Case Reports

A CASE OF THE ZOLLINGER-ELLISON SYNDROME WITH ASSOCIATED SPLENOMEGALY

W. R. O'FLYNN, M.B., B.Ch., F.R.C.S.

Senior Surgical Registrar; Royal Marsden Hospital, London, S.W.3

MANY case reports of the Zollinger-Ellison syndrome have appeared since the original description in 1955. The following case is considered worthy of reporting because unusual features made diagnosis difficult, and treatment hazardous.

Case Report

The patient (F. C., R.M.H. No. 038695), a male, aged 49, presented elsewhere with a duodenal ulcer of six months' duration, for which antecolic partial gastrectomy was performed on 23.6.58. Epigastric pain recurred within three months. Barium meal examination revealed an anastomotic ulcer, which was treated by excision of the ulcer with a further gastric resection, and again an antecolic anastomosis. His symptoms recurred after one month, and he was eventually referred to the Royal Marsden Hospital. Barium-meal examination then showed an anastomotic ulcer 3 cm. in diameter in the jejunum 2 cm. below the stoma. Night gastric secretion tests yielded 106 mEq. free HCl and 246 mEq. total acid; bile being present in quantity. He was admitted on 9.5.59 complaining of severe persistent epigastric pain, for which routine medical therapy was instituted without success.

Investigations: Hb 18.1g. (128%), w.b.c. 15,300/cu. mm., neutrophils 88.4%, lymphocytes 6.4%. There was no history of vomiting or abstaining from oral fluids to account for the high haemoglobin reading and its further elucidation was not undertaken at this stage because it was considered that his severe epigastric pain and tenderness demanded urgent surgical intervention.

Operation: He was explored on 11.5.59 when the presence of a large anastomotic ulcer was confirmed. This had penetrated the jejunum and become adherent to the parietal peritoneum of the anterior abdominal wall—the ulcer base being left on the peritoneum after mobilisation. The spleen was judged to be three times the normal size, extending to the left costal margin. No abnormality was detected in the pancreas. The ulcer was oversewn after mobilisation and a transhiatal vagotomy performed.

Progress: Post-operative progress was uneventful, with dramatic relief of his epigastric pain. At the time of his discharge from hospital on 17.7.59 he was symptom-free, and enjoying a normal diet.

Haematological Investigations: These were instituted post-operatively, and are set out below:

24.6.59: Hb., 14.8g. (100%), w.b.c. 15,100/cu. mm., neutrophils 89.0%, lymphocytes 5.0%, PCV 45%, r.b.c. 5,900,000/cu. mm., MCV 76 cu.μ, MCH 25 γγ, MCHC 33%, platelets 840,000/cu. mm. 29.6.59: **Sternal marrow aspirate:** 'Cellular particulate marrow aspirated easily. The marrow contains little fat and is

evidently very active, without any obvious abnormality in any series of cells. L:E ratio c. 2:1. Megakaryocytes are conspicuous and rather large, but not excessive in numbers. Basophil precursors are rather plentiful. This marrow is compatible with a disorder in the polycythæmia vera—haemorrhagic thrombocythæmia group.' **Marrow section:** 'Section confirms the hypercellularity of the marrow and shows that there is an excess of megakaryocytes.'

In view of these findings, and of the splenomegaly, it was considered that the diagnosis of polycythæmia vera was well established. 4.7 mc. of ³²P were administered on 1.7.59.

Progress: The patient did not attend again until 16.1.61. Nine months before (11 months after his vagotomy) he had noted an episode of severe diarrhoea which had lasted for two months. It had then cleared for two months, after which it had recurred, and persisted until the time of his attendance. The bowels tended to open after meals; the stools were loose and offensive, and occasionally contained undigested food. For four months the diarrhoea had been associated with severe lower abdominal pain which was colicky in nature, but there had been no recurrence of his original epigastric pain. He was readmitted to the Royal Marsden Hospital.

On examination, he was obviously wasted, having lost 22 lb. in weight, and was having frequent bouts of severe colicky lower abdominal pain. General examination was negative. The abdomen was diffusely tender, with hyperactive bowel sounds. No splenomegaly was detected. Rectal examination revealed loose offensive stools.

Investigations: Hb. 13.3g. (90%), w.b.c. 6,200/cu. mm., neutrophils 88.0%, lymphocytes 10.0%, platelets 337,000/cu. mm., Serum proteins 6.4 g/100 ml., albumin 3.9g., globulin 2.5g. Examination of stools: no excess of neutral fat. Night gastric secretion: 310 mEq. free HCl, 828 mEq. total acid, much bile was present. Barium meal: there was a large ulcer situated anteriorly in the efferent loop of the jejunum just below the anastomosis. A jejuno-colic fistula was present which arose at the site of the ulcer.

