CASE REPORTS

Levamisole treatment of a child with severe aphthous stomatitis and neutropenia

H. VERHAEGEN
M.D.

J. DE CRÉE
M.D.

W. DE COCK
M.Sc.

J. BRUGMANS
M.D.

Clinical Research Unit, St Bartholomeus Hospital, B-2060 Merksem (Antwerp), Belgium

Summary

The treatment of a 12-year-old girl with a lifelong history of recurrent infections and aphthous stomatitis is reported. A profound neutropenia, first noted at the age of 2 years, occurring at least every month was observed together with multiple mouth ulcers, a sore throat and swelling of the jugular glands.

Levamisole, originally described as an anthelmintic, has a beneficial effect on the symptoms of recurrent aphthous stomatitis.

After levamisole treatment aphthous stomatitis was milder and in the 1-year follow-up period the patient was asymptomatic several times during a phase of obvious neutrophil depression.

The child no longer complained of sore throat with swelling of the jugular glands and the recurrent staphylococcal infections of the skin disappeared. After therapy a marked increase in monocytes at the moment of neutropenia was observed.

Introduction

In cyclic neutropenia circulating neutrophils decrease in number or may even be absent temporarily. The disease is characterized by periodic febrile episodes beginning during infancy and is associated with otitis, furuncles, mastoiditis and stomatitis. The therapeutic management is limited to antibiotics during infections. For some patients one of the most frustrating aspects of the disease is recurrent aphthous stomatitis.

The beneficial effects of levamisole on the symptoms of recurrent aphthous stomatitis were recently reported (Verhaegen *et al.*, 1973a).

Levamisole, (-)-2,3,5,6-tetrahydro-6-phenylimidazole [2, 1-b] thiazole hydrochloride, originally described as an anthelmintic (Thienpont *et al.*, 1966), was found to render mice more resistant to subsequent challenges with *Brucella* after an initial

exposure to viable *Brucella* bacteria (Renoux and Renoux, 1971, 1972).

In man, levamisole enhanced the antibody response to A₂/Aichi/2/1968 influenza virus vaccine (Brugmans *et al.*, 1973) and restored cutaneous delayed hypersensitivity reactions in anergic elderly patients (Verhaegen *et al.*, 1973c) and patients suffering from cancer (Tripodi, Parks and Brugmans, 1973; Verhaegen *et al.*, 1973b).

A patient with a lifelong history of recurrent aphthous stomatitis caused by cyclic neutropenia, who was successfully treated with levamisole, is now reported.

Patient and methods

The patient, a girl now aged 12 years, first developed severe bronchitis at the age of 18 months. She was treated with chloramphenicol for 2 years. Since then she has suffered from aphthous stomatitis recurring at least every month and always accompanied by total neutropenia. Lesions were always severe; the child had multiple ulcers with a healing time of 8-10 days, a sore throat and swelling of the jugular glands. She also suffered from recurrent staphylococcal infections of the skin and had five episodes of severe bronchopneumonia.

Laboratory tests before admission showed normal leucocyte count, apart from neutropenia and a cyclic disappearance of neutrophils. Bone-marrow suspensions were normal but for eosinophilia and a diminished number of neutrophils during a neutropenic period.

The lymphoblast transformation test, the nitro-blue tetrazolium test and the immunoglobulins IgG, IgA and IgM were normal.

Before levamisole treatment was started, the patient was followed for 2 months, during which period the cyclic course of the disease could be

FIG. 1. Experimental data of a child with cyclic neutropenia accompanied by aphthous stomatitis, treated with levamisole for 1 year.

assessed (Fig. 1). She received antibiotic therapy during the active phases of the disease. She was then started on 150 mg levamisole daily, but as this dose was too high, three tablets of 50 mg levamisole were given on 3 consecutive days in each week. Antibiotic therapy was discontinued when levamisole was started.

Apart from the routine haematological tests, serum complement activity and serum immunoglobulins were followed.

Total serum haemolytic complement (CH_{50}) was determined by a modification of the method of

Mayer (1971). The serum concentrations of β_1C/β_1A globulin (C_3), β_1E globulin (C_4) and the immunoglobulins IgG, IgM, IgA were measured by the radial immunodiffusion technique of Mancini, Carbonara and Heremans (1965) using commercially prepared plates and commercial standards (Behringwerke AG).

Results

Observations made after a year of intermittent maintenance therapy confirm that levamisole still prevents the monthly recurrence of aphthous stomatitis.

When symptoms recurred after longer periods of well-being they were milder than before levamisole therapy, the number and size of the lesions were reduced, the healing time was shorter, there was no swelling of the jugular glands and the child no longer complained of a sore throat.

During levamisole treatment the child developed a staphylococcal skin infection and a moderate bronchitis, which were cured by 1 week of antibiotic therapy, whereas before levamisole therapy the child was constantly receiving antibiotics, since recurrent infections could not be controlled otherwise.

The most pertinent laboratory findings and the symptomatology of the disease are given in Fig. 1.

After the start of levamisole therapy numerous peripheral monocytes appeared when neutrophils disappeared from the blood stream; this had never been observed before levamisole treatment.

Before levamisole therapy disappearance of the neutrophils was always accompanied by severe aphthous stomatitis, whereas during levamisole therapy disappearance of the neutrophils was accompanied by mild or absent aphthous stomatitis.

Complement activity (CH_{50} , C_3 and C_4) was increased during episodes of aphthous stomatitis and normalized when the symptoms disappeared.

