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Pancreatic Glucagonoma with and without Syndrome

Immunocytochemical Study of 5 Tumour Cases and Review of the Literature

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Summary. In five patients single or multiple glucagonomas were characterized by immunocytochemistry. Two large single glucagonomas were associated with the glucagonoma syndrome, which completely dissappeared after removal of the tumours. The morphologic findings in these patients are compared with 48 others collected from literature.

In the other three patients, the glucagonomas were not associated with a clinical syndrome and were detected by chance (one accompanying an insulinoma; the other in pancreases of patients suffering from multiple endocrine neoplasia I; MEN I). These tumours appeared by their histological, immunocytochemical and ultrastructural features better organized than the glucagonomas with syndrome.

Glucagonomas not producing a syndrome can be classified into (a) solitary, often malignant endocrine pancreatic tumours, (b) glucagonomas associated with insulinomas and other tumours, (c) multiple glucagonomas in MEN I and (d) single microglucagonomas in elderly patients. It is emphasized that only immunohistology allows clear identification of these tumours as glucagonomas.

Key words: Glucagonomas – Morphological features – Immunocytochemistry – Review of literature – Classification.

Introduction

The use of immunohistological and radioimmunological methods allows to characterize hormones produced by endocrine pancreatic tumours (Heitz et al. 1979; Polak et al. 1976). The tumours are classified according to the principal hormone produced, whether or not it causes a clinical syndrome, as insulinoma, gastrinoma, vipoma, glucagonoma, somatostatinoma and PP-oma. While insulin-

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omas and gastrinomas are quite common, other types of tumours, including glucagonomas are rare (Klöppel et al. 1979). It must be pointed out, however, that when estimating the relative frequency of endocrine pancreatic tumours, only the tumours with endocrine syndromes have been considered. This is especially true for glucagonomas. Glucagonomas with a cutaneous syndrome are very uncommon, while glucagonomas without clinical manifestation appear to occur more frequently.

We report 5 patients suffering from a glucagonoma. The purpose of the study is to demonstrate the broad spectrum of the manifestation of these tumours.

Patients

Table 1 summarizes the main clinical and morphological details of 5 patients with glucagonomas. Two of the patients showed the necrolytic migratory erythema as part of the glucagonoma syndrome, which disappeared completely within two weeks after removal of the tumours (Fig. 1).

Table 1. Clinical and pathological data of five patients having glucagonomas with syndrome and without syndrome

Pat.	Age/sex	Rash	Diabetes	Other clinical features	Glucagon (ng/ml) before tumour resection	Site and size of tumours (cm)	Metastases	Treatment
1	60/M	+	–	weight loss	6.0	body 5 × 2.5	no evidence	resection of the tumour
2	51/F	+	–	weight loss	?	adhering to the posterior surface of pancreatic head, 8 × 8	no evidence	resection of the tumour
3	35/M	–	–	hypoglycemic episodes	?	tail 2.5 × 2.5 2 × 2	no evidence	body-tail resection
4	40/M	–	–	chronic recurrent ulcers, prim. hyperparathyreoidism	?	tail 17 small tumours (up to 1)	no evidence	resection of the tail
5	51/F	–	–	12 years history of ulcer duodeni, hyperparathyreoidism, hypoglycemic episodes	?	head-body 2.5 × 2 1 × 1.5 body-tail 28 small tumours (up to 0.5)	no evidence	resection of tumour in the head and body-tail resection

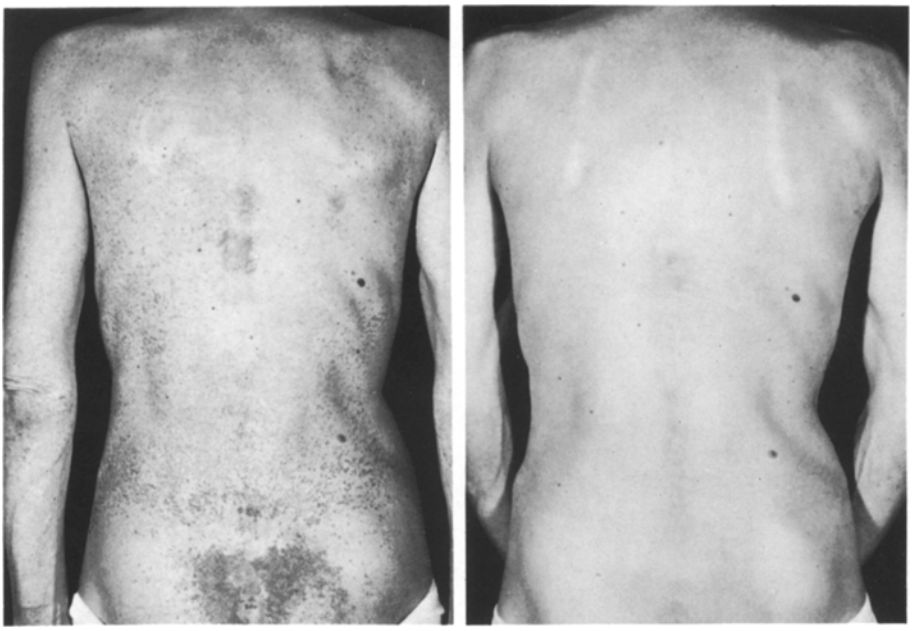

Fig. 1. Necrolytic migratory erythema as part of a glucagonoma syndrome in a 51-year-old woman (case 2) before (*left*) and after (*right*) resection of the glucagonoma

Material and Methods

The operative samples were fixed in Bouin's fluid for light microscopy and immunocytochemistry, and in phosphate buffered glutaraldehyde (2.5% pH 7.5) for electron microscopy (cases 1, 3, 5).

Light Microscopy. Serial paraffin-embedded sections were stained with hematoxylin and eosin, periodic acid Schiff (PAS), Gomori's aldehyde fuchsin (AF), phosphotungstic acid hematoxylin (PTAH) and Grimelius silver nitrate technique (Grimelius 1968).

Immunocytochemistry. Deparaffinized sections (5 μm) were incubated for insulin, glucagon, somatostatin, human pancreatic polypeptide (HPP), gastrin, vasoactive intestinal polypeptide (VIP) and ACTH using the unlabelled antibody enzyme method (Sternberger 1979). The first antibody was used at the following dilutions: anti-insulin 1/5,000, anti-glucagon 1/5,000, anti-somatostatin 1/7,500, anti-HPP (a gift from Dr. R. Chance, Indianapolis) 1/40,000, anti-gastrin 1/6,000, anti-VIP 1/5,000 and anti-ACTH 1/500. All antisera were raised in rabbits. They were tested by radioimmuno-assay and shown not to cross-react with antigens other than against which they are produced. Sheep anti-rabbit IgG (1/30) and soluble peroxidase anti peroxidase complexes (1/30–1/60) were used as second and third layers, respectively. The histochemical reaction for peroxidase was carried out using 3,3′-diaminobenzidine-tetrahydrochloride (0.05% w/v) and hydrogen peroxide (0.01%) in 0.05 M Tris-HCl buffer (pH 7.6). Specificity of the reactions was determined as described by Sternberger (1979): (1) non-immun rabbit serum as first layer, (2) specific antiserum absorbed with 50 μg of the antigen per ml diluted serum at 4° C for 24 h as first layer, (3) omission of 3,3′-diaminobenzidine-tertahydrochloride or H_2O_2 from the incubation medium for the peroxidase reaction.

