Cyclic Thrombocytopenia Associated with Multiple Autoantibodies

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Cyclic thrombocytopenia was first reported by Demmer (1921). Since that initial report 10 other cases have been investigated, and detailed metabolic, endocrinological, and haematological studies have failed to provide a satisfactory explanation. The cyclic nature of the platelet fluctuation is probably not of prime aetiological significance, as fluctuations in the platelet count in normal individuals may occur during the menstrual cycle (Genell, 1936; Pohle, 1939). Platelet antibodies can be shown in only a proportion of patients with idiopathic thrombocytopenic purpura (De Gruchy, 1964). This would suggest that thrombocytopenic purpura is not an immunological disease. Nevertheless, the observation that some patients with apparent idiopathic thrombocytopenia subsequently develop other immunological disorders such as disseminated lupus erythematosus and haemolytic anaemia (Evans et al., 1951) supports the concept that this is a disorder of the immunological system. Further evidence of this is provided by the following case report in which a patient with cyclic thrombocytopenia was found to have widespread immunological abnormalities.

CASE REPORT

A married woman aged 30, mother of two children aged 7 and 24 years, presented in November 1967 with a three-month history of excessive menstrual blood loss and the appearance of purpuric skin rash and bruising coinciding with menstruation. Each period lasted for 10 days, during which she had required two and a half packets of Tampax and half a roll of disposable nappy. During one of these periods she had a small epistaxis. Over the previous few months she had lost weight, felt weak, and complained of recurrent palpitations. She disliked heat and had noticed prominence of the eyes. She had been in good health previously apart from "bad nerves" for two years, for which she took amylobarbitone (Amytal) 30 mg. daily. There was no family history of relevant illnesses.

On examination she looked thin and anxious. The skin showed purpuric spots and bruises over the limbs and trunk. The Hess test was positive. A fine tremor was present in the outstretched hands, which were warm and moist. The pulse was 110-120/min., regular, and the blood pressure 150/90. The thyroid was enlarged, mainly over the left lobe. No bruit was heard. Liver, spleen, and lymph nodes were not enlarged. The fundi were normal.

Investigations.—Haemoglobin 13·0 g./100 ml. W.B.C. 8,700/cu. mm., differential normal. Platelets: cyclical variation of counts associated with menstrual periods. Sternal marrow —erythropoiesis —normoblastic, M/E ratio 4:1; megakaryocytes —many young and morphologically abnormal forms. Bleeding-time prolonged (25 minutes). Clotting-time normal. Liver-function tests and bromsulphalein excretion normal. Plasma urea 16 mg./100 ml. Serum protein-bound iodine 110 mg./100 ml. I131 uptake at four hours 50%. Serum cholesterol, calcium, and phosphorus, normal. Serum electrophoresis normal. Serum immunoglobulins: IgG 2,400 mg./100 ml., IgA 400 mg./100 ml., IgM 240 mg./100 ml.

Immunological studies carried out at different times between 19 November 1967 and 19 December 1968 showed: thryoglobulin tanned red cell agglutination titre 1:80, 1:160; cytoplasmic complement fixation antibody titre 1:16; mitochondrial antibodies: immunofluorescence strongly positive; complement-fixation test (rat liver) 1:64, 1:128, >1:256; antinuclear antibodies: all negative until December 1968, when “speckled variant” positive (rat liver); latex tests and L.E. cells negative; sheep cell agglutination titre, initially negative, borderline in September 1968—1:16; smooth muscle antibodies (×3) negative. Platelet agglutinin negative; indirect antiglobulin consumption test for incomplete platelet antibodies, negative; complement-fixation test for incomplete platelet antibodies, positive.

Treatment was started with 60 mg. of prednisone daily, later reduced to 30 mg. The menstrual loss, purpuric skin rash, and bruising became less pronounced; the cyclical thrombocytopenia, however, persisted (see Chart). Within four months on prednisone she developed Cushitoid features and complained bitterly of indigestion and epigastric pain, which persisted in spite of using enteric-coated tablets and antacids. Over the next two months steroids were gradually reduced and then discontinued. This resulted in the reappearance of skin bruising and purpuric rashes along with heavier menstrual loss in ensuing months. In October 1968 she was readmitted with severe blood loss (haemoglobin 9·5 g./100 ml., platelets 18,000/cu. mm.) requiring blood transfusion. Steroids were started and symptoms were well controlled on a maintenance dose of 15 mg. of prednisone daily.

The thyrotoxicosis was treated with carbimazole tablets with good response, and she has remained euthyroid for the past six months. The thyroid swelling remains unaltered.

COMMENT

Idiopathic thrombocytopenia has been included among the autoimmune diseases, but this has been criticized as platelet antibodies are not detected in every case. It has been argued that this is because the platelet antibodies have been absorbed on to the platelets and cannot in consequence be detected in the serum.

It might reasonably be thought that the cyclic thrombocytopenia was associated with the hormonal changes that occur during menstruation, but this is unlikely as the detailed endocrinological studies of Skoog et al. (1957) were negative. The reduction in the platelet count and the appearance of symptoms during menstruation probably represent an exaggeration of the normal physiological variation in the platelet count that may be seen in a healthy woman (see Chart). Recently we have studied another case of cyclic idiopathic thrombocytopenia suggesting that this phenomenon is not as uncommon as might be expected from a study of the literature. The importance of performing
the platelet counts weekly and the knowledge that a cyclical variation may occur, is important in assessing the severity of the thrombocytopenia, the response to treatment, and the timing of surgical procedures.

