Immunological phenomena accompany the course of various diseases, including infections. Complicated immunological findings in a patient with a febrile illness may mislead one into making a diagnosis of a collagen or an auto-immune disease, while an infection is hidden. This problem has therapeutic and prognostic significance, apart from the importance of making the correct diagnosis.

Physical, serological and histological findings due to immunological abnormalities are not unusual in patients with infective endocarditis, particularly the subacute form. We describe 2 patients with subacute bacterial endocarditis (SBE), who presented with fever accompanied by various immunological abnormalities, mimicking a lymphoproliferative disorder in case 1 and an autoimmune disease in case 2. In both patients the diagnosis of SBE was obscured because of this unusual presentation.

CASE REPORTS

Case 1

A 72-year-old man was admitted to hospital during May 1975 for investigation of fever of 4 weeks’ duration. During this period he had been treated intermittently with tetracycline. Except for hypersensitivity to penicillin, there was no past history of any disease. On physical examination he had a temperature of 38.6°C, enlarged lymph nodes in all regions, hepatosplenomegaly, and an apical pansystolic murmur, grade 3/6, radiating to the left axilla. Chest radiographs showed diffuse enlargement of the heart, with a dilated left ventricle, left atrium and right ventricle. The following laboratory findings were abnormal: an erythrocyte sedimentation rate of 100 mm/1st h (Westergren), a diffuse elevation of the gammaglobulins, with elevated levels of immunoglobulins G, A, and M, and a positive test for rheumatoid factor at a dilution of 1:80. The C3 component of complement was 0.7 mg/ml (normal 0.8 - 1.8 mg/ml). Mixed IgG-IgM cryoglobulins were found in the serum and the antistreptolysin titre was 2 048. A urine test revealed mild proteinuria, a few red blood cells, white blood cells, and granular casts. The results of renal function tests were normal. Twelve blood cultures were done and antibiotics (first erythromycin and then cephalothin and gentamicin) were administered intravenously for 17 days. The results of all blood cultures were negative. The patient was discharged in good health after 25 days in hospital, and was followed up in the outpatient clinic. During the follow-up period he had several episodes of fever which disappeared spontaneously. Enlarged lymph nodes and hepatosplenomegaly were persistent findings. These findings prompted a needle biopsy of the liver and a lymph node biopsy, which yielded no significant abnormal findings. Blood and urine cultures were negative.

Seven months later, during December 1975, he was again admitted because of arthralgia and purpuric lesions over the lower and upper extremities and trunk (Fig. 1). The results of physical examination had not changed, and the thrombocyte level was normal. Biopsy of one of his purpuric leg lesions disclosed an acute leucocytoclastic vasculitis (Fig. 2). This finding, without any other definitive diagnosis, prompted us to administer a steroid (prednisone). The patient improved, the purpuric eruption vanished, and he was discharged on a maintenance dose of 20 mg prednisone. A month later he was admitted for the last time because of a temperature of 39°C. On physical examination the findings were unchanged. The haemoglobin concentration was 10.4 g/dl, the white blood cell count was 14 900/μl, with 78% neutrophils, 12% band forms, and 3% atypical mononuclear cells classified as histiocytes, 3% lymphocytes and 4% plasma cells. The urine test for protein was positive. The sediment contained a few red blood cells, white blood cells and granular casts, without definite red cell casts. A bone marrow aspiration revealed a reactive marrow with 8% normal plasma cells. Echocardiography revealed typical vegetations involving the posterior mitral leaflet and possibly also the anterior leaflet. Twelve blood samples were drawn for culture, and cephalothin and
gentamicin were administered intravenously. Blood cultures grew *Streptococcus faecalis*. The intravenous administration of antibiotics was continued for 6 weeks.

**Fig. 1.** Extensive purpuric skin lesions with occasional necrotic ulcerations and some vesicles on the upper and lower limbs and buttocks.