Electron Microscopy. After postfixation in cacodylate buffered osmium tetroxide (1%) the tissue blocks were dehydrated in graded ethanol and embedded in Epon. Ultrathin sections were stained with uranylacetate and lead citrate, and examined in a Zeiss EM 10 electron microscope.

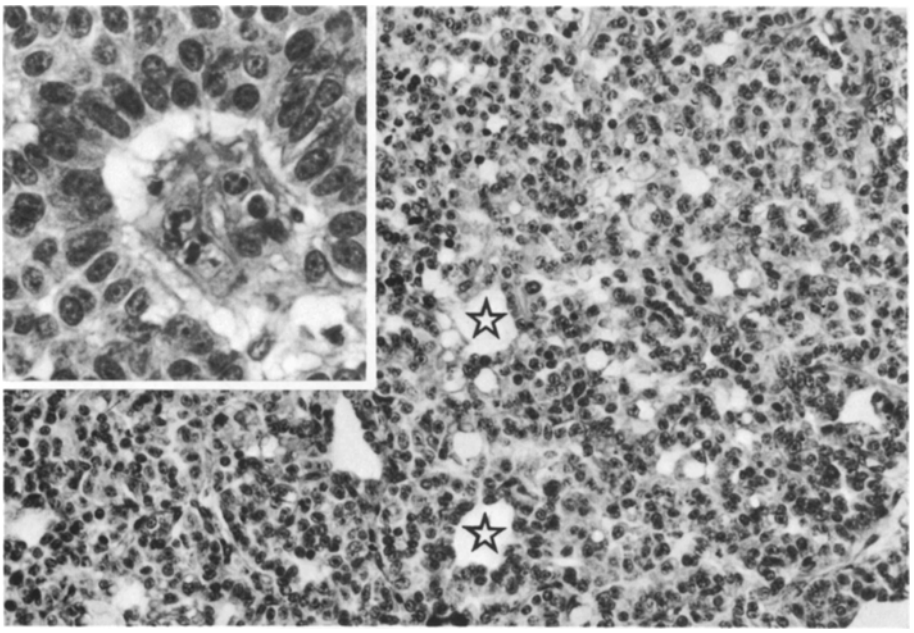

Fig. 2. Histopathology of a glucagonoma with syndrome showing a predominantely solid pattern with some gland-like spaces (*asterisks*). Note the trabecular arrangement of the endocrine cells forming pseudorosettes (*inlet*). Hematoxylin and eosin. ×140 and ×350

Results

Histology

The tissues from the tumours with the glucagonoma syndrome showed a mixed solid and trabecular pattern including pseudorosettes as well as some ductular and gland-like structures (Fig. 2). Palisading of the cells within the trabecular structures was often found. The cells were of a fairly monomorphic size, had a granular, occasionally slightly clear cytoplasm and nuclei of partly oval, partly elongated shape. Some of the cells stained weekly by the Grimelius or the PTAH method. Parts of the tumours were heavily sclerosed, others were well vascularized. The tissue from the tumours without a cutaneous syndrome mostly showed a trabecular to gyriform pattern, but some of them had also a mixed solid to trabecular or even a purely solid pattern. In general, the cells were of uniform shape and a great deal of them had a vacuolized clear cytoplasm. Almost all cells were argyrophil or stained well with PTAH. In the MEA cases the tumours were either of solid or of trabecular pattern often embedded in abundant fibrous tissue. At the periphery of some of the tumours there were conspicious nesidioblastic proliferations.

Immunocytochemistry

In the tumours causing the glucagonoma syndrome about 40–50% of the cells reacted weakly to glucagon, the hormone being stored at the basis of the cells.

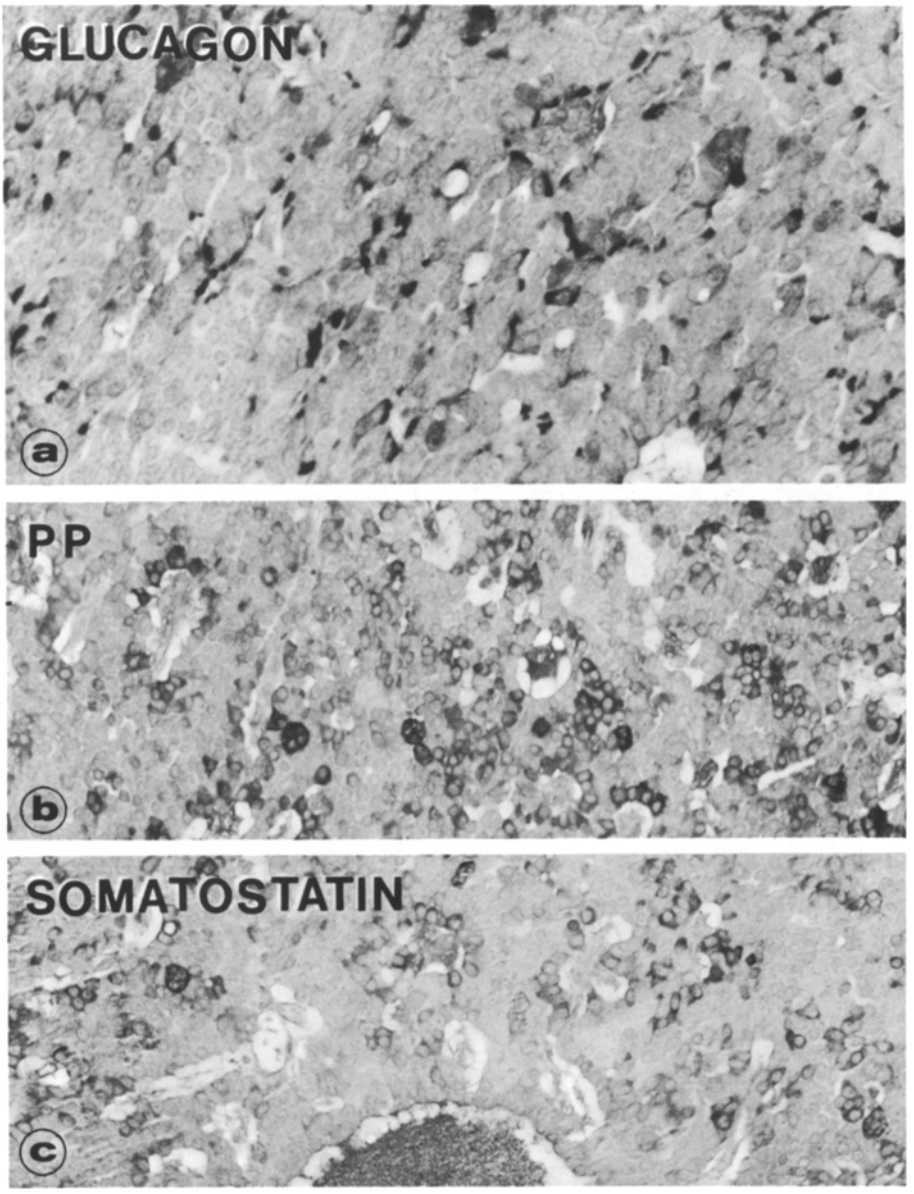

Fig. 3a–c. Immunocytochemistry of different areas in a glucagonoma with syndrome shows abundance either of glucagon, PP or somatostatin cells. **a** ×16, **b** ×10, **c** ×10

