Clinico-pathological Conference

A 20-year-old man with recurrent abdominal pain and vomiting since the age of 5 years

SIR GANGA RAM HOSPITAL, NEW DELHI

THE CASE

A 20-year-old man presented to Sir Ganga Ram Hospital (SGRH) with complaints of recurrent abdominal pain and vomiting since the age of 5 years. The pain was in the epigastrium and radiated to the back. Investigations at the time of onset of symptoms did not reveal any abnormality, and he was given analgesics. In 1998, when he was 11 years old, he underwent an endoscopic retrograde cholangiopancreatogram (ERCP), which revealed changes consistent with chronic pancreatitis. He was started on proton-pump inhibitors and pancreatic enzyme supplements. Two years later, he underwent stenting of the pancreatic duct with three changes of stents in the subsequent year. A year later, in 2001, when he was 14 years old, he developed diabetes and was treated with insulin. Since 2002, he had been followed up at SGRH and his pancreatic duct stent had been changed many times. In February 2006, the pancreatic stent was removed and he had complete relief from pain. However, 4 months later, he presented with episodes of weakness and sweating. Investigations at this time showed the following:

Time	Blood sugar (mg/dl)	Insulin (<40 mU/ml)	C-peptide (1.1–5 ng/ml)
Random	36	7.4	1.69
Fasting	34	14.26	2.44

His insulin was stopped but he had repeated episodes of hypoglycaemia. He was further investigated and an ultrasound revealed a calculus in the lower pole of the left kidney and an isoechoic pancreas with evidence of intraductal calculi. An MRI (Fig. 1) showed a hyperintense lesion in the mid-body of the pancreas on T2-weighted images, but not on T1-weighted images. The main pancreatic duct was 6 mm in diameter in the head and proximal body of the pancreas, and 4 mm in the distal body. A CT scan of the abdomen (Fig. 2) showed an atrophic pancreas with multiple foci of calcification. A biphasic scan did not reveal any focal lesion. An endoscopic ultrasound showed a hyperdense lesion in the body of the pancreas along with changes suggestive of chronic calcific pancreatitis. He had been

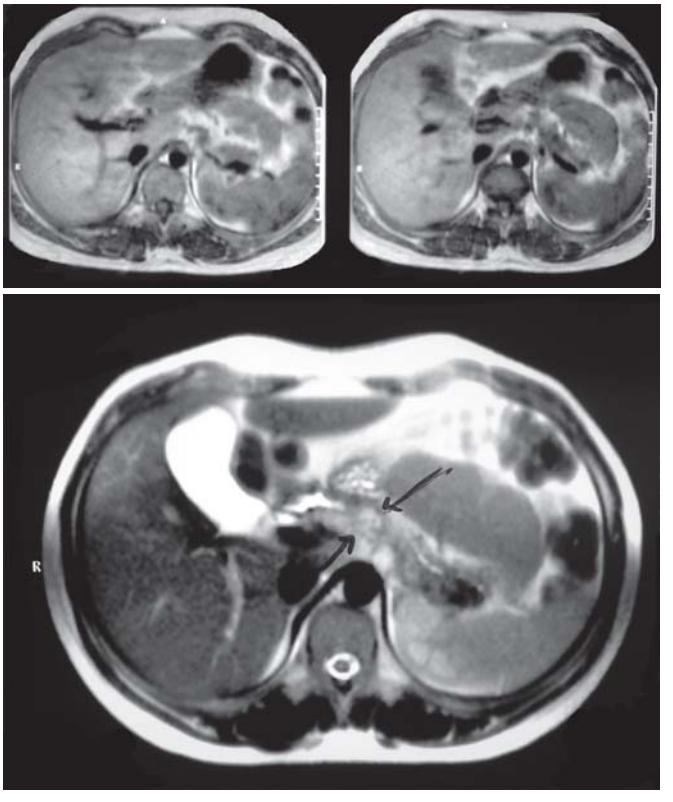

FIG 1. MRI showing a lesion in the mid-body of the pancreas on T2-weighted images