The concentration of IgG was increased throughout, but the greatest increases occurred when the symptoms were very severe. The concentrations of IgA and IgM, total leucocyte count, erythrocyte count, haemoglobin concentration and thrombocyte count remained, however, within the normal range throughout the study.

Discussion

Cyclic neutropenia is characterized by its strikingly periodic recurrence. Patients with cyclic neutropenia have periods of well-being for approximately 3 weeks, alternating with 1-week intervals of fever, mouth ulcers, malaise, headache and furunculosis (Paye and Good, 1957).

This case was very similar to those described in the literature (Cantel, Marel and Thancet, 1963;

Lin, Adam and Sullivan 1970; Paye and Good, 1957; Videback, 1962). The girl had been suffering for about 10 years from severe aphthous stomatitis, which recurred every 3 weeks.

After levamisole treatment aphthous stomatitis was milder, the size of the lesions was smaller and the healing time shorter. The patient reported as one of the most important changes that she could no longer follow the typical cycle she had experienced for years. Indeed, several times in the course of the 1-year follow-up period the patient was completely asymptomatic during a phase of obvious neutrophil depression.

Cyclic neutropenia is the consequence of a periodic failure of marrow production rather than a peripheral destruction (Guerry *et al.*, 1973). Recently, it has been shown that cyclic neutropenia may be associated with the cyclic production of colony stimulating factor, a humoral factor which stimulates granulopoiesis (Mangalik and Robinson, 1973) and is released by monocytes (Golde and Cline, 1972).

Meuret and Flidner (1974) have shown in a case of cyclic neutropenia that monocytosis occurring during the neutropenic phases of the disease was caused by a raise in the monocyte production rate which approximately equalled the monocyte turnover rate.

In the present case practically no monocytosis occurred in the neutropenic phase before the therapy was started. After levamisole therapy the disappearance of neutrophils was always accompanied by a marked increase in monocytes.

It has been shown that levamisole increases phagocytosis by macrophages and polymorphonuclear cells (De Crée *et al.*, 1974b; Oliveira *et al.*, 1974; Van Oss, 1973). Levamisole-stimulated macrophages become more hydrophilic and this phenomenon is associated with enhanced phagocytosis. The beneficial effect of levamisole in this case is probably due to a stimulation of the mononuclear phagocytic system.

An increase in complement activity has been observed after infection. In this case complement levels (CH_{50} , C_3 , C_4) followed the activity state of the disease. In a phase of neutropenia, when symptoms were severe, complement levels were increased and returned to normal levels in a remission phase. In an active phase of the disease, immediately after starting levamisole, the complement levels were higher than before. It has been shown in cancer patients (Verhaegen *et al.*, 1973b) and in HBAg positive patients (De Crée *et al.*, 1974a) that levamisole increased total haemolytic complement.

The lower complement levels in the further follow-up period are probably the result of the diminished infections. This is in agreement with the lower IgG concentration after 1 year of treatment.

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Carcinoid tumour of the ampulla of Vater associated with cutaneous neurofibromatosis

P. V. BARBER
 M.B., M.R.C.P.

North Manchester General Hospital

Summary

A case of carcinoid tumour of Vater's ampulla is described from a patient with widespread cutaneous neurofibromatosis. The literature concerning the few known cases of carcinoids occurring at this site is briefly reviewed and the presentation, prognosis and treatment discussed, together with the possible significance of such a clinical association.

Introduction

Carcinoid tumours arising in the ampulla of Vater are extremely rare, comprising about 0.3% of gastrointestinal carcinoids. The following case is believed to be the thirteenth in the literature and is of especial interest, since the patient also suffers from Von Recklinghausen's disease, a condition known to be associated with a variety of tumours of neural origin. The present case presented with obstructive jaundice and was successfully treated by local excision.

Case report

A 30-year-old male was admitted for investigation. Ten months previously he had noticed that his stools had become pale and offensive and his urine dark. Shortly afterwards he developed generalized pruritus and became deeply jaundiced. He had also lost some weight, and complained of upper abdominal discomfort. The jaundice regressed several weeks later but subsequently increased progressively.

At the age of 17 years, he had begun to develop multiple skin tumours of the trunk and limbs. There was no family history of this condition and no significant previous medical history.

On examination, he was deeply jaundiced. There were multiple sessile and pedunculated tumours involving the skin of almost the whole body, and several large *café-au-lait* patches on the back. The liver was greatly enlarged, firm and non-tender. There was no clinical evidence of hepatic failure or of portal hypertension. Rectal examination revealed pale faeces. There were no other abnormal findings.

Significant laboratory findings included a serum bilirubin of 7.8 mg/100 ml, an alkaline phosphatase of 95 KA units/100 ml and an elevated serum globulin at 4 g/100 ml. Haemoglobin and blood count were within normal limits apart from a slight lymphopenia; the ESR was elevated to 63 mm/hr. The urine was strongly positive for bilirubin and contained no urobilinogen.

Plain radiology of the abdomen showed only an enlarged liver, and a barium series showed no displacement or filling defect of the duodenum.

A diagnosis of post-hepatic obstructive jaundice was made and laparotomy was performed shortly after admission. The liver was enlarged and smooth, and the gall-bladder distended. The spleen was also slightly enlarged. The stomach, duodenum and pancreas were normal but there was a mobile nodule involving the ampulla of Vater. The nodule was excised completely and the common bile duct anastomosed to the duodenum. The pancreatic duct was found to exit below the common bile duct. The duodenum was closed and a liver biopsy taken. A skin tumour was removed, and was subsequently shown to be a neuro-fibroma.

Post-operative recovery was uneventful, and the serum bilirubin fell rapidly to normal levels. Urinary