Clinicopathological Conference

A case of septicaemia

DEMONSTRATED AT THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

British Medical Journal, 1976, 1, 207-212

The eleventh of the quarterly series of clinicopathological conferences was held at the Royal College of Physicians of London on 24 April 1975. Professor G P McNicol(1) presented the case, with Dr S H Taylor(2), Dr M F Dixon(3), and Dr R Freeman (5).

Clinical summary

History

A 45-year-old woman was admitted to hospital on 31 January 1974 confused and disoriented. She had apparently been unwell for three days, with rigors, loose stools, and an episode of vomiting. She had a mitral valvotomy for mitral stenosis in 1962; paranoid schizophrenia since 1962; temporal lobe epilepsy since 1949; and psoriasis since 1948. There was no history of rheumatic fever. Treatment immediately before admission was unknown but in recent months she had been on digoxin, chlorpromazine, pimozide, phenytoin, amitriptyline, nitrazepam, and Conovid E (oral contraceptive: mestranol and norethynodrel).

Examination on admission


The results of the initial investigations included: haemoglobin 12.4 g/dl; white blood count 17.5 x 10^9/l; polymorph neutrophil leucocytes; platelet count 6 x 10^11; electrocardiogram showed rapid atrial fibrillation; x-ray film of chest showed generalised cardiac enlargement; blood urea 10 mmol/l (60 mg/100 ml); serum sodium 135 mmol/l (135 mEq/l); serum potassium 3-2 mmol/l (3-2 mEq/l); CO₂ 20 mmol/l (20 mEq/l); blood culture gave a growth of coagulase-positive staphylococcus.

Two platelet infusions of eight units each were given and lumbar puncture was performed. This showed no evidence of meningitis and the cerebrospinal fluid (CSF) culture was sterile.

Progress after admission

For three days the patient's clinical condition remained essentially unchanged apart from the development of gangrene of the fingertips. Her general condition then gradually improved; her temperature fell to normal and her platelet count rose by 5 February to 94 x 10^9/l. Skin biopsy was performed on that day; the results will be presented. Further general improvement then gradually continued until she developed diarrhoea on 11 and 12 February. Blood urea on 12 February was 12.3 mmol/l (74 mg/100 ml). Gangrene of the fingertips was by this time fully established and the patient's condition began to deteriorate. On 13 February she had an episode of pulmonary oedema which appeared related to a brief cardiac dysrhythmia. The next day the platelet count was 77 x 10^9/l; blood urea had risen to 30 mmol/l (156 mg/100 ml). On 15 February there were two episodes of ventricular fibrillation, the second being fatal. The course is outlined in fig 1.

Comment

Professor G P McNicol: Would Professor A G W Whitfield, who is to lead the discussion, like to indicate what other investigations would be helpful?

Professor A G W Whitfield(4): I would be very surprised if the initial diagnosis was not that of meningococcal septicaemia. I would have done three blood cultures immediately, because the meningococcus grows poorly, and also a blood count. She clearly had a coecal septicaemia, and the haematologist might have seen Gram-negative diplococci within the leucocytes confirming its meningococcal nature. I would have been interested...
in her platelet count but would have expected the purpura to have been part of her septicæmia. But, unexpectedly, she had this extreme thrombocytopenia—which doubtless explains it. She was not anæmic.

The coccus, however, turned out to be a staphylococcus, but I am surprised that it took three days for the bacteriologist to find it. In a septicæmia of this severity one could expect a diagnosable growth within 24 hours.

The patient also needed a lumbar puncture in view of her meningeal signs. I would have put the patient on sulphadiazine, 1 g. hourly, and penicillin, 1 MU 4-hourly on the presumptive diagnosis of meningococcal septicæmia. Then I would have done the lumbar puncture. Dr Taylor, finding her platelet count was so low, gave a platelet transfusion in order to prevent any neurologial haemorrhage being provoked by the lumbar puncture. But the cerebrospinal fluid (CSF) was normal, so that she had meningeal rather than meningeal.

