PAPERS AND SHORT REPORTS

A case of Lassa fever: clinical and virological findings

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Abstract

Five days after arriving in London from Jos a young Nigerian woman developed a severe and prolonged illness that proved to be Lassa fever. Virus was not detected in urine during the first three weeks but then appeared and reached a peak during the sixth week, with continuing excretion for 67 days after the onset of illness. Laboratory investigations showed evidence of extensive tissue damage and disturbance of clotting, but there was no serious bleeding and she eventually made a complete recovery despite a high sustained viraemia and severe liver damage. Convalescent serum was used in treatment but it was difficult to assess its contribution to the favourable outcome.

Case report

An 18-year-old Nigerian woman visiting London fell ill on 28 December 1981 with fever, headache, myalgia, nausea, and vomiting. By 4 January she felt so unwell that she was referred by her general practitioner to the accident and emergency department of St Thomas's Hospital and was admitted for investigation.¹ Her fever persisted, and intensive investigation failed to disclose the cause; by 8 January a diagnosis of Lassa fever seemed to be a strong possibility. In view of this and the possible risk of infection in the event of haemorrhage she was transferred to the high-security infectious diseases unit at Coppetts Wood Hospital, where she was admitted into a Trexler negative-pressure patient isolator.²

When she arrived on 9 January her temperature was 39°C, pulse rate 132 beats/min, and blood pressure 90/60 mm Hg. There was florid oedema of the lower face and upper neck. The abdomen was distended and tender but bowel sounds were present. She was drowsy but rousable and orientated. There was no rash, pharyngitis, or

enlargement of lymph nodes. She had haematuria and proteinuria on chemical testing. White blood cell count was $16.2 \times 10^9/l$ with a differential count of 68% polymorphonuclear cells, 16% lymphocytes, 9% monocytes, and 7% abnormal mononuclear cells. Blood urea concentration was 12.6 mmol/l (76 mg/100 ml), plasma sodium 131 mmol(mEq)/l, and potassium 4.0 mmol(mEq)/l. The course of the illness strongly suggested Lassa fever, but the possibility of septicaemia could not be ruled out in view of the polymorphonuclear leucocytosis. Specimens were taken for virological and bacteriological studies and treatment started with chloramphenicol and one unit of Lassa fever convalescent serum. Supportive treatment was given with vitamin K, metoclopramide, and continuous intravenous infusion of an electrolyte and glucose solution.

The fever continued, but there was no further deterioration in her general condition. Blood pressure and blood urea concentration returned to normal after three days. The leucocytosis persisted and reached a peak of $26 \times 10^9/l$ on 11 January. The erythrocyte sedimentation rate was surprisingly low at 25 mm in the first hour. Though haematuria continued for nearly three weeks, the only other evidence of bleeding was a small amount of blood-streaked sputum during the second week of illness.

The diagnosis was confirmed on 13 January by the presence of Lassa virus in blood cultures though not in urine. Chloramphenicol was stopped and a second unit of Lassa convalescent serum given on 16 January. She remained gravely ill, and her temperature did not return to normal until 29 January, 32 days after the onset of fever. Outstanding features of the illness were her extreme lassitude and complete loss of appetite, which did not improve until the last week of January. She remained unwell for a further month and lost a considerable amount of hair during convalescence.

Virus had cleared from her blood by 28 January but persisted in her urine until 8 March. At this point she was removed from the Trexler isolator and transferred to safe accommodation pending final clearance of urine. She was finally discharged from hospital on 27 March after her urine had been reported free from virus on four consecutive occasions.

Virological investigations

Lassa virus was isolated in Vero cell cultures from a blood sample taken on 8 January, which was estimated to be 12 days after the onset of the illness. Examination of the tissue culture isolate by electron microscope revealed typical arenavirus particles. The diagnosis was confirmed by indirect immunofluorescence assay using standard positive anti-Lassa sera.

Virus isolations and serological studies were made on specimens of blood, urine, and throat washings collected during the acute and convalescent phases of the illness. The highest level of virus in the

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blood ($10^{5.2}$ median tissue culture infective dose/ml) was found in the sample taken on 8 January (figure); the level then declined, and the virus was undetectable by day 32 (28 January).

No virus was isolated from urine samples collected before day 22 (18 January). Thereafter it was evident until day 67. The peak level of virus ($10^{4.0}$ median tissue culture infective dose/ml) was found in the urine on day 36, but levels ranging from $10^{2.0}$ to $10^{4.0}$ median tissue culture infective dose/ml were evident from days 22 to 53. The level fell gradually, and the virus was undetectable by day 71.

Throat washings taken throughout the patient's isolation did not yield any virus.