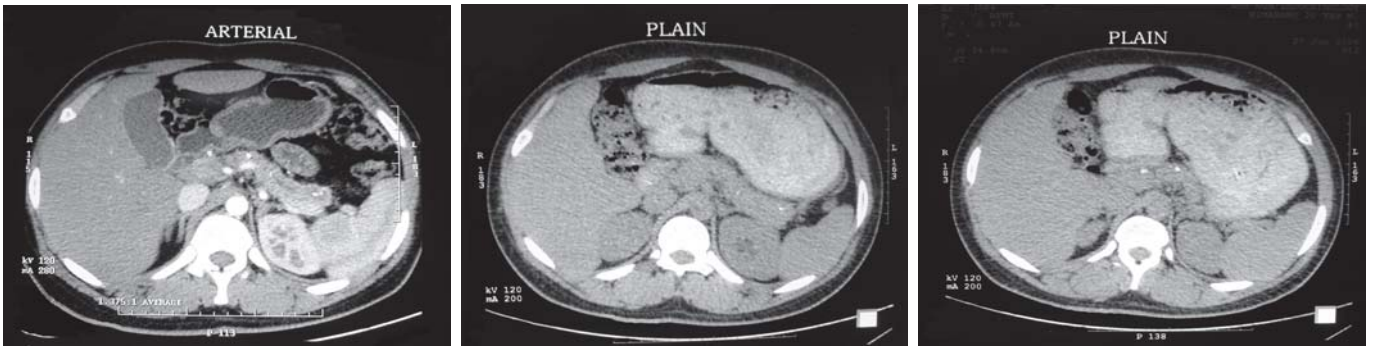

FIG 2. Abdominal CT scan before the first operation

treated for pulmonary tuberculosis in 2004. His father, who also had pancreatitis, had diabetes and died during an episode of hypoglycaemia.

In June 2006, the patient underwent a laparotomy and an excisional procedure was done. He had an uneventful post-operative recovery and was discharged on postoperative day 10. He remained asymptomatic for 3 months following the operation but again started having recurrent episodes of giddiness and sweating. Investigations showed a blood sugar of 45 mg/dl, an insulin level of 355 mU/ml and a C-peptide level of 3.5 ng/ml. As the tail of the pancreas and spleen were not seen in the CT scan done after the operation (Fig. 3), it was surmised that he had probably undergone a distal pancreatectomy and splenectomy. The arterial and venous phases in this CT scan showed a hyperdense area that became isodense but no hypervascularity was seen and there was no retroperitoneal lymphadenopathy. A plain X-ray of the abdomen showed a hyperdense lesion with calcific foci in the residual pancreas. All the other investigations during his hospital stay were normal. In October 2006, he underwent a second laparotomy, 4 months after his previous surgery.

DIFFERENTIAL DIAGNOSIS

DR J. D. WIG: This patient developed diabetes nearly 15 years after the initial episode of abdominal pain and nearly 10 years after the documentation of chronic pancreatitis, which was managed with insulin. In June 2006, he had a blood sugar level of 36 mg/dl with raised insulin and C-peptide levels. He underwent a resection of the pancreas at the end of June, the exact extent and amount of which are unclear. Two weeks after the surgery, his fasting blood sugar was 94 mg/dl with normal insulin and C-peptide levels. However, he subsequently presented with episodes of weakness and sweating. Investigations revealed hypoglycaemia; he had repeated attacks despite stopping insulin.