In addition, PP and somatostatin cells were found in the tumour of case 1. These cells occupied different areas of the tumour and were only slightly interspersed with glucagon cells (Fig. 3).

The tumours without a clinical syndrome were mostly composed of glucagon cells, the reactive product filling the entire cytoplasm. The cells were arranged in ribbons (Fig. 4) or solid structures (Fig. 5). Occasionally small groups of

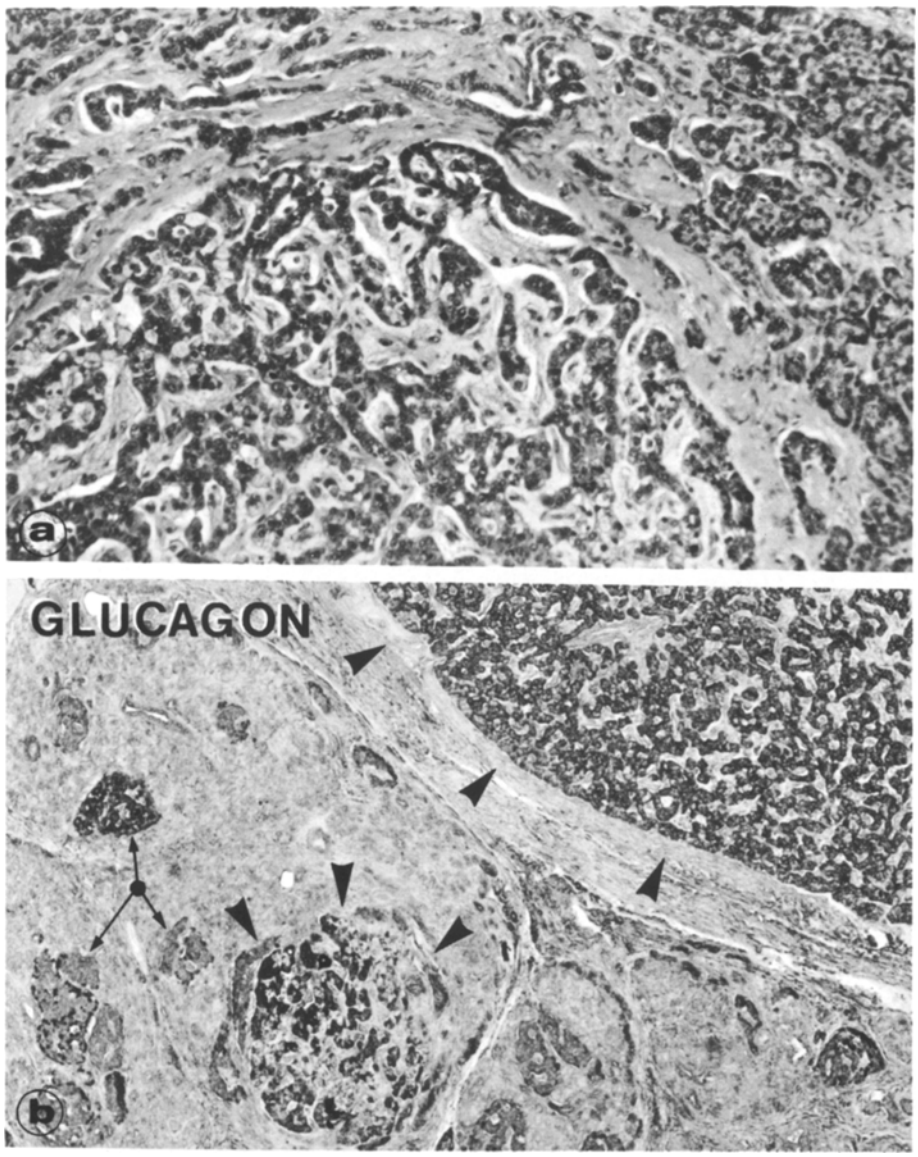

Fig. 4a and b. Trabecular glucagonoma in pancreas with MEN I **a** Tumour with gyriform pattern. Hematoxylin and eosin, ×140. **b** Positive immunocytochemistry for glucagon showing a large trabecular glucagonoma, a small glucagonoma (*arrow heads*) and normal islets with a peripheral layer of glucagon cells (*arrows*). ×58

PP-cells and single scattered somatostatin and insulin cells were seen. The resected pancreatic specimens from the two patients with MEN I contained 9 glucagonomas out of 17 tumours and 9 glucagonomas out of 28 tumours, respectively. The glucagon cells were intermingled with groups of PP-cells (Fig. 6) and to a lesser degree with insulin and somatostatin cells. Some of the glucagonomas

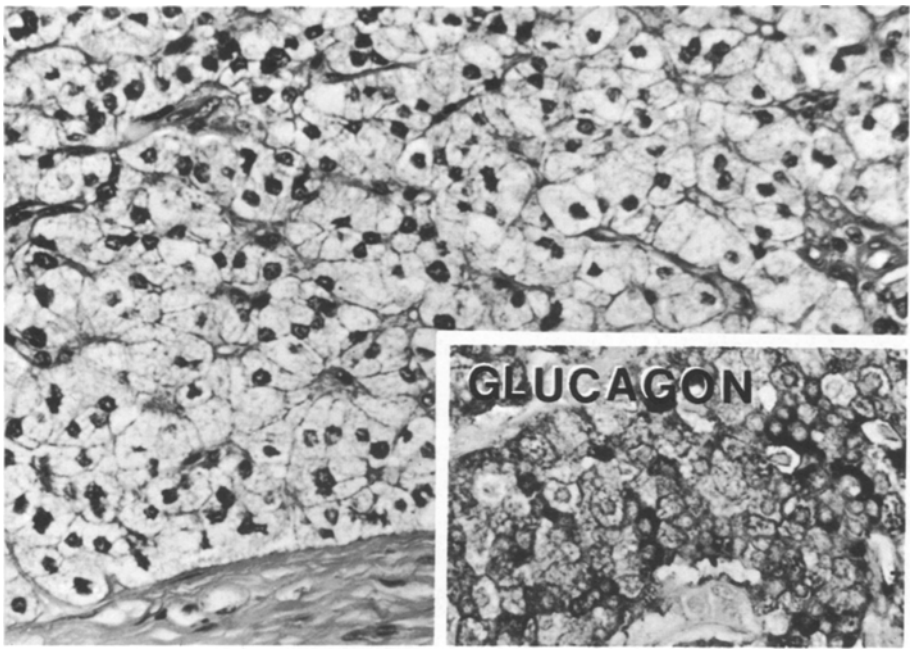

Fig. 5. Solid endocrine tumour in a pancreas with MEN I PAS ×350. Positive immunocytochemistry for glucagon (*inlet*)

