CASE REPORTS

Salmonella typhimurium pancarditis

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THE LESS virulent *Salmonellae*, among which is included *Salmonella typhimurium*, generally cause only gastro-enteric symptoms. A more severe infection may complicate this alimentary illness, especially if there is a co-existent reason for debilitation (Bennett & Hook, 1959). Infrequently in this circumstance is the heart involved and if so bacterial endocarditis is the likely consequence (Schneider, Nernoff & Gold, 1967). Pancarditis with extensive involvement of the pericardium, myocardium and endocardium has rarely been described (Hennigar *et al.*, 1953). The case of a patient seen at the Royal Perth Hospital who died of *S. typhimurium* pancarditis complicating systemic lupus erythematosus (SLE) is presented.

Case report

A 61-year-old European male had been unwell for 6 months. He had episodic pleuritic chest pain and cough, was anorexic and had lost 45 lb in weight. For 2 weeks he had been increasingly short of breath with severe left-sided anterior chest pain.

On examination he was moderately dyspnoeic, sweating profusely but afebrile. Auscultation of the heart was normal, the blood pressure was 130/80 mm Hg and the pulse 72/min. In the chest there were widespread coarse rales with moist crepitant sounds at both bases.

Within 36 hr he complained of pain in the shoulders, elbows, wrists, metacarpo-phalangeal joints and the left knee which were tender and hot to palpation but not swollen. His temperature had risen to 101.3°F and the pulse rate to 104/min. Chest pain was now localized to the left sub-sternal region and his dyspnoea had worsened. For the next 14 days he remained gravely ill with a high swinging fever. Coarse and moist sounds continued

to be heard in the lung fields. On the 17th hospital day the pulse rate dropped to 60/min and he became drowsy. He died 22 days after admission.

Investigations. Two days before death blood cultures were taken and *S. typhimurium* was grown. It was sensitive to streptomycin, tetracycline, chloramphenicol, kanamycin, colistin and ampicillin, but resistant to penicillin, erythromycin and methicillin. Investigations on admission gave the following results: haemoglobin 11.2 g/100 ml; WBC 4000/mm³ (neutrophils 78%, lymphocytes 15%, monocytes 4% and eosinophils 3%); serum electrolytes normal; the chest X-ray showed pleural thickening in both costophrenic angles and moderate cardiac enlargement; sputum cultures yielded no pathogens; the ECG demonstrated mild left axis deviation and widespread T-wave inversion. With the onset of the arthralgia and localization of the chest pain sub-sternally further investigations were: ESR 52 mm/hr (Westergren), later rising to 69 mm; latex screening test for rheumatoid factor and Rose and Ball test negative; LE cell test strongly positive; serum alkaline phosphatase 10.5 King-Armstrong units; serum glutamic oxaloacetic transaminase 64 Karmen units; serum glutamic pyruvic transaminase 95 units; serum protein electrophoresis was only abnormal in that the albumin was lowered to 1.92 g/100 ml; the ECG remained initially unchanged. On day 17 the ECG showed complete heart block.

Treatment. As an infection was suspected, from admission to the 10th day he was given oral ampicillin 500 mg 6-hourly. This was altered on day 11 to tetracycline 250 mg 6-hourly (McNally, Kennedy & Grace (1964) considered this type of antibiotic regime inadequate for *Salmonella* septicaemia, which probably explains why the blood culture was positive). As identification of the organism was not made until after the patient's death, adequate appropriate antibiotic therapy was not instituted. Diuretics and digitalis were first administered on day 17. At no stage did he receive steroid therapy.

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Necropsy. Macroscopic examination: The heart weighed 530 g. The parietal and visceral pericardium were thickened and adherent. In the right atrium there were many friable, flat plaques of 2–5 mm over the mural endocardium extending on to the tricuspid valve. Similar plaques were present in the valve pocket and the right ventricle. The ventricular muscle was diffusely discoloured yellow-red. Left atrial changes resembled those of the right chamber but were more severe. The mitral valve was involved and on both leaflets verrucae had developed. In the left ventricle, in addition to more mural endocardial plaques, there was extensive damage to the myocardium which was oedematous, thickened and mottled yellow-red. The major coronary arteries contained minimal atheroma and were patent.

Both pleural cavities were obliterated by dense fibrosis and the lungs were congested and oedematous. Throughout the colon there were small superficial ulcers. Other organs including the joints were macroscopically normal.

Culture of heart muscle yielded only an overgrowth of contaminants. Selective media were not used, the result of the ante-mortem blood cultures not being known at the time of necropsy.