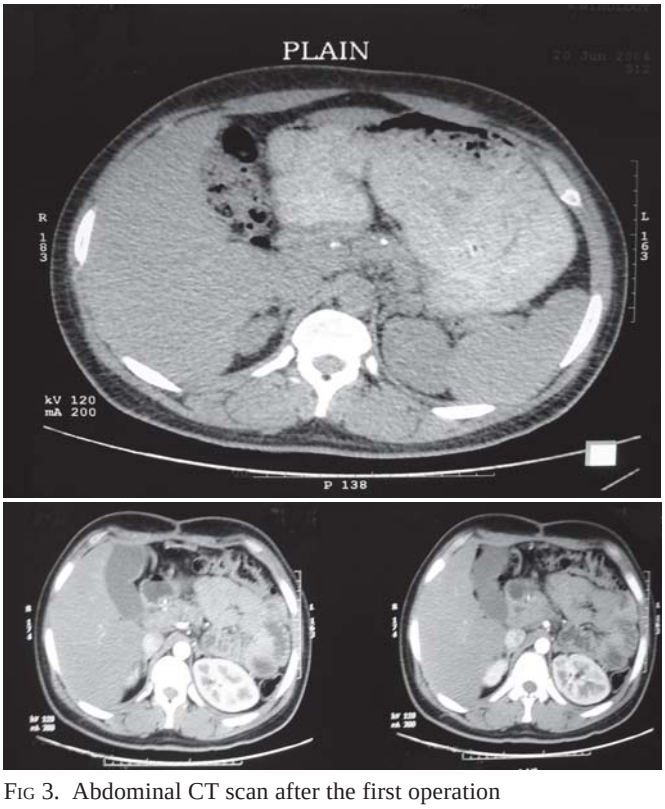

FIG 3. Abdominal CT scan after the first operation

After the surgery, he was asymptomatic for 3 months. His random blood sugar level in September 2007, nearly 3 months after surgery, was 65 mg/dl with high insulin and low C-peptide levels.

We need to consider the causes of chronic pancreatitis in this patient. The first possibility would be tropical calcific pancreatitis based on his symptoms in childhood and imaging findings of an atrophic pancreas, calculi and a prominent pancreatic duct. The second would be hereditary pancreatitis in view of his father also having pancreatitis and diabetes.

Chronic calcific pancreatitis of the tropics presents with abdominal pain, pancreatic calcification and diabetes. This term is used by gastroenterologists. The preferred term used by diabetologists is fibrocalculus pancreatic diabetes, a term introduced by the World Health Organization (WHO). The disease may occur at any age and the clinical profile is one of abdominal pain, pancreatic calculi, diabetes and steatorrhoea. However, all these features may not be present in every patient. Our patient had 3 of the 4 described features. Diabetes is an inevitable consequence of the disease, occurring a decade or two after the first episode of abdominal pain. Fibrocalculus pancreatic diabetes may affect many members of the same family. One study found 17 families with two or more relatives having evidence of pancreatitis.[1] In a recent study, nearly 8% of patients were shown to have a family history, which suggests, but does not necessarily prove, a hereditary aetiology.[2] C-peptide levels in these patients indicate partial preservation of pancreatic beta-cell function.[3] In the 1960s and 1970s, it was reported that patients with this entity developed abdominal pain in childhood, diabetes in adolescence and diarrhoea with complications of diabetes or chronic pancreatitis by early adulthood, and died early. These patients now survive much longer, perhaps due to better control of their diabetes. In patients with chronic calcific pancreatitis, spontaneous hypoglycaemia has been reported as well as an increased risk of malignancy, especially adenocarcinoma, with an incidence of up to 24%.[4] This is unlikely in this patient as he was re-operated nearly 3 months after the first surgery. If the previous resected specimen had shown a carcinoma, he would have been operated upon much earlier.

Familial hereditary pancreatitis is diagnosed in childhood or adolescence and presents with bouts of abdominal pain. This condition is increasingly being recognized and must be suspected in patients with a family history of pancreatitis. More than 80% of affected individuals develop pancreatic disease before the age of 20 years. Patients with hereditary pancreatitis have abdominal pain, diabetes and malnutrition. The risk of pancreatic cancer after 50 years of age has been estimated to be 53% higher than that in the general population.[5] A second surgery in this patient might have been done to remove the entire pancreas and eliminate the source of the problem. The ductal calculi seen in this patient are extremely uncommon in hereditary pancreatitis.

The hyperintense lesion seen on T2-weighted MRI may be because of a tumour, either neuroendocrine or carcinoma, or an inflammatory lesion such as focal pancreatitis or tuberculosis. One can rule out tuberculosis in the absence of retroperitoneal lymphadenopathy on various imaging studies and the fact that the patient had had a full course of anti-tubercular drugs when he developed pulmonary tuberculosis. Neuroendocrine tumours can be seen primarily on T2-weighted images on MRI, as seen in this patient, in whom they appeared as hypervascular lesions compared with the surrounding pancreas. The problem with CT