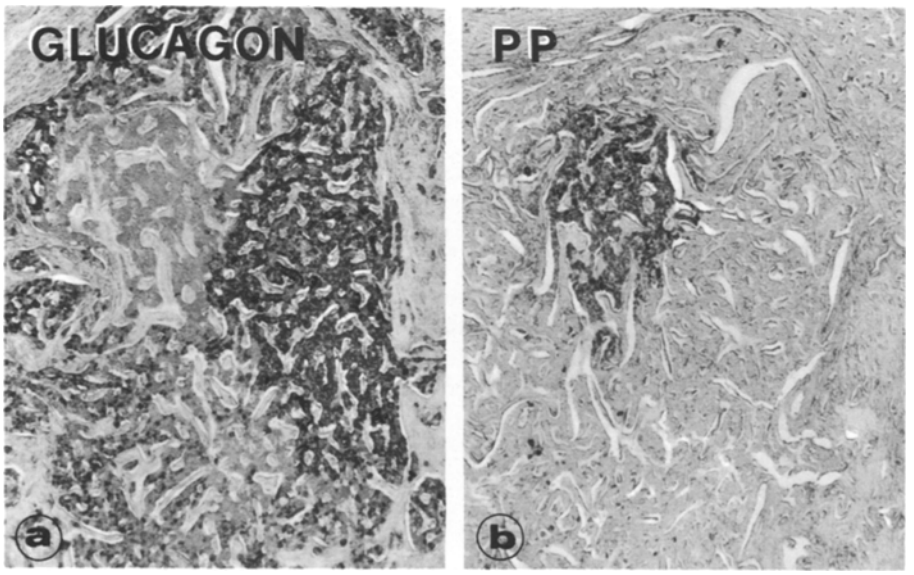

Fig. 6a and b. Immunocytochemistry on consecutive sections of a glucagonoma **a** incorporating a PP cell nodule **b** ×58

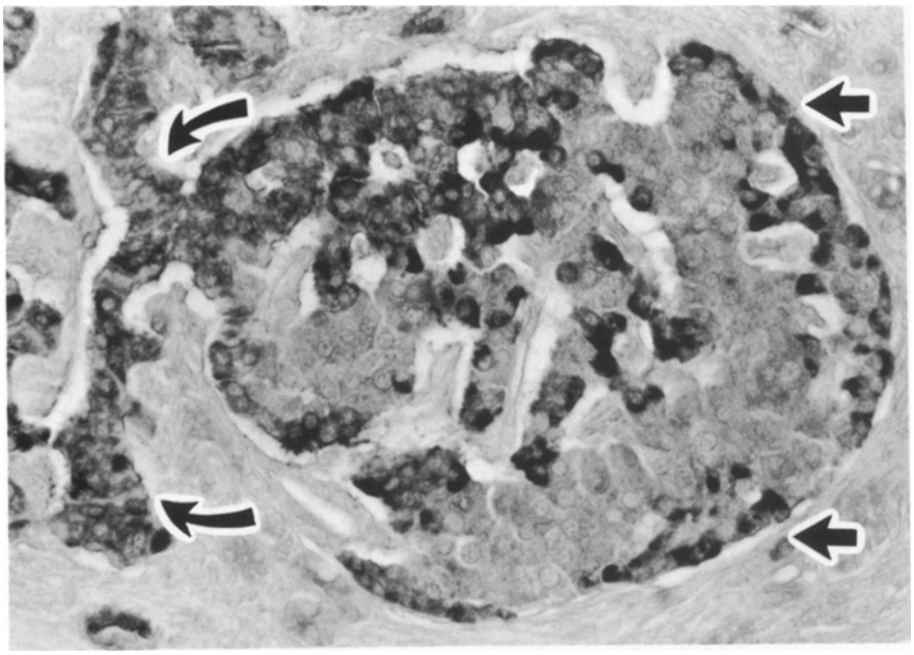

Fig. 7. Immunocytochemically stained glucagon cells of a normal islet (*straight arrows*) connected with a glucagonoma (*curved arrows*). ×350

were directly connected with ducts and islets (Fig. 7). Apart from the glucagonomas insulinomas, PP-omas and one pure somatostatinoma were observed.

Ultrastructure

In the tumours with a glucagonoma syndrome glucagon producing cells could not be clearly identified by their granule structure, since granules resembling typical A cell granules were not found. One tumour (case 2) contained a lot of virtually agranular cells in addition to cells with few small granules. In the other tumour (case 1) scarcely granulated cells with atypical granules (Fig. 8a) were found together with cells filled with granules of the PP and D cell type, respectively. The cells from the tumours without syndrome contained typical a cell granules (Fig. 8b), characterized by their dense cores eccentrically placed within semi-lunar less dense halos and tightly fitting membranes. Occasionally also PP cells could be identified by their granule structures. The cytoplasm of many A cells included large lipid droplets.

Discussion

The glucagon-secreting tumours of this series reflect the diverse possibilities of the occurrence of glucagonomas (Mallinson and Bloom 1978). Two of the glucagonomas were associated with a typical syndrome, the well-known gluca-