One day after completion of treatment the patient abruptly became unresponsive and died shortly afterwards. The postmortem examination revealed enlargement of both ventricles and atria of the heart. A fibrotic, calcified, floppy mitral valve with small vegetations was seen. The kidneys were enlarged and showed a slightly granular external surface. Generalized lymphadenopathy and hepatosplenomegaly were also found. Histological examination of the mitral valve was compatible with myxomatous degeneration and showed Gram-positive cocci inside the vegetations. Focal glomerulonephritis was found in the kidneys. Because of technical problems, immunofluorescence studies were not done. Electron microscopy of the kidneys revealed subendothelial and mesangial electron-dense deposits.

**Case 2**

A 21-year-old woman was admitted to hospital during November 1975 for investigation of low-grade fever of 3 months' duration, arthralgia, hepatosplenomegaly and macroscopic haematuria. In 1969 she had had a mitral valve replacement (Starr-Edwards valve) because of rheumatic mitral stenosis. Since then she had been on maintenance treatment with digoxin, furosemide and warfarin. She had felt well during the next 6 years. On admission her temperature was 38°C. Physical examination revealed heart sounds with the typical click of the artificial valve, and no signs of heart failure. Hepatosplenomegaly and diffuse purpura on the lower extremities were also found. The fundi were normal. Chest radiography showed enlargement of the left auricle. The following laboratory findings were abnormal: an erythrocyte sedimentation rate of 75 mm/1st h (Westergren), a haemoglobin concentration of 10.7 g/dl, reticulocytes 4.8%, free haptoglobin 25 mg/dl (normal 90-120 mg/dl), a positive direct Coombs test, diffuse elevation of the immunoglobulins, with elevated levels of the three main immunoglobulins (IgG, IgA, IgM), and a positive test for rheumatoid factor at a dilution of 1:160. The C3 component of complement was 0.6 mg/ml and the antistreptolysin titre was 512. Antinuclear antibodies (at a dilution greater than 1:10) and circulating anticoagulant were also found in the serum. Anti-DNA antibodies and cryoglobulins were not found. Renal and liver function tests were negative, and the thrombocyte count was 180 000/µl.

Protein was found in the urine, and examination of the sediment revealed many erythrocytes, 3-5 leucocytes and a few granular casts per high-power field. Repeated blood cultures were negative. The patient was treated with ampicillin, streptomycin and probenecid for 6 weeks. Biopsy of one of the purpuric lesions disclosed acute leucocytoclastic vasculitis. The patient was discharged when the fever subsided, but the microhaematuria persisted.

Two months later she was admitted for further evaluation. The findings of persistent erythrocyturia, hypocomplementaemia and antinuclear antibodies prompted us to perform a needle biopsy of the kidney which yielded a

**Fig. 2.** Electron photomicrograph of dermal capillary, showing large amounts of fibrin in the lumen and some fibrin in the extravascular space (right upper corner) (×10 000).
diffuse proliferative glomerulonephritis. Immunofluorescent microscopic examination revealed granular deposition of IgG, IgM, IgA, C3 and fibrinogen on the glomerular basement membrane, and electron microscopy disclosed subendothelial electron-dense deposits (Fig. 3). Because of these findings a possible diagnosis of systemic lupus erythematosus was made, and administration of prednisone 60 mg/d was started.

Fig. 3. Electron photomicrograph of kidney biopsy specimen, showing extensive electron-dense deposits in the subendothelial region. The basement membrane appears normal and the foot processes show focal fusion (× 10 000).

In March 1976 the patient was again admitted because of fever spikes in spite of maintenance treatment with prednisone 15 mg/d. On physical examination the findings were unchanged, apart from arthritis of the left ankle joint. Blood cultures were negative, but we again administered penicillin intravenously and continued with prednisone administration.

The patient was followed up in the outpatient clinic and complained of low-grade fever. The levels of C3 and C4 components of the complement were persistently low, and antinuclear antibodies and rheumatoid factor were found.

During November 1977 the patient was admitted for the last time, because of acute left heart failure and fever. This time an apical diastolic murmur, grade 3/6, was audible, and blood cultures grew Strep. viridans. We started treatment with penicillin 20 000 000 U/d and continued administration of digoxin, furosemide and warfarin. On the 6th hospital day no pulse could be found, and the patient died shortly afterwards.