is that it images only about 40% of neuroendocrine tumours.[6] Functional pancreatic tumours would have led to a rise in insulin and C-peptide levels with a low glucose level. This patient had hypoglycaemia but normal insulin and C-peptide levels before surgery, raising doubts about the possibility of an insulinoma. The plasma glucose levels revert to normal and hypoglycaemia may not recur after a successful surgical excision. There may be a mesothelioma or similar tumour as part of the multiple endocrine neoplasia (MEN)-1 syndrome, producing insulin-like substances causing hypoglycaemia as well as normal C-peptide levels. However, the patient's insulin levels were high and a review of the imaging studies did not show any evidence of an endocrine tumour or parathyroid hyperplasia. In the MEN-1 syndrome, parathyroid hyperplasia is reported in 94% of patients, pituitary adenoma in 35%, pancreatic endocrine tumours in about 50%, and 10%–25% have non-functioning endocrine tumours. As we cannot exclude a functional endocrine tumour based on the available laboratory work-up and/or imaging, we should consider the MEN-1 syndrome in this patient. He had pancreatic calcification as well as renal calcification, which may be explained by hyperparathyroidism. However, this diagnosis cannot be substantiated because the serum calcium and parathyroid hormone levels were not available and an ultrasound of the neck was not done. A recent study has shown that functioning endocrine tumours were present in 64% and non-functioning tumours in 36% of those with the MEN-1 syndrome.[7]

The next problem is to try and explain why this patient had postoperative recurrent hypoglycaemia. There is a long list of conditions that can cause hypoglycaemia. Insulinoma is only one of the many causes; others include inadvertent or deliberate administration of insulin, other extrapancreatic tumours and ingestion of oral hypoglycaemic agents. In insulinoma, the characteristic findings are low blood sugar, raised insulin and serum C-peptide levels, and a negative sulphonylurea screen. However, neoplasms even as large as 10 mm may escape detection by conventional imaging. Therefore, there is a need to do a diagnostic procedure capable of detecting or excluding an insulinoma with greater certainty. In our patient, the pre-operative serum C-peptide levels were normal and, following the first operation, were below normal levels. The preoperative serum insulin levels were normal and the postoperative levels were high. However, the importance of serum C-peptide levels is not very clear. A report published in 2007[8] emphasized the unusual features of an insulinoma, including a positive insulin response to secretin and decreased C-peptide levels. In this context, an intravenous secretin study would have been useful. Another study[9] suggests that C-peptide but not insulin can be selectively metabolized within human insulinoma cells. Responsiveness to secretin and glucose in patients with insulinoma might be associated with multiple and/or malignant tumours. Moreover, insulinoma rarely occurs in adolescence; the mean age at presentation is 40–50 years and 60% occur in women. However, a malignant insulinoma has been reported in a 10-year-old girl who presented with an episode of hypoglycaemia.[10] I am not considering the possibility of a malignant insulinoma in this patient because, if it was present, he would have had surgery much earlier.

This patient had hyperinsulinaemic hypoglycaemia after the first surgery. Thus, he probably had a syndrome of non-insulinoma and pancreatogenous hypoglycaemia from diffuse beta-cell hyperfunction. In this syndrome, symptoms usually occur after meals and never in the food-deprived state in contrast to those with insulinoma. However, we do not know from the available records whether the symptoms occurred post-prandially. Such patients have a negative prolonged fasting test and no lesion is seen on radiological studies. Hyperinsulinaemic hypoglycaemia is important in patients with diffuse nesidioblastosis which may coexist with a non-functional tumour of the pancreas. Nesidioblastosis is rare and is derived from the pancreatic duct epithelium. Its clinical and histopathological features are not very well known. In a study from Germany published in 2007,[11] 4 of 128 patients suffering from hyperinsulinaemic hypoglycaemia were found to have diffuse nesidioblastosis. The remaining patients had insulinomas. Resection of up to 90% of the pancreas relieved 2 of the 4 patients of their symptoms. Treatment consists of operative reduction of the cell mass but the extent of pancreatic resection required is hard to judge and there is a thin line between successful treatment, persistence of the disease and pancreatic endocrine insufficiency. Is it possible that following the first operation, a diagnosis of nesidioblastosis was confirmed histologically and a second operation, a subtotal pancreatic resection was performed? We do not have the findings at the second laparotomy and hence it is difficult to be sure.