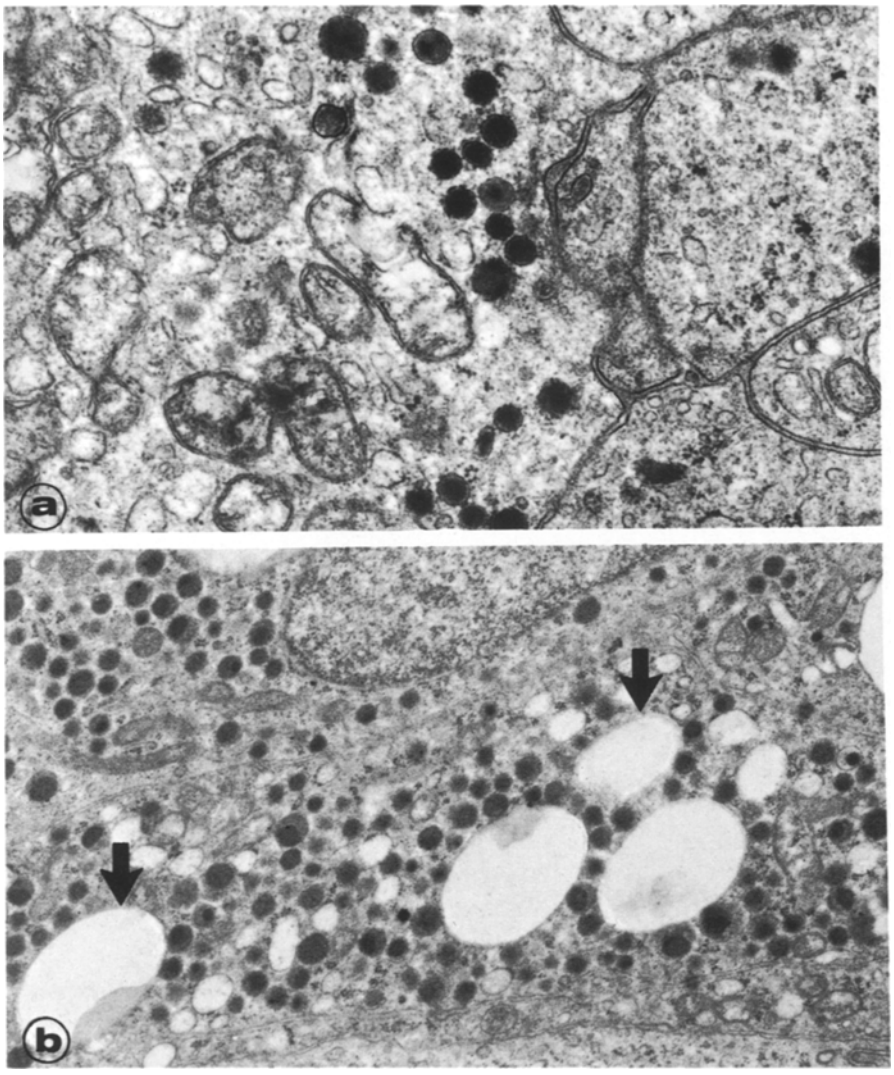

Fig. 8 a and b. Ultrastructural appearance of secretory granules in glucagonomas. **a** Atypical granules in a cell of glucagonoma with syndrome. ×30,400. **b** Typical A cell granules in a glucagonoma without syndrome. Note also the lipid droplets (*arrows*). ×9,100

gonoma syndrome, while the others were not. The discovery of the latter tumours was fortuitous. The glucagonoma syndrome, which in its complete form comprises the following features (Mallinson et al. 1974); necrolytic migratory erythema (Wilkinson 1971), glossitis, stomatitis, diabetes mellitus, normochromic anaemia, weight-loss, was first described by Becker et al. (1942) and Gössner and Korting (1960). In 1966 McGavran et al. proved that this syndrome is associated with hyperglucagonaemia and the presence of an A-cell tumour in the pancreas. So far at least 48 glucagonomas with syndrome (Table 2) have been reported

Table 2. Features of glucagonomas associated with a cutaneous syndrome

	Authors	Age/Sex	Rash Gloss-itis	Dia-betes	Anemia Weight loss	Glucagon ng/ml	Site and size (cm)	Metastases
1	Becker et al. (1942)	45/F	+ +	+	+ 7.7 kg		body-tail	lymphnodes adrenal gland
2	Zhdanov (1956)	51/F	+	+	+		tail 4.5 × 3.5	liver
3	Gössner and Korting (1960)	51/M	+	+	+		twice as big as a fist	liver
4	McGavran et al. (1966)	42/F	+	+	+	36–55	tail	liver
5	Church and Crane (1967)	61/F	+ +	+	+ +		body 8	liver lymphnodes
6	Wilkinson (1971, 1973)	55/F	+	+	+		head 2	liver lymphnodes
7	Auerbach and Koehler (1973)	42/F	+	+			tail	liver
8	Mallinson et al. (1974)	50/F	+ +	+	+ 8 kg	3.5	head 4	malignant cells in duodenal juice
9	(Lightman and Bloom 1974;	52/F	+ +	+	+ 6 kg	1.5	neck 5	liver and spine, extensive
10	Warin 1974; Sweet 1974)	65/F	+	+	+ 7 kg	1.47	tail 8	liver and local
11		58/F	+ +	+	+ 9 kg	0.85	tail 8	none
12		56/F	+ +	+	+		tail 5	none
13		65/M	+ +	−	+ 14 kg		body 4	none
14		48/F	+ +	+	+ 16 kg		tail 6	liver
15		51/F	+ +	−	 18 kg		body ?	liver massive
16		50/F	+ +	+	+ 15 kg		tail 10	liver massive
17	Scully (1975) (Kahan 1977; Weir 1977; Strauss 1977)	40/M	+ +	+	+ 25 kg	2.2	body ?	liver
18	Soler et al. (1976)	38/M	+ +	+	+ +	1.27	tail 5 × 4	multiple
19	Recant et al. (1976) (Boden et al. 1977)	52/M	+ +	+	+ 25 kg	5–13	tail 11 × 5.5 × 3	spleen lymph nodes

Table 2 (continued)

	Authors	Age/Sex	Rash Gloss-itis	Dia-betes	Anemia Weight loss	Glucagon ng/ml	Site and size (cm)	Metastases
20	Danforth et al. (1976)	51/M	+ +	+	 9 kg 7 kg	4.8	body 12 × 17 neck 5	none recurrence liver
21	Valverde et al. (1976)	54/F	+ +	+	+ 4.5 kg	2.6	 ?	liver massive lymph nodes
22	Pedersen et al. (1976) (Holst et al. 1975)	71/F	+ +		+ 20 kg	6.6	body 5 × 6 × 7	none
23	Holst (1975) (Pedersen et al. 1976; Ingemans-son 1977; Holst 1979)	69/M	+ +	+	+ 8 kg	0.7–1.0	tail 3 × 4 × 5	none
24	Amon (1976) (Swenson 1978, Riddle 1978)	19/F	+ +	+	+ 4.5 kg	0.8	tail 2.5	liver
25	Kramer et al. (1976)	50/F	+	+		2.6–4.0	body ?	none
26	Tiengo (1976)	63/F	+ +	+	 ++	3.0	body-tail ?	none
27	Binnick (1977)	58/F	+ +	+	+ 5 kg	6.75	tail ?	liver
28		52/F	+ +	+	+	2.5	tail 10	none
29	Kahan (1977)	39/M	+ +	+	– 11 kg	0.7	body-tail 4 × 6	recurrance
30	Weir et al. (1977)	53/F	+	+	 +	0.79	tail 10	none
31		58/F	+ +	+	 5 kg	2.7	tail ?	liver
32	Ingemannson et al. (1977) (Holst et al. 1979)	62/M	+	+		2.9	tail ?	none
33	Kessinger et al. (1977)	56/F	+ +	+	+ 4.5 kg	3.0	?	liver
34	Jaspan and Rubenstein (1977)	39/F	+	+	 +	0.9	tail 4 × 4	none
35		40/M	+ +	+	 +	3.2	body ?	liver
36		37/M	+	+	 +	7.8	body ?	liver