The postmortem examination revealed severe stenosis of the artificial mitral valve caused by organized vegetations, severe dilatation of both atria and the right ventricle, and complete occlusion of the left descending coronary artery due to embolic vegetation and hepatosplenomegaly. Histological examination of the mitral valve showed Gram-positive cocci inside the vegetations. The kidneys showed proliferative diffuse glomerulonephritis.

DISCUSSION

There is increasing awareness of the occurrence of immunological phenomena in cases of bacterial endocarditis. Immunological mechanisms play an important role in the pathogenesis, course and extravalvular complications of the disease, especially in the subacute form. Showers of bacteria from the infected valve may provide a continuous source of antigenic challenge, and consequently lead to the formation of antigen-antibody complexes. These complexes are distributed throughout the body, where they may become attached to the endothelium of small blood vessels, and induce generalized vasculitis and glomerulonephritis. The finding of soluble immune complexes in the blood of patients with SBE is consistent with this sequence of events.

Various serum components appear in SBE, and their levels vary during the clinical course of the disease. In our patients we found significant levels of rheumatoid factor, antinuclear antibodies, circulating anticoagulant, anti-erythrocyte antibodies (positive direct Coombs test), cryoglobulins, increased levels of immunoglobulins and hypocomplementaemia (Table I). Of special interest is the association of a rise in titre of IgM anti-IgG antibody (rheumatoid factor) with established SBE, and a fall in titre of this antibody with successful therapy. About 50% of patients with longstanding SBE develop rheumatoid factor during their illness, chiefly detectable by the latex agglutination test with human globulin as antigen. The appearance of rheumatoid factor and its subsequent disappearance after eradication of bacteria supply further evidence for a state of chronic immunisation in SBE. Thus, in animal experiments, the repeated injection of various antigens results in a rising titre of rheumatoid factor which disappears on cessation of antigenic stimulation. The role of rheumatoid factor in the pathogenesis and clinical course of the disease is undetermined. The experiments of Gough and Davis and Parker and Schmid suggest that it might serve as a protective mechanism, while studies by other workers show that it may diminish phagocytosis of bacteria by polymorphonuclear leucocytes, probably by altering opsonic activity.

The presence of circulating anticoagulant and anti-erythrocyte antibodies (as found in patient 2) has not been shown in SBE previously. The finding of antinuclear antibodies (case 2) has been noted only occasionally in the past.

However, the presence of other auto-antibodies (tissue and non-tissue-specific) has been established in two series of SBE. The association of a bacteriological cure with a reduction in titre of various auto-antibodies suggests that these auto-antibodies reflect only a non-specific stimulation of humoral immunity by the disease activity. The presence of high titres of Candida antibodies in patients with SBE and without apparent Candida infection lends support to this suggestion.

In this connection it is of interest to note the finding of generalized lymphadenopathy in patient 1. This is a very rare manifestation of SBE, and it most probably reflects overstimulation of the reticulo-endothelial system by the longstanding bacteraemia.
two lymph node biopsy specimens of our patient revealed only a non-specific reaction. The finding of hypercellularity of the bone marrow with 5 - 10% normal plasma cells fits the above assumption. Atypical mononuclear cells, classified as histiocytes, appeared in the peripheral blood, late in the course of the disease of patient 1. This phenomenon has previously been noted in the blood, particularly from the ear lobe, of patients with SBE.25

These histiocytes were ascribed to proliferation of the reticulo-endothelial cells or to proliferation and transformation of the endothelium of small blood vessels in cases of SBE.25,26

The renal lesions of SBE are important in the diagnosis, treatment and prognosis of the disease. For years the nephritis which sometimes accompanies SBE was thought to be a result of embolization to the kidney; hence the term 'focal embolic glomerulonephritis'. In 1962, Williams and Kunkel26 noted hypocomplementaemia in 8 patients with SBE who had moderate-to-severe renal disease. They suggested that an immune mechanism might be the cause of the renal disease. The demonstration of electron-dense deposits on the glomerular basement membrane in patients with SBE,4,5 the finding of granular deposits of immunoglobulins,5,7 and of immunoglobulins and complement,4,5,7 on the glomerular basement membrane in patients with SBE and nephritis, the presence of circulating immune complexes in patients with SBE,2 and the reported nephritis in 2 patients with bacterial endocarditis involving only the right side of the heart25 have suggested that the diffuse glomerulonephritis in patients with SBE represents an immune-complex nephritis. The results of immunofluorescence and electron microscopic studies of the kidney biopsy specimens in our patients fit this concept.