STAPHYLOCOCCAL SEPTICÆMIA

Now, staphylococcal septicæmia is a disease which has altered very materially during my lifetime. It used to complicated acute osteomyelitis—boils, and carbuncles, particularly those within the distribution of the angular vein—and sometimes genitourinary and other infections. But now we see it most commonly as an opportunistic infection in people who are severely ill, particularly those on steroids. It seems to happen sometimes after operations, although how the organism gets in is always a mystery. In this patient the only clues are her psoriasis—although I have never heard of staphylococcal septicæmia complicating psoriasis—and the fact that she also vomited and had diarrhœa, so she might have had a staphylococcal enterocolitis.

She had had a valvotomy when she was 33, 12 years before this illness. She must therefore have had definite mitral stenosis, which was presumably rheumatic—40% of patients with this lesion give no history of rheumatic fever. The operation was effective. The left ventricle was more dominant than the right and the x-ray film suggests that she no longer had pure mitral stenosis, and that incompetence was the dominant mitral lesion on her admission. You wouldn’t expect to bear a mid-diastolic murmur as she had rapid fibrillation and the pansystolic murmur was that of incompetence. She had been on digoxin and I presume that she had been fibrillating for some time. Hence she might very well have developed infective endocarditis and emboli. This could have explained her cold fingertips.

On her electrocardiogram she had inverted T-waves in leads II and III and aVF and V5 and V6. This might have resulted from right ventricular dominance or digoxin but I think that they were ischaemic changes and related to her fatal disease.

Her psoriasis may have been where the staphylococcus entered, but has no other relevance to her problem. She had had temporal lobe epilepsy since she was 20. This is often associated with a schizophrenic state and she did develop paranoid schizophrenia after her valvotomy. It is often of late onset and often provoked by surgery. One must consider her drug treatment. Could her new illness be the result of it? The thrombotic tendency of the contraceptive pill might have contributed to the ischaemia in her fingers but the other drugs merely represent psychiatric enthusiasm and the intractability of paranoid schizophrenia and temporal lobe epilepsy.

MOSCHCOWITZ SYNDROME

Now, what about those cyanosed fingertips? Her peripheral pulses were all present and her systolic blood pressure was 130 mm Hg, so I don’t think she had peripheral circulatory failure. Her platelet count was low, and her fingers developed gangrene. Her blood urea level gradually rose to 30 mmol/l (156 mg/100 ml), and her diarrhœa recurred before death. My strong feeling is that she had the disease described first by Moschowitz in 1925. So this is its 50th anniversary, during which time it has collected more names than any other disease.

This condition is chiefly seen as a complication of septicæmia states and collagen disorders. Its features are fever, thrombocytopenia, and haemorrhagic manifestations—which she had. Another feature is haemolytic anaæmia. She had a haemoglobin of 12.4 g/dl on admission. Did it fall? Did she develop jaundice? Did her haptoglobins fall? Did she have reticuloctysis?

Professor McNICOL: The reticuloocyte count was raised to 3 or 4%,

PROFESSOR WHITFIELD: That is a feature of haemolysis. Do you have a blood film to show the characteristic fragmented red cells? Another feature is the acute degeneration of capillary and arteriolar walls with little or no inflammatory reaction and occlusion of the lumina with fibrinous material. These lesions are seen particularly in the renal cortex and in the myocardium, brain, adrenals, and pancreas. They are similar to the Schwartzman phenomenon, produced by giving two intravenous injections of bacteria.