Table 2 (continued)

	Authors	Age/Sex	Rash Gloss-itis	Dia-betes	Anemia Weight loss	Glucagon ng/ml	Site and size (cm)	Metastases
37	Cho et al. (1977)	65/M	+	+	+ 27 kg	3–5	head 12	liver
38	Shupack et al. (1978)	42/F	+ +	+	+ 9 kg	6	tail ?	liver
39	Krebs and Teuscher (1978) (Teuscher et al. 1979; Bordi et al. 1979)	66/M	+ +	+	+ 10 kg	8.5	tail 4 × 6 × 6	none
40	Higgins et al. (1979)	55/M	+	+	+ 18 kg	4.8–7.1	tail 3 × 3 × 4	none
41		54/M	+ +	+	+ ++	96.0	extensive	local and lymphnodes
42	Katz et al. (1979)	54/M	+ +	+	+ 11 kg	4.8	tail 4 × 3	none
43	Holst et al. (1979)	67/M	+	–		0.56	tail ?	?
44		46/F	+	–		0.32	head ?	?
45	Schenck et al. (1979) (Bordi et al. 1979)	68/M	+	–	16 kg	2.2	tail 4 × 6 × 5	none
46	Bordi et al. (1979)	66/F	+	+		6.4	tail 4 × 6	none
47		49/F	+	+		3.7	head 3 × 3	liver
48		48/M	+	+		86.0	head 15 × 25 × 35	local invasion
49	Present Series 1979	60/M	+	–	2–3 kg	6.0	body 5 × 2.5	none
50		51/F	+	–	7 kg		head 8 × 8	none

showing that the characteristic manifestation of this syndrome is the necrolytic migratory erythema, while the other manifestations may be absent. In fact, none of the cases observed by us presented the complete syndrome; the cutaneous manifestations, however, with their characteristical caudal localization were seen in each patient.

It is suggested that the cutaneous lesions are caused by hypoaminoacidaemia due to hyperglucagonaemia (Mallinson et al. 1974), although there appears to be no correlation between the glucagon levels and the severity of the dermal

Table 3. Classification of glucagonomas

1) Glucagonomas associated with a clinical syndrome
2) Glucagonomas not associated with a clinical syndrome
   a) Solitary malignant endocrine pancreatic tumours, associated or not with diabetes.
   b) Glucagonoma associated with a single insulinoma, gastrinoma or other pancreatic endocrine tumours.
   c) Multiple glucagonomas associated with MEN I.
   d) Single microglucagonomas in elderly patients.

changes (Mallinson et al. 1977). The normal epidermis was shown to contain a high concentration of aminoacids (Mallinson and Bloom 1974); it may, therefore, be assumed that the cutaneous lesions are due to the lack of important aminoacids. Another point that supports this hypothesis is the fact that similar alterations of the skin are observed in patients suffering from protein deficiency, such as in Kwashiorkor (Adams et al. 1967; Behar 1970). Barber (1976) reported the case of a 26 year old man who was treated with high doses of glucagon. During treatment yellowish papulous alterations of the skin with erythemateous borders appeard on his right shoulder and his abdomen. After treatment the erythema disappeared. Similarly disappearance of the erythema is noted after removing the glucagonomas.

All reported glucagonomas with the cutaneous syndrome were single pancreatic tumours of considerable size (largest diameter 1.5–35 cm), either directly located in the gland or, as in our second case, adhering to it. All tumours appeared in those regions of the pancreas in which A-cells are normally abundant and which derive from the dorsal anlage of the pancreas (Baetens et al. 1979). The localization of glucagonomas was found with about 50% in cauda, 24% in corpus, 14% in caput and 12% concerning the whole organ. At the time of diagnosis, 62% of the tumours had set metastases, that means in about 40% there is still a chance for complete cure by removal of the primary tumour, despite the considerable size the tumours may have reached already.

Glucagonomas not associated with a syndrome, which are solely characterized on morphological and/or biochemical grounds are found in various constellations (Table 3). The first type is for the most part a malignant endocrine pancreatic tumour which is discovered due to local growth, either expansive or invasive and/or metastases. The tumour can be associated with diabetes (Hess 1946; Hamperl 1952; Behrendt 1962; Unger et al. 1963; Yoshinaga et al. 1966; Sturner 1972; Friesen et al. 1974; Leichter et al. 1975; Leclere et al. 1977). The second type is a glucagonoma associated with an insulinoma or gastrinoma (Bordi and Bussolati 1974). The third type of glucagonoma occurs in multiple endocrine neoplasia, type I (MEN I) (Lomsky et al. 1969; Croisier et al. 1971; Croughs 1974; Woodtli et al. 1976; Lagiadèr et al. 1977; Creutzfeldt 1977; Bordi et al. 1979). The fourth type of glucagonoma, mainly a single microadenoma is found at post-mortem examination of older patients (Grimelius 1975).

The histology of active and inactive but metastasizing glucagonomas principally does not differ from that of other endocrine tumours in the pancreas,

showing mostly a mixed solid to trabecular architecture with focally accentuated sclerosis and slight cellular anaplasia. In contrast, glucagonomas found by chance, disclosed mainly an uniform trabecular to gyriform pattern, already pointed out by Bordi et al. (1979). Occasionally, however, completely solid tumours were observed. On immunocytochemistry most cells of these tumours stained intensively for glucagon, while in the glucagonomas with syndrome only a small number of cells reacted for glucagon, the reaction product being mainly localized at the capillary pole of the cells. Bordi et al. (1979) showed that the glucagon positive cells contained also glicentin probably one of the precursor molecules of glucagon (Patzelt et al. 1979; Ravazzola et al. 1979).

Apart from glucagon cells glucagonomas of both types contained also PP-cells and in declining order somatostatin and insulin cells. In MEN I, glucagonomas make up a great deal of tumours occuring in the pancreas (Lomsky et al. 1969; Croisier et al. 1971; Woodtli et al. 1976; Bordi et al. 1979). This is confirmed by our MEN I cases, in which glucagonomas represented the most frequent tumour type in the one case while in the other they were second only to insulinomas. A glucagonoma syndrome however has never been reported to be associated with MEN I.

What determines a glucagonoma to be an active or an inactive tumour in terms of their endocrine symptomatology? In the case of glucagonomas found in association with insulinomas or gastrinomas, one possible explanation is that the effects of glucagon released by the tumour are masked by the hormone(s) of the accompanying tumours. Moreover, it could be possible that glucagon secretion by these tumours may more appropriate in response to physiological stimuli than glucagon secretion by glucagonomas associated with a syndrome, because the aspect of the former tumours is more differentiated than that of their actively secreting counterparts. Why, however, some obviously malignant glucagonomas, as shown by their metastases, are not associated with any endocrine symptomatology except diabetes (which might be secondary to the tumour growth) is so far not known. However, it is tempting to speculate that these tumours release forms of glucagon (proglucagon or big glucagon), which are immunoreactive but biologically inactive.