The disease persisted in spite of pancreatic resection and the patient developed recurrent hypoglycaemia. Step sectioning of the pancreas may have helped to prove the presence of an endocrine pancreatic neoplasm. The major criteria of diffuse nesidioblastosis include macroscopic, microscopic and immunohistochemical exclusion of an insulinoma in addition to three other criteria (hypoglycaemic symptoms, low blood sugar and reversal of symptoms after ingestion of glucose). However, the diagnosis is established postoperatively on histopathological examination. A study published in 2005[12] reported that diffuse nesidioblastosis in adults is not as rare as had been thought earlier, and more and more reports of this entity are appearing in the literature. Considering all the available information, it will be difficult to suggest one or another possible diagnosis. The first possibility is an insulinoma, based on the hyperintense lesion on the MRI, which favours a functioning neuroendocrine tumour. Pancreatic calcification, a renal stone and an endocrine tumour, all as part of the MEN-1 syndrome, is difficult to postulate. The other possibility that I would consider is nesidioblastosis in the setting of chronic calcific pancreatitis to explain the postoperative hyperinsulinaemia and hypoglycaemia.

DR J. D. WIG'S DIAGNOSIS

Chronic pancreatitis with insulinoma or nesidioblastosis

CLINICAL DISCUSSION

DR N.C. NAYAK: Thank you, Dr Wig, for a lucid and complete discussion on this difficult case. I would request the clinical unit for their working diagnosis.

DR SURENDER KUMAR: This young man with a diagnosis of chronic pancreatitis was being looked after by the Gastroenterology department for over a decade. He developed pancreatic diabetes which was being managed with insulin. We were asked to see this patient because he started having episodes of hypoglycaemia. Hence, we started by reducing the insulin dose presuming that there may have been some regeneration of the beta cells. Over a period of time, the insulin was stopped. However, after about 3–4 months, despite stopping the insulin, the patient started having episodes of mild hypoglycaemia, which he was able to manage by eating, but gradually the severity and frequency of the hypoglycaemia increased. We then

suspected that we were missing something. It was not exogenous insulin causing these episodes as insulin had been stopped a few months ago. We advised the patient that whenever he got symptoms of hypoglycaemia, he should test his blood sugar and immediately try to give us a sample of blood so that we could estimate the C-peptide and insulin levels. The patient continued to use a glucometer and recorded blood sugar levels as low as 20–30 mg/dl. Intake of sugar would reverse his symptoms. The Whipple criteria for insulinoma were being fulfilled. However, since he was recovering and the tests cost money, he stopped getting his blood tested. We gradually realized that something more radical had to be done. When the patient became symptomatic, his family treated him first and then took him to a nearby laboratory where a blood sample was taken. Later, the patient's hypoglycaemic episodes could not be managed at home and he was admitted so that the episodes of hypoglycaemia could be studied. The insulin level was found to be high and thus we were confident that we were dealing with hyperinsulinaemic hypoglycaemia. We did consider the possibility of a MEN-1 syndrome but the parathyroid and T3 hormone levels were normal. We then did imaging studies that suggested a doubtful lesion in the pancreas. We thought that removal of this lesion would solve his problem. However, following the surgery, after an initial improvement, the symptoms recurred.

DR T. B. S. BUXI: In the original MRI (Fig. 1), no mass was seen on T1-weighted images but the T2-weighted images showed a hyperintense lesion at the junction of the head and body of the pancreas. The pancreatic duct was dilated and the rest of the pancreas could be visualized. These findings suggest an insulinoma or tumour. The CT scan also shows similar findings (Fig. 2) with the lesion seen in the same location as on the MRI.

DR S. NUNDY: The first procedure was done by another surgeon who said that he could not localize the tumour intraoperatively even after doing an intraoperative ultrasound. Hence, he did a 'blind' distal pancreatectomy and splenectomy. We could argue that this was an incorrect procedure. However, in our limited experience of 4 such patients with insulinoma-like symptoms in whom we could not localize the lesion intraoperatively even with an intraoperative ultrasound, blind distal pancreatectomy led to 3 of them becoming symptom-free. However, on pathological examination, an insulinoma was not found in any of them.