The diagnosis of thrombotic thrombocytopenic purpura is best confirmed by skin or muscle biopsy, which shows the vascular lesions. The prognosis is almost invariably death in a few days or weeks, though some patients have survived longer with recurrent haemolytic crises. This patient lived for 16 days. I don’t know what treatment she was given but there is no effective treatment. I would have hesitated to give her steroids in the presence of her staphylococcal septicæmia, and you couldn’t have removed the spleen in this patient. The giving of heparin to double the clotting time has a rational basis and I expect that it was done. Platelet transfusions and aminocaproic acid are given for haemorrhagic complications, but this treats only one aspect of the disease. I wouldn’t be surprised if her coronary, renal, and cerebral arteries were affected, and also her mesenteric arteries, although her terminal diarrhœa may have been due to antibiotics.

Professor McNICOL: Thank you. The table shows the additional haematological data.

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Professor WHITFIELD: Yes, the plasma fibrinogen level is usually low in this condition, but so are the Factor V and VIII levels, and also the prothrombin time is prolonged.

Professor McNICOL: At the time, my analysis was that it was diagnostic of disseminated intravascular coagulation. The results of the tests do not fit, but one must not commit the sin of diagnostic greed, and there were more than enough compatible results here. The factor V and VIII levels may have been normal because she started off with high levels, or because the disseminated intravascular coagulation had taken place many hours earlier. Incidentally, I prefer to restrict the term, Moschowitz syndrome, to the syndrome of intravascular coagulation of unknown aetiology. But there are other forms of disseminated intravascular coagulation which are compatible with the restoration of normal health—for example, in obstetrics and Gram-negative septicæmia. Fig 2 shows the blood film you asked for. It showed fragmented red cells and lack of platelets. No cocci were seen in the white cells.

During treatment the platelet count responded well. She had the treatment you suggested and corticosteroids. Do you think
her platelets responded to the antibiotics, to heparin, or to the corticosteroids?

Professor Whitfield: It used to be thought that the platelets were all used in blocking the capillaries and arterioles. That idea has been discarded but the true explanation of the thrombocytopaenia is not known. The increase in their number was probably due to the corticosteroids but the heparin may have played a part.

**Choice of Antibiotics**

Professor McNicol: I'd like to ask Dr Freeman to explain the thinking that lay behind our choice of antibiotic treatment.

Dr Freeman: This patient presented with the clinical appearances of septicemia and had neck stiffness. We considered that she might have septicemia with “meningitis” or bacterial meningitis complicated by septicemia.

Meningitis with septicemia in an adult might be due to Neisseria meningitidis or Streptococcus pneumoniae. The associated disseminated intravascular coagulation supported the former but the high white cell count and the pronounced neutrophilia supported the latter. Haemophilus influenzae meningitis would be unlikely in a patient of this age, although not impossible. Appropriate drugs in meningitis would be either ampicillin or chloramphenicol with sulphonamides.

If the primary disease was septicemia, in a patient coming from home and with no predisposition to infection, we considered Staphylococcus aureus to be the likely organism. One would have to assume resistance to penicillin. The neutrophilia would be in keeping with this diagnosis. In Gram-negative septicemia, although the white cell count is typically low, disseminated intravascular coagulation is often a feature and this possibility could not be discounted. We considered resistant Gram-negative bacilli, such as pseudomonads, unlikely. For “blind” treatment of septicemia we would choose either ampicillin plus cloxacillin or gentamicin plus penicillin or lincomycin.

Our initial choice of treatment was, therefore, large doses of ampicillin and cloxacillin since this regimen seemed to cover most of the possibilities which we had considered. This produced a good response in temperature and pulse rate.

Meningitis was then excluded and all the blood cultures yielded Staphylococcus aureus. This strain produced penicillinase and its minimum inhibitory concentration (MIC) to penicillin was 0-25 µg. Our choice of specific treatment lay between a penicillinase-resistant penicillin, such as cloxacillin, or one of the cephalosporins, both these drugs being bactericidal and relatively non-toxic. Cloxacillin was, therefore, continued, but since its action may be incompletely bactericidal or slow we decided to add a second effective drug because of the possibility of endocarditis.