In summary, glucagonomas constitute a heterogenous group of tumours with regard to their biological behavior, and this is partly reflected by their morphology.

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References

Adams EB, Scragg JN, Naidoo BT, Liljestrand SK, Cockram VI (1967) Observations on the aetiology and treatment of anaemia in Kwashiorkor. Br Med J 3:451–454

Amon RB, Swenson KH, Hanifin JM, Hambidge KM (1976) The glucagonoma syndrome (necrolytic migratory erythema) and zinc. N Eng J Med 295:962

Auerbach RC, Koehler R (1973) The many faces of islet cell tumors. Am J Roentgenol 119:133–140

Barber SG, Hamer JD (1976) Skin rash in patient receiving glucagon. Lancet 1138

Baetens D, Malaisse-Lagae F, Perrelet A, Orci L (1979) Endocrine pancreas: three-dimensional reconstruction shows two types of islets of Langerhans. Science 206:1323–1325

Becker SW, Kahn D, Rothman S (1942) Cutaneous manifestations of internal malignant tumors. Arch Dermatol Syph 45:1069–1080

Behar M (1970) Disturbance of nutrition. (1) Protein-calorie malnutrition. In: DB Jellife (ed) Diseases of children in the subtropics and tropics. London pp 161–184

Behrendt W (1962) Ein Beitrag zur Pathologie des A-Zellkarzinoms. Zentralbl Allg Pathol Anat 104: 199–204

Binnick AN, Spencer SK, Dennison WL, Horton ES (1977) Glucagonoma syndrome. Arch Dermatol 113:749–754

Boden G, Owen OE, Rezvani I, Elfenbein BI, Quickel KE (1977) An islet cell carcinoma containing glucagon and insulin. Diabetes 26:128–137

Bordi C, Bussolati G (1974) Immunofluorescence, histochemical and ultrastructural studies for the detection of multiple endocrine polypeptide tumours of the pancreas. Virchows Arch B Cell Path 17:13–27

Bordi C, Ravazzola M, Beatens D, Gordon P, Unger RH, Orci L (1979) A study of glucagonomas by light and electron mikroscopy and immunfluorescence. Diabetes 28:925–936

Cho KJ, Wilcox CW, Reuter SR (1977) Glucagon-producing islet cell tumor of the pancreas. Am J Roentgenol 129:159–161

Church RE, Crane WAJ (1967) A cutaneous syndrome associated with islet-cell carcinoma of the pancreas. Br J Dermatol 79:284–286

Creutzfeldt W (1977) Endocrine tumors of the pancreas. In: Volk BW, Wellmann KF (eds), The diabetic pancreas, Chapt 22, Plenum Publishing Corporation, New York-London, pp 551–590

Croisier JC, Lehy T, Zeitoun P (1971) A_2-cell pancreatic microadenomas in a case of multiple endocrine adenomatosis. Cancer (Philad.) 28:707–713

Croughs RJM (1974) Glucagonoma and A-cell hyperplasia. Clin Gastroenterol 3:609–619

Danforth DN, Triche T, Doppman JL, Beazley RM, Perino PV, Recant L (1976) Elevated plasma proglucagon-like component with a glucagon-secreting tumor. Effect of streptozotocin. N Engl J Med 295:242–245

Friesen SR, Hermreck AS, Mantz FA (1973) Glucagon, gastrin, and carcinoid tumors of the duodenum, pancreas, and stomach: polypeptide "apudomas" of the foregut. Am J Surg 127:90–101

Gössner W, Korting G (1960) Metastasierendes Inselzellkarzinom vom A-Zelltyp bei einem Fall von Pemphigus foliaceus und Diabetes renalis. Dtsch Med Wochenschr 11:434–437

Grimelius L (1968) A silver nitrate stain for A_2 cells in human pancreatic islets. Acta Soc Med Upsalien 73:243–270

Grimelius L, Hultquist G, Stenkvist B (1975) Cytological differentiation of asymptomatic pancreatic islet cell tumors in autopsy material. Virchows Arch A Path Anat and Histol 365:275–288

Hamperl H (1952) Über argyrophile Zellen. Virchows Arch 321:482–507

Heitz PhU, Kasper M, Polak JM, Klöppel G (1979) Pathology of the endocrine pancreas. J Histochem Cytochem 27:1401–1402

Hess W (1946) Über ein endokrin inaktives Carcinom der Langerhansschen Inseln. Schw med Wochenschr 35:802–804

Higgins GA, Recant L, Fischmann AB (1979) The glucagonoma syndrome: Surgically curable diabetes. Am J Surg 137:142–148

Holst JJ, Pedersen NB (1975) Glucagon-producing tumors of the pancreas. Acta Endocrinol (KBH) Suppl 199:379

Holst JJ, Jonsson L, Pedersen NB, Thomsen K (1975) Glukagonomsyndromet. Ugeskr Laeger 137:2531–2633

Holst JJ, Helland S, Ingemannson S, Bang Pedersen N, von Schenck H (1979) Functional studies in patients with the glucagonoma syndrome. Diabetologia 17:151–156

Ingemansson S, Holst J, Larsson LI, Lunderquist A (1977) Localization of glucagonomas by cathederization of the pancreatic veins and glucagon assay. Surg Gynecol Obstet 145:509–516

Jaspan JB, Rubenstein AH (1977) Circulating glucagon. Plasma profiles and metabolism in health and disease. Diabetes 26:887–904

Kahan RS, Perez-Figaredo MRA, Neimanis CA (1977) Necrolytic migratory erythema. Arch Dermatol 113:792–797

Katz R, Fishmann AB, Galotto J, Gucci JG, Higgins A, Ortega LG (1979) Necrolytic migratory erythema, presenting as candidiasis, due to pancreatic glucagonoma. Cancer 44:558–563

Kessinger A, Lemon HM, Foley JF (1977) The glucagonoma syndrome and its management. J Surg Oncol 9:419–424

Klöppel G, Seifert G, Heitz Ph (1979) Endokrine Pankreastumoren. Morphologie und Syndrome. Dtsch Med Wochenschr 104:1571–1577

Kramer S, Machina T, Marcus R (1976) Metabolic studies in the malignant glucagonoma syndrome. Diabetes 25:(Suppl 1), 370

Krebs A, Teuscher A, Armagni C (1978) Syndrome de glucagonome: Manifestations cutanées. Ann Dermatol Venerol (Paris) 105:637–639

Largiadèr F (1977) Endokrin aktive Pankreasgeschwülste. Helv Chir Acta 44:747–756