When this patient's symptoms recurred, we were very reluctant to operate again because we would have had to do a Whipple pancreaticoduodenectomy. He had already undergone a distal pancreatectomy and was being managed conservatively with glucose. However, he came again to the emergency services in hypoglycaemic coma, was admitted and required large doses of glucose to maintain his blood sugar. Dr Surender Kumar said that we should go ahead and do a completion total pancreatectomy because a 95% pancreatectomy may have resulted in a recurrence of his hypoglycaemia. Therefore, we did a Whipple procedure. It was difficult but after the procedure his blood sugars became normal and now, about 6 months postoperatively, he is well.

DR N. C. NAYAK: The case is open for discussion. Any questions to the clinical discussant?

DR S. NUNDY: How often does hypoglycaemia occur in chronic pancreatitis? The usual symptoms are pain, hyperglycaemia and malabsorption but here we have chronic pancreatitis with episodes of hypoglycaemia. How do you reconcile both of these because you have given a differential diagnosis of hypoglycaemia but not hypoglycaemia in the setting of chronic pancreatitis?

DR J. D. WIG: I think there is a report from Kochi which mentions this association, i.e. chronic calcific pancreatitis with hypoglycaemia due to nesidioblastosis. What is the sensitivity of MRI compared with a CT angiography? Is it better to do a conventional angiogram?

DR T. B. S. BUXI: In a conventional angiogram we try to detect increased vascularity. To pick up such lesions, a superselective angiogram would be needed to detect a minimal blush. The detection rates of CT angiography using the current multislice scanners are about 60%–70%; an increase from about 40% earlier. There are very few false-positive findings.

DR J. D. WIG: I showed the scans to many radiologists at my institution but they were unable to detect the lesion on the scans.

DR T. B. S. BUXI: The unit that does the CT scan has an advantage. It can view a thousand slices on the monitor.

DR N. C. NAYAK: Dr Buxi, how often is the converse true; that you detect a lesion radiologically but the pathologist does not?

DR T. B. S. BUXI: If the pathologist cannot find the lesion seen on imaging, the possible explanation is that the lesion was not removed during the surgical procedure or was not 'hit' while doing a fine needle aspiration.

DR SURENDER KUMAR: The most sensitive method of localizing an insulinoma is a peroperative ultrasound and palpation of the pancreas by the surgeon who is operating because feeling with experienced fingers is more sensitive in picking up tumours than conventional investigations.

DR N. C. NAYAK: This is still short of seeing all the slices under the microscope.

DR S. NUNDY: Though we do not have much experience of surgery for insulinoma, I must have operated on at least 30–40 patients with a suspected insulinoma and tried to feel the lesion. I find it very difficult to do so in a normal pancreas and in a patient with chronic pancreatitis it must be even more difficult. The surgeon who did the first surgery said that on intraoperative ultrasound they found a suspicious lesion in the head but as preoperative imaging had suggested something in the distal pancreas and they could not confirm the lesion in the head of pancreas they went ahead and did a distal pancreatectomy. I think he must have cut the pancreas just to the left of the superior mesenteric vein and on the right of the superior mesenteric artery. This would have included the lesion found on imaging.

DR K. C. MITTAL: The tactile sensations of surgeons are disappearing because of endoscopic and laparoscopic procedures.

DR SURENDER KUMAR: Books still mention that the fingers of a surgeon are better at localizing pancreatic tumours.

DR J. D. WIG: I agree with Dr Nundy. It would be difficult to find a lesion in a pancreas that is very hard.

PATHOLOGICAL DISCUSSION

DR N. C. NAYAK: We will now let the cat out of the bag. The specimens came in two containers on separate occasions. The first one, I understand, was actually from the area where the nodule was seen on imaging and the second specimen came from the distal part of the pancreas. The histological appearance on multiple sections was identical. There was evidence of chronic pancreatitis with marked chronic inflammation around the pancreatic ducts (Fig. 4). There was almost complete loss of elements in the exocrine pancreas. Scattered throughout were areas of calcification. Thus, there was marked sclerosis, loss of exocrine pancreatic tissue, dilatation of the ducts and chronic