Microscopic findings: The pericardial thickening was due to fibrosis and a dense fibrinous exudate. There was a scattered infiltration of the pericardium with lymphocytes and plasma cells and also many foci of neutrophil polymorphs. Most of the myocardium contained a diffuse or focal infiltration of polymorphonuclear leucocytes (Fig. 1). There was considerable accompanying myocardial necrosis. Small vessels were often directly involved by the inflammatory process but many small arteries remote from severe lesions also showed an acute vasculitis (Fig. 2). Larger coronary arteries were normal. In zones of the myocardium less affected by acute lesions there was an increase of interstitial histiocytes, lymphocytes and plasma cells. Most endocardial plaques consisted of degenerating polymorphonuclear leucocytes within a dense fibrin network but some were composed mainly of mononuclear cells and fibrinoid material, and were characteristic of SLE (Gross, 1940). In the aortic, mitral and tricuspid valve rings changes were typical of SLE and included haematoxyphil bodies. Along the free margin of the cusps many vegetations resembled those described in SLE, but there were also acute inflammatory vegetations. Gram stains demonstrated the presence of intracellular Gram-negative bacilli in the acute foci of the pericardium, myocardium and endocardium.

The pleura showed a non-specific collagenous thickening. In the colon the mucosal lesions consisted of acute superficial necrosis. Plasma cells were considerably increased in the axillary lymph nodes.

FIG. 1. Myocarditis. The main inflammatory cell is the neutrophil polymorph. H & E, $\times 200$.

FIG. 2. Arteritis. Acute inflammation of the vessel wall with minimal extension into the adjacent myocardium. H & E, $\times 45$.

There was a mild polymyositis. Joint and synovial changes were consistent with SLE. In the kidney focal thickening of the basement membrane had occurred.

Discussion

The features of this patient's illness are those of SLE complicated by a terminal bacterial infection—*S. typhimurium* septicaemia, resulting in superinfection of the Libman-Sacks lesion in the heart. Acute infective myocarditis, pericarditis, endocarditis and coronary arteritis developed. Although the organism was not recovered at necropsy the presence, histologically, of intracellular Gram-negative bacilli in the acute inflammatory foci of the heart is interpreted as evidence that the *Salmonella* was responsible for these lesions. The infection may have arisen from the gut where (despite the absence, clinically, of gastroenteritis) there were acute infective lesions at necropsy.

Bacterial endocarditis due to a *Salmonella* (other than *S. typhi*) has occasionally been recorded and in a summary of individual cases reported to 1967 some twenty-four could be listed (Schneider *et al.*, 1967). Of these only three were due to *S. typhimurium*. Pericarditis due to the group has been reviewed (Levin & Hosier, 1961), covering eight case reports, three of which were due to *S. typhimurium*. However, in broader epidemiological surveys of salmonellosis additional cases are documented. In one series twenty cases of endocarditis and pericarditis are listed, four due to *S. typhimurium* (Saphra & Winter, 1957).

The myocardium would appear to be the most resistant cardiac tissue there being but two detailed descriptions. One concerned a *Salmonella* C₁ group organism which in a previously healthy 2-year-old Negro boy caused pancarditis (Hennigar *et al.*, 1953). The other, occurring in a 62-year-old Negro, was due to *S. choleraesuis* which produced myocarditis in a heart already diseased by infiltration with lymphosarcoma (Sanders & Misanik, 1964). Nevertheless myocardial involvement is probably not as exceptionally rare as such isolated reports would indicate, for in a *S. typhimurium* epidemic of 654 verified cases, histological evidence of myocarditis was stated to have been present in five of the eleven cases that came to necropsy (Bengtsson *et al.*, 1955). In three of these there had been clinical and electrocardiographic evidence of damage to the myocardium. Some descriptions (De Swiet, 1949; Stumpe & Baroody, 1951; Thomas, 1952) of *Salmonella* endocarditis briefly allude to minor non-specific 'toxic' myocardial changes but this was neither prominent nor accompanied by a polymorphonuclear leucocytic response.

Isolated coronary arteritis may occur. Barnett & Zimmerman's (1947) patient died as a result of myocardial infarction due to coronary arteritis and thrombosis complicating *S. choleraesuis* septicaemia.

Valvular lesions of the type described by Libman & Sacks (1924) and Gross (1940) as occurring in SLE are known to be prone to bacterial superinfection (Gross, 1940; Bunim, 1940; Harvey *et al.*, 1954; Hejtmancik *et al.*, 1964). Only once has *S. typhimurium* been proved as the cause of endocarditis in SLE (Weinstein, Lerner & Chew, 1964).

Because of the observation that *Salmonellae* infect atherosclerotic aneurysms and diseased valvular and mural endocardium it has been suggested that these organisms have a predilection for abnormal vascular endothelium (McNally *et al.*, 1964). In this present case damage to the cardiac endothelium by SLE may partly explain why the *S. typhimurium* became localized in the heart.