Larsson LI, Sundler F, Grimelius L, Hakanson R, Holst J (1973) Immunohistochemical demonstration of glucagon in an A_2-cell carcinoma. Experientia 29:698–699

Leclere J, Vicari F, Laurent J, Jeanpierre R, Floquet J, Grignon G, Hartemann P (1977) Tumeur insulaire avec diarrhée et diabète (glucagonome?) associée àun hyperparathyroidisme. Ann Endocrinol (Paris) 38:153–154

Leichter SB, Pagliara AS, Greider MH, Pohl S, Rosai J, Kipnis DM (1975) Uncontrolled diabetes mellitus and hyperglucagonemia. Am J Med 58:285–293

Lightman SL, Bloom SR (1974) Cure of insulin-dependent diabetes mellitus by removal of a glucagonoma. Br Med J 1:367–368

Lomsky R, Langr F, Vortel V (1969) Demonstration of glucagon in islet cell adenomas of the pancreas by immunofluorescent technic. Am J Clin Pathol 51:245–250

Mallinson CN, Bloom SR, Warin AP, Salmon PR, Cox B (1974) A glucagonoma syndrome. Lancet 1–5

Mallinson CN, Bloom SR (1974) Plasma levels of amino acids and glucagon in patients with pancreatic glucagonomas. Gut 15:340

Mallinson C, Adrian T, Hanley J, Bryant M, Bloom SR (1977) Metabolic and clinical responses in patients with pancreatic glucagonomas. Ir J Med Sci 146:37–38

Mallinson C, Bloom SR (1978) The hyperglycemic, cutaneous syndrome: pancreatic glucagonoma. In: Friesen SR (ed), Surgical endocrinology: clinical syndromes, Philadelphia Toronto, Lippincott, p 171

McGavran MH, Unger RH, Recant L, Polk HC, Kilo Ch, Levin ME (1966) A glucagon-secreting alpha-cell carcinoma of the pancreas. N Engl J Med 274:1408–1413

Patzelt C, Tager HS, Carroll RJ, Steiner DF (1979) Identification and processing of proglucagon in pancreatic islets. Nature 282:260–266

Pedersen NB, Jonsson L, Holst JJ (1976) Necrolytic migratory erythema and glucagon cell tumor of the pancreas: The glucagonoma syndrome. Acta Dermatol Venerol (Stockholm) 56:391–395

Polak JM, Bloom SR, Adrian TE, Heitz PhU, Bryant MG, Pearse AGE (1976) Pancreatic polypeptide in insulinomas, gastrinomas, vipomas, and glucagonomas. Lancet I:328–330

Ravazzola M, Siperstein A, Moody AJ, Sundby F, Jacobsen H, Orci L (1979) Glicentin immunoreactive cells: their relationship with glucagon producing cells. Endocrinology 105:499–508

Recant L, Perrino PV, Bhathena SJ, Danforth DN, Lavine RL (1976) Plasma immunreactive glucagon fractions in four cases of glucagonoma: Increased "large glucagon-immunoreactivity." Diabetologia 12:319–326

Riddle MC, Golper TA, Flechter WS, Ensinck JW, Smith PhH (1978) Glucagonoma syndrome in a 19-year-old woman. Western J Med 129:68–72

Schenck H v, Thorell JI, Berg J, Bojs G, Dymling JF (1979) Metabolic studies and glucagon gel filtration pattern before and after surgery in a case of glucagonoma syndrome. Acta Med Scand 205:155–162

Scully RE, McNeely BU (1975) Case records. N Engl J Med 292:1117–1123

Shupack JL, Berczeller PH, Stevens DM (1978) The glucagonoma syndrome. J Dermatol Surg Oncol 4:242–247

Soler NG, Oates GD, Malins JM (1976) Glucagonoma syndrome in a young man. Proc R Soc Med 69:429–431

Sternberger LA (1979) Immunochemistry, 2nd edn Wiley, New York, Chichester, Brisbane, Toronto

Strauss GM, Weitzman SA, Aoki TT (1979) Dimethyltriazenoimidazole Carboximide therapy of malignant glucagonoma. Ann Int Med 90:57–58

Sturner WQ (1972) Sudden death from non-insulin secreting islet cell tumor of the pancreas ("Glucagonoma"). Hum Pathol 3:113–119

Sweet RD (1974) A dermatosis specifically associated with a tumor of pancreatic alpha cells. Br J Dermatol 90:301–308

Swenson KH, Amon RB, Hanifin JM (1978) The glucagonoma syndrome. A distinctive marker of systemic disease. Arch Dermatol 114:224–228

Teuscher A, Studer PP, Krebs A, Berger M, Aberhard P (1979) Diabetesverlauf und klinisches Bild bei Glucagonom. Schweiz Med Wochenschr 109:1273–1280

Tiengo A, Fedele D, Marchiori E, Nosadini R, Muggeo M (1976) Suppression and stimulation mechanism controlling secretion in a case of islet-cell tumor producing glucagon, insulin, and gastrin. Diabetes 25:408–412

Unger RH, Eisentraut A, Lochner JD (1963) Glucagon-producing tumors of the islets of Langerhans. J Clin Invest 42:987–988

Valverde I, Lemon H, Kessinger A, Unger RH (1976) Distribution of plasma glucagon immunoreactivity in a patient with suspected glucagonoma. J Clin Endocrinol Metab 42:804–808

Warin AP (1974) Necrolytic migratory erythema with carcinoma of pancreas. Proc Soc Med 67:24–26

Weir GC, Horton ES, Aoki TT, Slovik D, Jaspan J, Rubenstein AH (1977) Secretion by glucagonomas of a possible glucagon precursor. J Clin Invest 59:325–330

Weir GC, Novelline RA (1977) The glucagonoma syndrome. Am Fam Physician 16:83–84

Wilkinson DS (1971) Necrolytic migratory erythema with pancreatic carcinoma. Proc R Soc Med 64:26–27

Wilkinson DS (1973) Nekrolytic migratory erythema with carcinom of the pancreas. Trans St Johns Hosp Dermatol Soc 59:244–250

Woodtli W, Hedinger Chr, Amman R, Zimmermann K, Säuberli H (1976) Glucagon-produzierende Inseladenomatose des Pankreas mit polyendokriner Symptomatik. Schw Med Wochenschr 106:749–754

Woodtli W, Hedinger Chr (1977) Inselzelltumoren des Pankreas und ihre Syndrome. Schw Med Wochenschr 107:685–693

Woodtli W, Hedinger Chr (1978) Inselzelltumoren des Pankreas und ihre Syndrome. Schweiz Med Wochenschr 108:1997–2007

Yoshiga T, Okuno G, Shinji Y, Tsujii T, Nishikawa M (1966) Pancreatic A-cell tumor associated with severe Diabetes mellitus. Diabetes 15:709–713

Zhdanov VC (1956) Diabetes and malignancy of islet cells in pancreas (in Russian). Arch Patologii (Moskva) 18:92–93

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