inflammation. In addition, in many areas there were variable-sized islands of islet cells of Langerhans (Fig. 5). They were irregularly distributed focal aggregates of islet tissue. There were also some areas in the first specimen where there were foci of acute inflammation. We searched very carefully for a tumour but did not find any. On the other hand, there were only islands of islet cell proliferation. In the second specimen, we saw the same changes both in the head of the pancreas as well as the tail, the same morphological alterations, extensive sclerosis, more or less complete loss of exocrine pancreatic tissue and islands of islet tissue. These islands were budding out of the duct epithelium, which was previously referred to as nesidio-dysplasia. That term has been dropped now and this is a part of nesidioblastosis where one sees the islet cells arising from the outer aspect of the ducts as individual cells as well as small leaves of cells. We did various immunostains for beta cells, alpha cells, gastrin-producing cells, etc. but in these specimens the pathological picture throughout the pancreas was of marked calcific chronic pancreatitis and nesidioblastosis, which Dr Wig has already mentioned, along with some publications on this type of lesion in the pancreas. Therefore, the pathological diagnosis in both these specimens was chronic calcific pancreatitis with diffuse nesidioblastosis. There was no islet cell tumour, small or large.

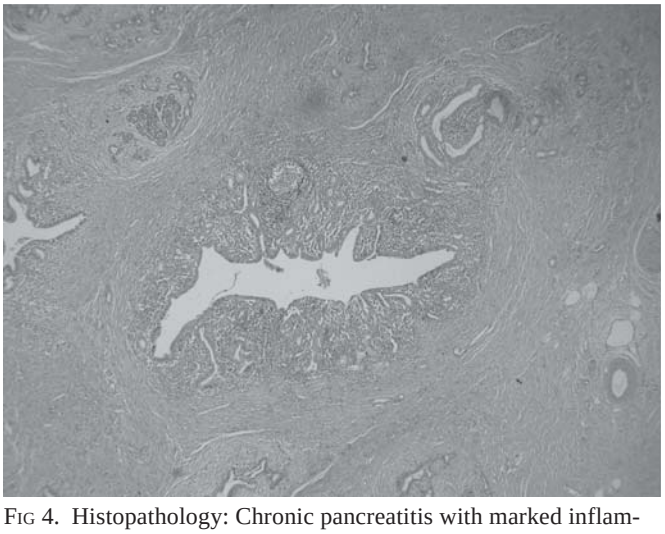

FIG 4. Histopathology: Chronic pancreatitis with marked inflammation around the pancreatic ducts

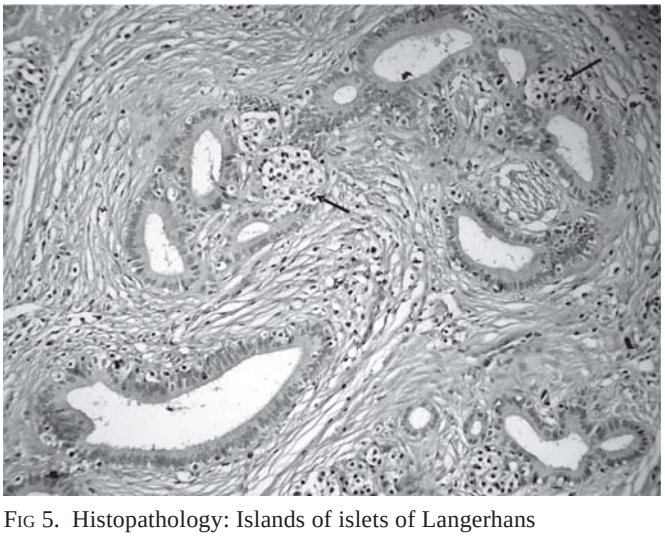

FIG 5. Histopathology: Islands of islets of Langerhans

Nesidioblastosis is a term for hyperinsulinaemic hypoglycaemia attributed to excessive functioning of the pancreatic beta cells, which have an abnormal microscopic appearance. These include islet cell proliferation, enlargement and dysplasia. Beta cells bud from islet cells near the ducts. The size of the islet cells vary, but there is no true tumour. Nesidioblastosis, as currently recognized, is generally of two types. The congenital type is common and has a genetic background; the adult type is rather rare. In the late 1980s, it was recognized that congenital hyperinsulinaemic hypoglycaemia was not due to islet cell increase since infants and adults with this structural abnormality may not have the syndrome of hyperinsulinaemic hypoglycaemia. The present case is not one of congenital nesidioblastosis and falls into the adult type because our patient also had chronic calcific pancreatitis and at the age of 15 years had diabetes mellitus rather than episodes of hypoglycaemia. Almost all adult cases of nesidioblastosis have a small islet cell tumour but we very carefully examined the entire pancreas available to us on two occasions and there was no such tumour. On the other hand, there was diffuse nesidioblastosis throughout the pancreas.