The finding of dermal purpuric vasculitis in both patients has been noted occasionally,25,26 and its immunological nature was established recently.27 Joint pain during the course of the disease, as in our patients, has been studied recently in two series,28,29 and is claimed to be due to deposition of immune complexes in the synovia.30

Renal injury and other extravalvular complications, including purpura, appear to be at least partially reversible if appropriate antimicrobial therapy is instituted.1,21 This is probably due to elimination of the antigenic stimulus. Therefore, patients who suffer from vasculitis and rheumatoid phenomena and who are suspected of having SBE, should always receive antibiotics before any therapy aimed at the immunological phenomena is started.

The immunological manifestations in our 2 patients obscured and delayed the diagnosis of bacterial endocarditis. A high degree of alertness to the diagnosis of SBE, and thus earlier diagnosis, might have led to their cure and survival.

REFERENCES

Hypophosphataemia with Intravascular Haemolysis
A Case Report

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SUMMARY

Severe hypophosphataemia in an alcoholic patient during active treatment for acute pancreatitis and diabetic keto-acidosis was associated with a transient intravascular haemolytic anaemia, thrombocytopenia and some evidence of muscular disorder. The mechanism of the clinical changes is briefly discussed, and it is stressed that such complications could easily be overlooked in a patient with other serious disorders.


CASE REPORT

A 55-year-old White man was admitted to hospital with complaints of severe epigastric pain of 1 day's duration spreading to the left hypochondrium and into his back. He was nauseous and had vomited. He admitted having consumed considerable quantities of alcohol during the previous 36 hours. On admission he was in a state of severe shock, and was sweating. He had a pulse rate of 120/min and a temperature of 38,5°C. Examination revealed considerable upper abdominal tenderness with muscle guarding. Knee and ankle jerks were absent. The calves were not unduly tender. The liver was palpable 4 cm and the spleen 2 cm below the costal margin. The urine contained large amounts of glucose and acetone. Both parotid glands were enlarged but not tender. The patient had hypertension for 3 years and medication had been prescribed. Three years previously he had developed acute myocardial infarction. He was known to have had diabetes mellitus for at least 5 years, and this was apparently controlled by diet and insulin therapy.

One of the patient's brothers was a diabetic, and another had recently suffered myocardial infarction. The patient admitted to a considerable alcohol intake over a period of many years.

An ECG showed evidence of previous inferior myocardial infarction. The creatinine kinase level was slightly elevated. The clinical picture was that of acute pancreatitis, and this was confirmed by amylase determinations (Table I).

The glycosuria and acetonuria were controlled by intravenous fluids and soluble insulin, and after 6 days it was possible to stabilize the patient on 55 units lente insulin daily. The abdominal complaints gradually subsided over a period of 6-8 days, but pyrexia persisted for about 3 weeks. Blood cultures revealed Staphylococcus aureus, for which appropriate therapy was given. Radiographs of the abdomen revealed no evidence of pancreatic calcification. In view of the previous ethanol intake and the hepatosplenomegaly, further investigations were carried out. A barium swallow showed evidence of oesophageal varices.

In carrying out a bromsulphalein retention test a blue colour developed in the serum and subsequent tests revealed the presence of methaemalbumin. Further studies revealed additional evidence of an intravascular haemolysis, haemosiderinuria, elevated serum bilirubin values (? pancreatitis), a raised reticulocyte response, and a reduction of 1 million erythrocytes and of the haemoglobin level during the first week of hospitalization. Serum haptoglobin was 5,2 g/l (normal 1,0 - 3,0 g/l) on 23 February 1979.