucagonoma syndrome is not known as the majority of patients have not undergone a small intestinal biopsy. Giant intestinal villi have been recorded in a 44 year old female patient, presenting with polyuria and constipation, who was found to have an enteroglucagon producing tumour of the kidney.³ The patient had a transient erythematous rash, however the description in the case report is not that of the severe necrolytic dermatosis of the pancreatic glucagonoma syndrome. The mean villous height in this patient (1150 μm) was greater than in our patient (733 μm) but the biopsy in the former was from the mid-jejunum³ and in the latter from the proximal duodenum. In controls the villi are longer in the jejunum than in the duodenum.¹⁹

It has been suggested that the enteroglucagon secreted by the renal tumour may have induced the intestinal morphological abnormalities, as these

changes regressed after operative removal of the tumour,^{20 21} and saline extracts of the tumour, when injected intraperitoneally in mice, resulted in macroscopic enlargement of the small bowel.²¹ In the present patient an unusual high molecular weight glucagon (molecular weight 12 000) has been isolated. It is possible that this glucagon induces villous hypertrophy although it is larger than the enteroglucagon (molecular weight 7000 approximately) extracted from the renal tumour of the patient with the giant villi.²⁰ Affinity chromatography showed our patient to be devoid of glucagon-like immunoreactivity reacting only with N-GLI antibody. In normal subjects glucagon-like immunoreactivity from plasma adheres to a C-terminal reactive antibody column but the washings from this column contain glucagon-like immunoreactivity which adheres to an N-terminal column. The reason for this abnormality is not clear but it may be due to degradation or concealment of the N-terminal sequence or the possession of a sequence not recognised by the antibodies.

Experimental studies have shown various factors exhibit a trophic effect on the small intestinal mucosa. Exogenous gastrin stimulates growth of the duodenal mucosa, without a similar effect being demonstrable distally in the small intestine.²² In our patient, with normal fasting gastrin concentration, hypertrophic villi were seen throughout the area examined, which was confined to the duodenal cap and the descending duodenum. Another regulatory peptide, epidermal growth factor, EGF, extracted from salivary and duodenal glands has been suggested as a candidate for the role of enterotrophin, the hormonal controller of intestinal growth.²³ An increase in duodenal weight, DNA synthesis and total DNA and RNA content of the duodenal mucosa has been documented after epidermal growth factor administration, but this conflicts with a previous report failing to demonstrate similar growth.²³ Epidermal growth factor assay was not available in our patient. The effect of luminal factors on intestinal adaptation after gut resection has been studied. Pancreaticobiliary secretions²⁴ and luminal nutrients in hyperphagia²⁵ resulted in increased mucosal growth. The severe atrophy of the small intestine occurring in rats on total parenteral nutrition can be prevented by the administration of 15% of total calories by the enteral route.²⁵ Enteral lipids, especially long chain triglycerides, are superior to glycogen and egg albumen in maintaining mucosal DNA and total protein weight.²⁵ It is unclear whether the luminal factors act directly or by releasing a trophic hormone. In our patient we had no evidence of excessive exocrine pancreaticobiliary secretion and

his diet (10 kJ) was restricted to control his diabetes mellitus.

The abnormal mental state of the patient influenced his investigation and treatment. His mood rapidly changed from full cooperation to complete obstinacy. Mental symptoms, usually depression, have been noted in the pancreatic glucagonoma syndrome.^{13 14} The metabolic basis for these symptoms and the other neurological abnormality found in this patient, namely altered peripheral sensation, is unexplained.

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