A publication in *Surgery* in February 2007 reported,[11] as has been mentioned by Professor Wig, 128 cases of adults with hypoglycaemic hyperinsulinaemic syndrome. Only 4 (about 3%) had diffuse nesidioblastosis while the rest had small islet cell tumours. Our case is one of chronic calcific pancreatitis of the familial type, which is described as familial idiopathic or the so-called tropical or chronic calcific pancreatitis because this young man had been symptomatic since early childhood and developed diabetes mellitus later. His father also had chronic calcific pancreatitis and diabetes mellitus. The patient's father died, presumably during one of the episodes of hypoglycaemia. However, we do not know whether he had had episodes of these after administration of insulin or whether these episodes occurred spontaneously. A morphological study of 27 cases of chronic calcific pancreatitis from Italy in 1990 showed prominent nesidioblastosis in 6 of 7 patients who had moderate-to-severe sclerosis. Therefore, the presumptive sequence of events is as follows: chronic pancreatitis leads to sclerosis and once there is extensive sclerosis, this extends into the islet cells; there is islet cell loss which results in diabetes mellitus followed by islet cell proliferation, probably as a compensatory mechanism, which then goes out of control.

Nesidioblastosis ultimately gives rise to a hyperinsulinaemic hypoglycaemic syndrome. Sometimes, these cells may not produce enough beta cells but produce other cells, in which case the syndrome may not occur. Lately, it has been reported that some patients who had undergone gastric bypass surgery for obesity developed typical nesidioblastosis and hyperinsulinaemia.[12] We know that some of these patients do develop cirrhosis of the liver of the type that is morphologically indistinguishable from alcoholic cirrhosis and this has been attributed to possibly some toxic absorption from the shunted gastrointestinal tract, which damages the liver in a manner similar to alcohol. Some of these patients also develop nesidioblastosis. There is an interesting report from Brazil about an experimental counterpart of nesidioblastosis after chronic pancreatitis. When rats were injected intravenously for 30 days with purified venom of the Brazilian scorpion *Tityus serrulatus*, they developed chronic calcific pancreatitis and symptomatic nesidioblastosis.[13] The recommended treatment, as has already been suggested for symptomatic nesidioblastosis, is a 90%–95% pancreatectomy.

FINAL DIAGNOSIS

Familial chronic calcific pancreatitis with nesidioblastosis and hyperinsulinaemic hypoglycaemia

CONCLUDING DISCUSSION

DR J. D. WIG: A recent study[14] evaluated 15 adult patients with nesidioblastosis. This entity is not uncommon in adults and very difficult to diagnose on the operating table. Multiple sequential slicing of the pancreas, which is known as graded pancreatectomy, might help. However, in the present case, whatever was done was perfectly justified. The diagnosis was made only on final histopathological examination.

DR S. NUNDY: What is peculiar in this patient is that after the operation the insulin requirement was low and his blood sugar was very well controlled. I thought after a total pancreatectomy there would be brittle diabetes.

DR SURENDER KUMAR: The problem comes when there is insulin resistance and then the requirement is variable. When the entire pancreas is gone, the requirement is fixed. Before pancreatectomy, there is infection, pain and multiple problems which affect the insulin requirement but once the patient is stable and there is no insulin resistance, he has a fixed requirement of 25–30 units per day. In this patient my hypothesis is that there was a low insulin requirement because some pancreatic tissue and viable islet cells might have been left behind after the 'total' pancreatectomy.

DR P. S. GUPTA: Is nesidioblastosis a premalignant condition?

DR N. C. NAYAK: Yes, in younger age groups, it has a malignant potential but in adults, there is more of hyperplasia and only 5%–7% patients of MEN develop a malignancy later.

DR K. C. MITTAL: Dr Nayak, can a small tumour be missed when you take serial sections?

DR N. C. NAYAK: In this case, multiple thin sections have been taken.

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