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References

- BARNETT, R.N. & ZIMMERMAN, S.L. (1947) Coronary arteritis with fatal thrombosis due to *Salmonella choleraesuis*, variety *Kunzendorf*. *Amer. Heart J.* **34**, 441.
- BENGTSSON, E., HEDLAND, P., NISELL, A. & NORDENSTAM, H. (1955) An epidemic due to *Salmonella typhimurium* (Breslau) occurring in Sweden in 1953. *Acta med. scand.* **153**, 1.
- BENNETT, I.L. & HOOK, E.W. (1959) Salmonellosis—a review of some unusual aspects. *Ann. rev. Med.* **10**, 1.
- BUNIM, J.J. (1940) Lupus erythematosus disseminatus. *Ann. intern. Med.* **13**, 1390.
- DE SWIET, J. (1949) Subacute bacterial endocarditis due to *Salmonella typhimurium*. *Brit. med. J.* **ii**, 1155.
- GROSS, L. (1940) The cardiac lesion in Libman-Sacks disease. With a consideration of its relationship to acute diffuse lupus erythematosus. *Amer. J. Path.* **16**, 375.
- HARVEY, A.M., SHULMAN, L.E., TUMULTY, P.A., CONLEY, C.L. & SCHOENRICH, E.H. (1954) Systemic lupus erythematosus: review of the literature and clinical analysis of 136 cases. *Medicine (Baltimore)*, **33**, 291.
- HEJTMANCIK, M.R., WRIGHT, J.L., QUINT, R. & JENNINGS, F.L. (1964) The cardiovascular manifestations of systemic lupus erythematosus. *Amer. Heart J.* **68**, 119.
- HENNIGAR, G.R., THABET, R., BUNDY, W.E. & SUTTON, L.E. (1953) Salmonellosis complicated by pancarditis. *J. Pediat.* **43**, 524.
- LEVIN, H.S. & HOSIER, D.M. (1961) *Salmonella* pericarditis: report of case and review of the literature. *Ann. intern. Med.* **55**, 817.
- LIBMAN, E. & SACKS, B. (1924) A hitherto undescribed form of valvular and mural endocarditis. *Arch. intern. Med.* **33**, 701.
- MCNALLY, E.J., KENNEDY, R.J. & GRACE, W.R. (1964) *Salmonella infantis* infection in a pre-existent ventricular aneurysm. *Amer. Heart J.* **68**, 541.

- SANDERS, V. & MISANIK, L.F. (1964) *Salmonella* myocarditis: report of a case with ventricular rupture. *Amer. Heart J.* **68**, 682.
- SAPHRA, I. & WINTER, J.W. (1957) Clinical manifestations of salmonellosis in man. *New Engl. J. Med.* **256**, 1128.
- SCHNEIDER, P.J., NERNOFF, J. & GOLD, J.A. (1967) Acute *Salmonella* endocarditis: report of a case and review. *Arch. intern. Med.* **120**, 478.

- STUMPE, A.R. & BAROODY, N.B. (1951) *Salmonella* endocarditis. *Arch. intern. Med.* **88**, 679.
- THOMAS, A.M. (1952) A case of acute infective endocarditis caused by *Salmonella dublin*. *Arch. Path.* **53**, 408.
- WEINSTEIN, L., LERNER, P.I. & CHEW, W.H. (1964) Clinical and bacteriologic studies of the effect of 'massive' doses of penicillin G on infections due to Gram-negative bacilli. *New Engl. J. Med.* **271**, 525.

A fatal reaction to diazoxide

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DIAZOXIDE has been available for over 5 years for the treatment of hypoglycaemia from any cause. This is the first published report of a fatal reaction to the drug.

Case report

A 58-year-old spinster was first seen in April 1967 complaining of cough and dyspnoea following a chest infection 4 months previously.

On examination she was found to have atrial fibrillation, mitral stenosis and a large right pleural effusion. The fluid was bloodstained and contained no malignant cells. The effusion was thought to be due to pulmonary infarction, so she was treated with anticoagulants and her dyspnoea improved.

In July 1967 she still had radiological evidence of a right pleural effusion but aspiration was unsuccessful, suggesting collapse of part of the right lower lobe. In October 1967 Mr G. Keen performed a closed mitral valvotomy from which she made a good recovery.

One month later she became confused and sweaty at about 06.00 hours on several consecutive mornings and the blood sugar during an attack was found to be 20 mg/100 ml.

Further investigation revealed a persistently low fasting blood sugar and plasma insulin (10 μ U/ml) neither of which was raised by glucagon, 1 mg i.v. A 6-hr glucose-tolerance curve (Fig. 1) showed diminished glucose tolerance with early and late hypoglycaemia. Tolbutamide 1 g i.v. and glucose 50 g by mouth produced a normal rise in plasma insulin from 10 μ U/ml (fasting) to 50 μ U/ml in 10 min. A normal level of 'insulin-like activity' was also found.

FIG. 1. Six-hour glucose-tolerance curve.

The conclusions drawn from these investigations were that there was no evidence of an insulinoma and that she probably had an extra-pancreatic tumour which was causing hypoglycaemia. There was no mass in the abdomen and bronchoscopy was normal. As the site of the tumour was not obvious she was treated with prednisone in an attempt to raise her blood sugar sufficiently to prevent her symptoms. Five milligrams nightly had no effect, but 60 mg/day abolished her symptoms and her fasting blood sugar rose to 70 mg/100 ml. After 10 days the dose was reduced to 30 mg daily and continued for 5 weeks during which time she had no hypoglycaemic reactions whatsoever. This naturally caused undesirable side effects, so the drug was withdrawn and treatment with diazoxide 100 mg t.d.s. was started on 14 March 1968 (see Table 1). Two days later there was no improvement, so bendrofluazide 10 mg daily was added. The dose of diazoxide was subsequently increased until on 600

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