Operation: At further exploration on 23.2.61 the upper abdominal cavity was obliterated by dense adhesions. The jejuno-colic fistula was isolated and after separation of jejunum from colon, the defect in the latter was closed. A further gastric resection was then undertaken, this being rendered most arduous by dense adhesions, by the spleen which was still estimated to be three times the normal size, and by grossly dilated veins in the gastro-splenic ligament, and about the cardia. It was remarked at the time that these veins resembled the veins seen in this region in cases of portal hypertension. As dissection proceeded, a tumour 6.5 cm. in diameter was noted in the splenic

FIG. 1.—Islet cell tumour showing characteristic endocrine arrangement. H.E. x 80.

FIG. 2.—Islet cell tumour filling lumen of vein. H.E. x 80.

hilum, apparently arising from the tail of the pancreas. A sub-total gastrectomy with splenectomy and excision of the tail of the pancreas containing the tumour was performed.

The postoperative course was complicated by a severe wound infection, and by a bullous erythema multiforme with arthritis of the right wrist and of the left knee. Both conditions cleared satisfactorily before his discharge on 26.4.61. He was then well, and without symptoms.

Pathological Report: Two specimens were received. 1. Main surgical specimen comprising the spleen, 16.5 x 12 x 7.5 cm., a tumour mass in the tail of the pancreas, and attached adipose tissue and lymph nodes. The tumour measures 6.5 cm. in diameter. It is firm in consistency and the cut surface shows broad greyish bands of fibrous tissue separating softer, pinkish areas; it is not encapsulated. 2. A 'sleeve' of stomach wall 5 cm. long.

Histology The neoplasm (Fig. 1.) is a typical islet-cell tumour composed of polyhedral, cuboidal and columnar cells arranged as masses and sinuous strands in a highly vascular stroma. In many fields the tumour cells come into intimate contact with the vessel walls—a characteristic 'endocrine' arrangement. The stroma varies greatly in amount and consistency; in some areas it is scanty whilst in other parts it is abundant and either oedematous or hyaline. There is some patchy necrosis. Staining with Gomori's aldehyde-fuchsin fails to reveal any definite β granules: with Gomori's chrome-alum haematoxylin, phloxine-tartrazine technique many of the cells stain bright red, suggesting α cell differentiation. No argentaffin or argyrophil granules can be demonstrated. In the stroma at the periphery of the growth and in the adjacent lymph nodes there are a number of 'tuberculoid' granulomata, probably representing a reaction to tissue breakdown products. No metastases

FIG. 3.—Spleen. Sinusoids dilated and walls thickened. Note small Malpighian body near left lower border. H.E. x 80.

are present in the nodes but invasion of a medium-sized vein is seen (Fig. 2). Diagnosis *Islet-cell carcinoma*.

The spleen (Fig. 3) shows thickening of the sinusoidal walls and increased prominence of the littoral cells; the Malpighian bodies are rather small and are widely separated. The appearances are not typical of polycythæmia but suggest a vascular 'back-pressure' effect, possibly due to pressure of the tumour on the splenic vein.

In one of the sections prepared from the portion of stomach, there is an area of active peptic ulceration with fibrosis extending through to the serosa. The adjacent mucosa is entirely of the fundal type, and displays prominent oxyntic and zymogenic cells. There is no evidence of neoplasia.

Gastrin-like activity: A portion of the tumour, fresh and unfixed, was deep-frozen, and submitted to Professor R. A. Gregory, but no trace of gastrin-like activity could be demonstrated in it (Gregory, Tracy, French and Sircus, 1960).

Progress: The patient was admitted for review on 2.3.63 (two years after excision of his tumour). There were no symptoms, he was eating a normal diet and his bowel function was normal.

Investigations: Night secretion test: no free or combined acid present. Examination of stools for occult blood: negative. Hb 15.9 g. (107%), w.b.c. 27,200/cu. mm. neutrophils 84.0%, lymphocytes 10.5%, monocytes 5.0%. PCV 50%, r.b.c. 5,340,000/cu. mm., MCV 94 cu. μ , MCH 30 γ , MCHC 32%, platelets 2,085,000/cu. mm.

The high platelet count was confirmed and ^{32}P , (5 mc.) was administered to diminish the risk of thrombosis.

Discussion

This patient illustrates well the recurrence of ulcer symptoms, and the persistence of hyperacidity after routine gastric resection, which are features of the Zollinger-Ellison syndrome (Zollinger and Ellison, 1955).

At the time of his third exploration (the first operation undertaken at the Royal Marsden Hos-

pital) the pancreas appeared normal on palpation, the large fragile spleen and dense adhesions making exploration of the left upper quadrant very difficult. The splenomegaly together with the elevated hæmoglobin reading was considered, most probably to be a manifestation of polycythæmia vera, a condition in which approximately 15% of the cases have peptic ulceration (Fitts, Eade, Peskin and Frost, 1960). The findings in the subsequent hæmatological investigation were compatible with this diagnosis and ^{32}P was given. At the moment he has a great excess of platelets without polycythæmia and the final hæmatological diagnosis is still obscure.