We also practise combination treatment for serious staphylococcal infection throughout the hospital to keep the emergence of resistant strains to the minimum. We chose lincomycin because it is bactericidal to most strains of staphylococci; does not antagonise cloxacillin; and is compatible with the latter in intravenous fluids—an important point where giving intramuscular drugs was precluded. We were prepared to give a long course if endocarditis was present, and our chosen drugs were both capable of oral administration in convalescence, clindamycin being substituted for lincomycin at that stage.

We were assuming the presence of endocarditis because it is common in staphylococcal septicemia. Staphylococcus aureus may attack and damage previously normal hearts, but this patient was known to have a longstanding valve lesion.

**Role of Heparin**

Professor McNicol: Thank you. She was given cloxacillin and ampicillin, changed to cloxacillin and lincomycin plus steroids, but no heparin. The reason for not giving her heparin was that there are no good data on the role of heparin in this syndrome and, although there are many anecdotal reports of improvement after giving heparin, disaster with heparin has also been recorded. This patient had haemorrhages in the skin and we thought at first that her meningism might be due to red cells in the CSF.

The next day the results of her coagulation studies had improved, and although she was still thrombocytopenic her kaolin cephalin time was shorter, the plasma fibrinogen level had risen, and the levels of fibrinogen/fibrinogen degradation products had fallen to 16 mg/l. This striking improvement was produced with antibiotics without heparin. The blood film still showed microangiopathic haemolytic anaemia. A skin biopsy was performed on the fifth day, which Dr Dixon will review.

Dr Dixon: The biopsy came from the edge of a haemorrhagic area of psoriasis. The small blood vessels in the dermis all contained homogenous fibrinous material. There were no platelet thrombi nor any angiopathy.

Professor McNicol: On the day of the skin biopsy the microangiopathic features had disappeared from the blood film and platelets were reappearing. The patient was improving generally. Three days later, however, the electrocardiogram (ECG) shows increased S-T segment change. She also had diarrhoea, which we thought might be due to clindamycin—so that was stopped. Clindamycin diarrhoea usually occurs within seven days with characteristic sigmoidoscopic appearances which she did not have, but takes a long time to recover.

Gangrene of the fingers was then fully developed but the coagulation data were normal with no evidence of disseminated intravascular coagulation. The diarrhoea settled spontaneously but pulmonary oedema occurred.

Professor Whitfield: I think her coronary arterial disease was caused by her thrombotic thrombocytopenic purpura. But she had a severe illness and a bad heart and maybe some other arrhythmia developed. This ECG suggests she had had a myocardial infarction.

Professor McNicol: That was our clinical interpretation. On the day of her death there were two episodes of ventricular fibrillation, the second being fatal.

Professor Whitfield: To summarise, then, she had staphylococcal septicemia, possibly infective endocarditis—though without great relevance to the outcome. The important part of her illness was the thrombotic thrombocytopenic purpura, which destroyed an already diseased heart and caused progressive renal failure. I accept the unproved value of heparin and think that the important thing was to control her infection. The steroids do seem to have been effective in raising her platelet levels. You had controlled her infection and her disseminated intravascular coagulation and she died from a cardiac death.

Professor Booth: Was the left atrium enlarged on the x-ray film?
Professor McNicol: None of the x-ray films of the chest show this. Would Dr Dixon please give us the necropsy findings.

Necropsy findings

Dr Dixon: The most striking external feature was the gangrene of four fingers of the right hand and of the tips of the 4th and 5th fingers of the left hand. There was also haemorrhage into patches of psoriasis on both arms and face, and histologically this was associated with persistence of bland fibrin thrombi in dermal capillaries. Such fibrin thrombi were not found elsewhere.