Circulating antibody levels were determined by immunofluorescence. Anti-Lassa antibody was present at a titre of 1/64 on day 22, and peak titres of 1/24 000 and 1/32 000 were reached on days 40 and 55: this level was sustained throughout the remainder of the illness. Circulating anti-Lassa antibody of 1/16 to 1/32 was detectable only between days 19 and 24.

Immunofluorescence titres of convalescent sera given on 9 January and 16 January were 1/1024 and 1/2048 respectively.

Surveillance

When the patient was transferred to Coppetts Wood Hospital the 24 staff looking after her were placed under surveillance and their temperature and state of health recorded daily. Several developed acute respiratory illness of short duration, but none produced antibody to Lassa virus.

Course of Lassa fever in patient.

Discussion

J B McCormick and others (unpublished information) assessed the factors influencing the prognosis of Lassa fever and found that 17 patients died out of 18 patients with serum aspartate transaminase activity in excess of 150 IU/l and a viraemia greater than 10^4 median tissue culture infective dose/ml. Our patient survived with a transaminase activity of 4440 IU/l and a viraemia greater than 10^5 median tissue culture infective dose/ml. Whether this favourable outcome was attributable to the use of convalescent serum or to intensive nursing care and supportive treatment is impossible to decide.

The value of convalescent serum in the treatment of Lassa fever has not been established. Some have found it to be beneficial,³ while others have been less impressed.^{4,5} In our patient there did not appear to be any harmful effects, and in particular no deterioration in renal function occurred. Although her temperature fell briefly after the first infusion of serum, there was no obvious change in her general condition and no apparent effect on the concentration of virus in her blood. Moreover, virus did not appear in her urine until after the first infusion and persisted after the second.

Restoration of water and electrolytes improved renal function, and infusion of glucose appeared clinically to arrest deterioration in liver function. Apart from giving regular injections of vitamin K we made no attempt to restore clotting factors, but fortunately no serious haemorrhage occurred.

During the acute stage of the illness the presence of virus in blood severely restricted haematological and biochemical investigations to guide management. The striking polymorphonuclear leucocytosis is an unusual finding in an acute virus infection but could well be attributed to the extensive cellular damage. Abnormal mononuclear cells are common in some virus infections and are of uncertain importance. The kidneys in particular were affected in this patient, who showed an initial rise in blood urea concentration followed by prolonged haematuria and proteinuria. The lack of evidence of disseminated intravascular coagulation¹ suggests that the disturbance of clotting and tendency to bleed were probably related to impaired liver function and vascular endothelial damage. She also had some evidence suggesting serious liver damage, in particular grossly raised serum aspartate transaminase activity and hydroxybutyrate concentrations (detected at St Thomas's Hospital),¹ but in view of the relatively lower activity of serum alanine transaminase and the normal bilirubin concentration that cannot be the whole explanation. It is more likely that a variety of tissues, such as kidney, muscle, and blood, also suffered cellular damage and contributed to the high enzyme activities.

Persistence of virus in the urine for 67 days from the onset of illness delayed the patient's discharge from strict isolation. In previous cases the longest reported period of urinary excretion was 42 days.

During the first three weeks of the illness virus was present only in blood and there was little risk to casual contacts. By the time virus appeared in the urine the patient was in strict isolation and precautions were being enforced. Experience with this case supports the views expressed by Galbraith and his colleagues⁷ that there is minimal risk to the community and that serious risk is confined to those dealing with blood and urine. Surveillance would seem to be unnecessary for casual contacts in the United Kingdom but justifiable for those dealing with body fluids.

We are grateful to Dr H A K Rowland, of the Hospital for Tropical Diseases, for supplying the Lassa fever convalescent sera.

References

- Cooper CB, Gransden WR, Webster M, et al. A case of Lassa fever: experiences at St Thomas's Hospital. *Br Med J* 1982;285:1003-5.
- Trexler PC, Emond RTD, Evans B. Negative-pressure plastic isolator for patients with dangerous infections. *Br Med J* 1977;iii:559-61.
- Leifer E, Gocke DJ, Bourne H. Lassa fever, a new virus disease of man from West Africa. II. Report of a laboratory-acquired infection treated with plasma from a person recently recovered from the disease. *Am J Trop Med Hyg* 1970;19:677-9.
- Keane E, Gilles HM. Lassa fever in Panguma Hospital, Sierra Leone 1973-6. *Br Med J* 1977;ii:1399-402.
- Clayton AJ. Lassa immune serum. *Bull WHO* 1977;55:435-9.
- Emond RTD. Hospitalisation of patients suspected of highly infectious disease. In: Pattyn SR, ed. *Ebola virus haemorrhagic fever*. Amsterdam: Elsevier/North Holland Biomedical Press, 1978:389-96.
- Galbraith NS, Berrie JRH, Forbes P, Young S. Public health aspects of viral haemorrhagic fevers. *Journal of the Royal Society of Health* 1978;98:152-60.

(Accepted 2 August 1982)