The documented case in which a patient with clinical thymotoxicosis and cyclic thrombocytopenia was found to have platelet, thyroid, and mitochondrial antibodies—the latter thought to be suggestive of primary biliary cirrhosis (Doniach et al., 1966)—and a positive antinuclear test (speckled variety) with clinical response to steroids, lends support to the concept that thrombocytopenia may be attributed to disorders of the immunological system.

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\[ \text{REFERENCES} \]


\[ \text{Fatal Intestinal Atony in Myxoedema} \]

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Constipation and abdominal distension are well-recognized features of hypothyroidism, but serious atony of the gastrointestinal tract and urinary bladder may result in retention or incontinence of faeces or urine and even in death from intestinal obstruction without external features of hypothyroidism being obvious.

**CASE REPORT**

In 1958 a man aged 59 complained of sore tongue, tiredness, dyspnoea on exertion, paraesthesiae, and intermittent constipation and diarrhoea. He had a normoblastic macrocytic anaemia (haemoglobin 13 g./100 ml.) with histamine-fast achlorhydria. X-ray examination showed normal stomach, small intestine, and colon. The vitamin-B12 therapy that he was already receiving was continued. In 1960 the macrocytic anaemia was still present. In 1964 he again complained of intermittent constipation and diarrhoea. A barium enema showed a voluminous colon requiring three times the normal quantity of barium.

In January 1967 he was readmitted with persistent bouts of constipation and diarrhoea with distension. For the first time there were external features of hypothyroidism. His skin was coarse and dry, his speech was slow and hoarse, and his movements were lethargic. Psychomotor retardation and delayed tendon jerks were present. The thyroid was not enlarged. Pubic and axillary hair were present. The abdomen was distended and tympanic. Ascites could not be detected. The pulse was 80 and the heart slightly enlarged. The electrocardiogram showed no features of hypothyroidism. There was anaemia (HB 9 g./100 ml., P.C.V. 27%, M.C.H.C. 33.3%). X-ray examination of the abdomen showed distension of stomach, small intestine, and colon with fluid levels. Barium enema showed gross megacolon; five times the normal quantity of barium was required. The right side of the colon could not be filled, being distended by faeces, but the left half emptied well. The serum cholesterol was 280 mg./100 ml. and serum carotene 60 μg./100 ml. Thyroid function tests showed P.B.I. 2.6 μg./100 ml. (normal 3–8 μg./100 ml.); 24-hour iodine uptake was only 2% of a 5-μCi tracer dose.

Although the possibility of mechanical obstruction was entertained it had become evident that the megacolon was part of the gastrointestinal atony of "internal myxoedema." He was treated by gastre aspiration, intravenous fluids, and triiodothyronine 10 μg. b.d., but he died on 23 February 1967. Bladder retention was present for 24 hours before death.

At necropsy there was slight left ventricular enlargement. The peritoneal cavity contained 750 ml. of fluid (protein 3.7 g./100 ml., cholesterol 25 mg./100 ml.). The stomach showed a smooth congested mucosa. Both small and large intestines were dilated, oedematous, and necrotic, but there was no mechanical obstruction.

The bladder was not distended. The pituitary and adrenal glands were normal macroscopically and histologically. The thyroid gland weighed only 8 g. Histologically it consisted mainly of fibrous tissue with a few distorted acini. There was only moderate lymphocytic infiltration without follicle formation.

**COMMENT**

In 1935 Escamilla, Lissner, and Shepardson described under the term "internal myxoedema" a case showing cardiac, intestinal, and bladder atony, ascites, secondary anaemia, and carotenaemia due to hypothyroidism, although the external features of this were only scanty. Our patient showed atony of the small and large bowel, ascites, macrocytic anaemia, and bladder retention. He was observed intermittently over nine years; there were at first no external features of myxoedema, and barium studies of small intestine and colon were initially normal. During the subsequent years there was progressive enlargement of the colon and ultimately generalized intestinal atony. Only in this latter phase did the external signs of myxoedema appear. Thus internal myxoedema can present insidiously as unexplained atony of the gastrointestinal tract or bladder, cardiomegaly, ascites, or macrocytic anaemia. Intestinal atony may affect the stomach, small intestine, and colon. It is rare for it to cause intestinal obstruction as in the case of Escamilla et al. (1935) or our own, and has not to our knowledge been previously described as a cause of death.

Combination of gradually developing constipation with bladder retention or incontinence and slowness of ambulation may simulate a neurological disorder.

The term "internal myxoedema" (Escamilla–Lissner syndrome) embraces anaemia of various types. It is usually normocytic; but macrocytic anaemia, unresponsive to vitamin B12, as in the present instance, may be found. Steadily progressing atonic megacolon should raise the suspicion of internal myxoedema even with paucity of external signs. Early treatment by thyroid replacement will result in resumption of normal bowel habit and abdominal girth, whereas parenteral thyroid replacement at the time of generalized dilatation and atony of the bowel may not be sufficient to save the patient. The dangers are atonic intestinal obstruction and perforation.

\[ \text{REFERENCE} \]