The heart weighed 450 g. The right atrium and the tricuspid and pulmonary valves were healthy. The right ventricle was hypertrophied. The left atrium was dilated and its endocardium thickened. It contained a large pale polypoid pedunculated thrombus, which was laminated on section. On microscopy it showed mucoid degeneration but no evidence of superimposed infection. The mitral valve admitted only one finger. The leaflets were nodular and calcified and the chordae tendineae shortened and thickened. A single large friable vegetation was attached to the anterior leaflet (fig 3). The aortic valve showed slight fusion of its commissures and its thickened cusps contained foci of calcification (fig 4). In addition, there was a row of small vegetations close to the line of closure. Microscopically these consisted of fibrin, fibroblasts, macrophages, and many polymorphs, and, like the mitral valve vegetation, contained Gram-positive cocci.

The coronary arteries showed only mild atherosclerosis and were free from thrombus but, on sectioning, the septal and posterior myocardium was pale, indicative of recent infarction. On microscopy this was unusually focal, with scattered small groups of muscle fibres undergoing necrosis frequently related to occlusion of arterioles and capillaries by platelet thrombi (fig 5). A block of tissue from a gangrenous finger showed necrotising arteritis affecting a small digital artery (fig 6).

The trachea and bronchi were mildly inflamed. The lungs, which were normal grossly, showed numerous foci of broncho-pneumonia on microscopy. Elsewhere there were foci of haemosiderin-laden macrophages with mild interstitial fibrosis. The small muscular pulmonary arteries showed moderate medial hypertrophy but no intimal fibrosis.

![FIG 3—Heart opened through left atrium and ventricle showing a large polypoid thrombus attached to the interatrial septum and a friable vegetation attached to the anterior leaflet of the mitral valve.](image)

![FIG 4—Aortic valve. The cusp is distorted by heavily collagenised fibrous tissue containing foci of calcification and superimposed fibrinous vegetations. (H and E x 7.)](image)

![FIG 5—Myocardium showing scattered degenerating fibres (darker staining) and an arteriole occluded by platelet thrombus. (H and E x 270.)](image)

![FIG 6—Small digital artery with destruction of its wall, dense polymorph infiltration, and occlusion by fibrin showing early organisation towards the narrow lumen. (Martius-scarlet-blue x 93.)](image)
The kidneys were smaller than normal—the right weighed 125 g and the left 120 g. There was patchy congestion of the cortex and punctate depressed scarring, shown to be old infarcts histologically. There were a few small pyaemic abscesses in the medulla. The glomeruli were hypercellular, showing loss of peripheral capillary lumina, increased polymorphs, and relatively few red blood cells (figs 7 and 8). In 1-μm resin-embedded sections the hypercellularity was predominantly endothelial, with some non-specific increase in mesangial matrix and slight thickening of capillary loops (fig 9). On electron microscopy there were no granular deposits in the subepithelial region, identical to those seen in poststreptococcal glomerulonephritis. These have been reported in cases of proliferative glomerulonephritis associated with coagulase-positive staphylococcal endocarditis, and have been interpreted as deposits of antigen-antibody complexes. Despite their absence in this case, the peripheral vasculitis and the diffuse proliferative glomerulonephritis can best be explained on the basis of immune complex deposition.

There was no evidence of pseudomembranous colitis. The pancreas was macroscopically normal but showed patchy acinar ectasia on microscopy (fig 10). This feature is found with increased frequency in patients dying of uraemia. There was no meningitis and no abnormality was found in the brain.

The main pathological findings, therefore, were focal myocardial infarction and diffuse proliferative glomerulonephritis complicating staphylococcal endocarditis which was a consequence of old aortic and mitral valve disease and widespread psoriasis.

Conclusions

Professor McNicol: We were surprised by this form of glomerulonephritis. Would Professor Whitfield like to comment?

Professor Whitfield: I had not expected it to be present either.

Professor McNicol: Would Dr Taylor like to comment?