It is interesting to note that vagotomy relieved his pain. The jejuno-colic fistula occurred 11 months after vagotomy, and was presumably preceded by ulceration, but there was no complaint of recurrence of his epigastric pain. The pain, when it did occur, was in the lower abdomen, was colicky in nature, and appeared to be due to his enteritis.

When he was explored for the fourth time, 20 months after his vagotomy, the large spleen again appeared, and the very large veins between the fundus of the stomach and the spleen, and about the cardia, were a striking feature. No other evidence of portal hypertension was noted, and those parts of the liver which were seen appeared normal. Liver function tests carried out after operation showed no abnormality. The tumour, which presented in the hilum of the spleen, arose from the extreme end of the tail of the pancreas, and was not a tumour arising from aberrant pancreatic tissue. It is presumed that it escaped detection previously because of its inaccessible position, and smaller size.

The splenomegaly was presumably caused by venous congestion due to occlusion of the splenic vein. In the specimen invasion of a medium-sized vein was noted (Fig. 2).

Total gastrectomy has been advocated by Zollinger and Craig (1960a and b) in the treatment of these cases, whether or not a resectable pancreatic tumour is present. This procedure was not carried out in our case, because of the patient's poor general condition, the magnitude of the surgery already undertaken, and the presence of the great dilated veins in the fundal and hiatal regions. However, a radical subtotal gastrectomy was achieved. He has remained well for two years, having now a high platelet count but no evidence of polycythæmia. The tumour being malignant, it is feared that further ulceration may occur, as metastases develop. It is proposed to estimate the night acid secretion, and to test for faecal occult blood at intervals, in an effort to anticipate further ulceration and its complications.

Summary

A case of the Zollinger-Ellison syndrome is described. A large non-beta-cell carcinoma arising in the tail of the pancreas apparently caused a 'back pressure' effect on the spleen. The resulting splenomegaly and venous engorgement made detection of the tumour difficult. The clinical problem was further complicated by an abnormal blood picture initially suggestive of polycythæmia vera.

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FOLIC ACID DEFICIENCY IN HAEMOLYTIC ANAEMIA

J. FORSHAW, M.A., M.D.(Camb.), M.R.C.P.

Consultant Physician

Hæmatology Laboratory, Sefton General Hospital, Liverpool, 15

LILIAN HARWOOD, F.I.M.L.T.

Senior Technician

FOLIC acid deficiency with a megaloblastic bone marrow picture may develop in both the acquired and hereditary types of hæmolytic anaemia (Chanarin, Dacie and Mollin, 1959). This is attributed to the demands of increased erythropoiesis, and it is particularly liable to occur when the dietary intake of folic acid is poor (MacIver and Went, 1960).

The purpose of the present paper is to describe a patient in whom an acute hæmolytic episode rapidly produced folic acid deficiency, and after spontaneous recovery of the hæmolysis the folic acid deficiency was almost completely corrected without treatment.

Case Report

A man, aged 34, was admitted to hospital in July 1962, complaining of breathlessness on exertion, lassitude and intermittent lower abdominal pain for two weeks. He had never had any previous illnesses and he had not taken any drugs. There was no family history of anaemia. His diet had consisted mainly of corned beef, sausages, fish cakes, potatoes and bread, and he ate green vegetables very rarely.

On examination he was pale and the spleen was

palpable 4 cm. below the costal margin. His weight was 9st. 2lb.

Investigations: Hb. 7.8 g./100 ml., w.b.c. 1,450/cu. mm. (polys 67%, lymphs 29%, monos 1%, eosins 2%, basophils 1%), platelets 160,000/cu. mm., reticulocytes 1%. Examination of the stained blood film showed moderate anisocytosis and poikilocytosis. Bone marrow examination showed erythroid hyperplasia, numerous megaloblasts and a decrease in the polymorphs, the differential count being: blast cells 4%, myelocytes and metamyelocytes 43%, polymorphs and band cells 8%, proerythroblasts 7%, normoblasts 11%, megaloblasts 24%. 54% of the megaloblasts were in the basophilic stage.

The serum vitamin B₁₂ level was 140 µg./ml. (normal range 140-950 µg./ml.). In the histidine loading test (Kohn, Mollin and Rosenbach, 1961) there was a large amount of FIGLU in the urine. Schumm's test was positive. The direct Coombs' test was positive to an anti-human globulin dilution of 1/64. In the gamma-globulin neutralization test (Dacie, 1951) agglutination of the red cells was not inhibited by addition of gamma-globulin to the antiglobulin serum. Twenty-four autohæmolysis was increased to 4.6%. No antibodies were demonstrated in the serum.

Virus complement fixation tests were negative three weeks and six weeks after admission. L.E. cells were