Dr Taylor: The chain of pathological events started with a staphylococcal infection of a psoriatic plaque; then bacterial infection of a damaged heart valve, which led to an immune complex disorder with associated disseminated intravascular coagulation. That went on to focal vascular lesions affecting the heart, kidneys, and fingers. Those in the heart finally gave rise to a fatal dysrhythmia. Even in retrospect I am at a loss to know how we could have prevented her death.

Professor McNicol: The one aspect of treatment that was controversial was not to give heparin. Would heparin have inhibited the evolution of the immune complex disease? There is little evidence from published work that it would. If you apply Bertrand Russell’s “habit of forming opinions on the evidence
and holding them with that degree of certainty which the evidence warrants" to the use of heparin in either disseminated intravascular coagulation or immune complex disease, you don’t use it. Samuel Butler gave another view, that “life is the art of drawing significant conclusions from insufficient evidence,” and I have no doubt that some would have treated the patient with heparin. The patient died and who knows if the treatment was right or wrong?

APPOINTMENTS OF SPEAKERS

(1) Professor G P McNicol, MD, PhD, head of department of medicine, University of Leeds.
(2) Dr S H Taylor, BSc, FRCPed, senior lecturer in medicine, deputy director of cardiovascular unit, University of Leeds.

Hospital Topics

Why do people use paracetamol for suicide?

B G GAZZARD, M DAVIS, J SPOONER, ROGER WILLIAMS

British Medical Journal, 1976, 1, 212-213

Summary

A questionnaire to assess motives for choosing paracetamol as a suicidal agent was completed by 107 patients admitted after an overdose of the drug. None of the 48 patients interviewed would have chosen paracetamol had they known that there would be an interval of two to three days before the onset of serious symptoms. Only five of the patients had obtained the drug on prescription, but the remainder had obtained it easily from a retail pharmacy. There was no apparent reason for the preference for paracetamol. It would be difficult to restrict the availability of paracetamol, and educating the public about the effects of an overdose would be more appropriate.

Introduction

Taking an overdose of a drug is now so common that it warrants the description of “the modern epidemic.” In Britain at least 15% of acute adult medical admissions to hospital are for self-poisoning. This amounts to some 100 000 admissions a year in England and Wales, a figure that has nearly doubled since 1965. One analysis has shown that the chief agents used are sedatives, tranquillisers, and antidepressants, and they accounted for over 2300 deaths in Great Britain in 1973. In the same year analgesic preparations containing salicylates and paracetamol caused 17% of hospital admissions for self-poisoning, and no fewer than 201 patients died from salicylate overdose, and 66 from paracetamol. In strong contrast to the effects of an overdose of salicylates or of sedative and antidepressant drugs, taking large quantities of paracetamol does not lead to rapid loss of consciousness. Apart from some early nausea and vomiting due to gastric irritation the patient may feel quite well until hepatic necrosis develops some two to three days later. Nevertheless, in spite of its lack of immediate clinical toxicity there has recently been an increasing number of cases of overdosage with paracetamol, while the incidence of deaths from salicylates has remained fairly constant. In view of the different effects of overdose with paracetamol compared with other agents, we studied the reasons for selecting the drug for self-poisoning to try and identify means of dealing with this abuse. We asked patients who had taken an overdose of paracetamol to complete a questionnaire.

Patients and methods

The questionnaire asked four basic questions: how were the tablets obtained; were they originally obtained specifically for taking an overdose; why was paracetamol chosen in preference to other drugs; and did you know that liver failure was a feature of paracetamol overdose? The patients were also asked whether they would have taken the same quantity if the tablets had been foil-wrapped. A total of 107 patients (69 females and 38 males) answered the questionnaire. Forty-eight of them were interviewed and completed the questionnaire while they were still in hospital and 31 were interviewed as outpatients; the remaining 28 completed it by post. All these patients had been admitted to the liver unit at King’s College Hospital, but, as some of them had been transferred from other hospitals after developing hepatic dysfunction, probably relatively more had taken a hepatotoxic overdose of paracetamol than might have been admitted to a general hospital. The study was carried out

References