Treatment failure with penicillin in early syphilis

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SUMMARY A patient with primary syphilis had a recurrence of his penile chancre after generally acceptable penicillin treatment. Retreatment with a similar but extended penicillin regimen was successful. This is the first report of such a treatment failure.

Case report

HISTORY

A 32-year-old Spanish homosexual man presented at the venereal diseases clinic at St Stephen's Hospital on 10 March 1978. He had noticed a sore on his penis for one week, to which he had applied a proprietary cream (not identified but bought in England). He admitted to sexual exposure in Paris on 17 December 1977 with a casual, untraceable contact and again in London on 3 March with a friend. He denied passive anal intercourse and orogenital activity. The only relevant past history was an episode of hepatitis in 1972.

EXAMINATION

On examination the foreskin was retractile, and there was a classical Hunterian primary chancre on the dorsal surface of the shaft of the penis at the coronal sulcus. The lesion measured 1 cm across. There was a painless, discrete, palpable lymph node in the left groin, but there were no other clinical findings.

INVESTIGATIONS

The results of investigations were as follows:

Darkground examination

Many characteristic motile treponemes were seen on 10 March 1978.

Serology

The results of both the Venereal Disease Research Laboratory (VDRL) and fluorescent treponemal antibody absorption (FTA-ABS) tests were positive (VDRL test at a 1/2 dilution).

The *Treponema pallidum* haemagglutination (TPHA) and Reiter protein complement-fixation (RPCFT) tests also gave positive results. The results for HBs antigen and viral culture for herpes simplex virus were negative. *Neisseria meningitidis* was isolated from a throat culture.

MANAGEMENT AND COURSE OF ILLNESS

A diagnosis of primary syphilis was made and routine treatment with daily injections of 0.6 mega-units of aqueous procaine penicillin (Depocillin, Brocades GB Ltd) intramuscularly for 12 days was given. After the first injection the patient experienced a severe Jarisch-Herxheimer reaction. Treatment finished on the 21 March.

The patient attended the clinic 13 days later for his first follow-up blood test; he complained at this stage that his sore had not healed. He denied any sexual activity since 3 March. On examination, the site of the chancre was still distinctly visible and indurated. No darkground examination was carried out on this day. Three weeks later when the patient attended on 28 April it was clinically apparent that the patient again had a classical chancre 8 mm in diameter at exactly the same site as the initial lesion six weeks previously. There was a degree of sclerosing lymphangitis underlying the ulcer; this added thickness to the lesion when palpated. The patient described how the original sore had appeared to close over the surface but had remained tender and swollen as if 'pus remained inside'. The lesion then broke down two days later and fluid oozed from it. The patient had not received any other medication since his clinic treatment. The investigations on 28 April 1978 were as follows:

Darkground examination

Many characteristic motile treponemes were seen. For confirmation, a direct fluorescent treponemal antibody (FTA) test was performed at the Venereal

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Diseases Reference Laboratory at the London Hospital. This showed numerous bright fluorescing treponemes with the characteristic morphology of *Treponema pallidum* together with numerous pus cells and very few bacilli.

Serology

The VDRL test gave positive results (no dilution), as did the TPHA and RPCFT tests. The FTA test gave positive results for IgG antibody but negative results for IgM antibody.

No abnormalities were found on chest x-ray examination. The full blood count (FBC) was normal, and the urine analysis gave negative results for glucose, protein, and bilirubin.

RETREATMENT

Retreatment was started on 28 April 1978 with the same penicillin regimen; again a Jarisch-Herxheimer reaction occurred. After a week of treatment the ulcer was smaller (5mm) and darkground examination gave negative results. After 10 days' treatment the ulcer was a great deal smaller but was still indurated, and a small central area remained raw and oozed serum. After 15 days' treatment the ulcer surface had healed, although it was still indurated. A repeat VDRL test gave positive results (no dilution). The patient last attended five days after finishing his treatment on the 19 May 1978. There was minimal induration (1 cm) and no sign of the ulcer beginning to break down.

Discussion

The WHO recommendations for treatment of primary and secondary syphilis include a regimen of daily injections of aqueous procaine penicillin G at a dose of 600 000 units for a total of eight to 10 days (total 4.8–6.0 megaunits) (Idsøe *et al.* (1972)).

The United States Public Health Service also includes this regimen in their recommendations for early syphilis treatment (US Center for Disease Control, 1968). This recommended schedule was originally based on unpublished data; however, reports of results of treatment are now available. Schroeter *et al.* (1972) report on the results of treating 41 patients with primary and secondary syphilis who were followed up for more than one year. The retreatment rate at the end of one year was 3.8% and at the end of two years was 10.2%. The retreatment rate is a useful term in that it is not necessary to distinguish reinfections from treatment failures, often an impossible task. A recent report by Fiumara (1977a, b) gives a cure rate for treatment of primary and secondary syphilis with benzathine penicillin injections as

100%. However, he excluded all patients who needed retreatment from his figures, hence the possibly unrealistic cure rate. In England penicillin regimens vary from clinic to clinic; it has become accepted, however, that a regimen of daily treatments is the ideal treatment.

It cannot be doubted that our patient had primary syphilis, a chancre, on 10 March 1978 and again on 28 April 1978. In this case we do not think that a secondary microbial infection is likely to have been a complicating factor. Herpes culture showed negative results and healing occurred, albeit gradually, with the second course of treatment without the addition of any other antibiotics. A chancre redux—that is, a recurrence of the chancre at the same site following apparent healing—was said to be less rare in pre-penicillin days (Willcox, 1964). A pseudo chancre redux, a gummatous recurrence at the site of the original primary lesion, was excluded by finding live *Treponema pallidum* organisms (Hardy *et al.*, 1970).

The following are points which suggest a treatment failure:

1. The chancre recurred at the identical site.
2. The chancre was seen by one of us 13 days after the end of the first course of treatment (this is a shortish incubation period for syphilis).
3. During the second course of treatment it was noted that after only 10 days of treatment the ulcer had not healed over and was still oozing from a central erosion.
4. After treatment of primary syphilis there is thought to be a variable period of partial immunity to reinfection. Experimentally it is difficult to produce a primary chancre by inoculation during this period (Schofield, 1975).
5. Lastly, although it is difficult to accept, the patient absolutely denied any further sexual exposure. Needless to say this aspect was repeatedly investigated and must remain in question. (We were convinced that the patient would readily have admitted to a possibility of reinfection.)

To establish that nothing untoward had happened in the management of this patient, thorough discussion with all personnel concerned merely confirmed that the patient attended regularly for daily injections; this brought to light that the care with which penicillin doses were calculated and administered by the nursing staff was exemplary and they are to be congratulated.

There are two points which could suggest reinfection. Firstly, there was a gap of four weeks after the first treatment and before the second diagnosis was

made; and, secondly, there was a skin lesion remaining from the first chancre through which reinfection could have occurred and so produced an ulcer at the same site.

Conclusion

We do not consider there is evidence in this case to show that this was an infection with a treponeme which was less sensitive to penicillin. An extended course of treatment had produced what appears to be a satisfactory cure. The experience of this case indicates that there is no place for complacency in the treatment of early syphilis, and it re-emphasises what has been stressed by all preceding generations of syphilologists—the need for full surveillance after treatment.

In this case the possible reason for the failure of the initial treatment may have been the intense cell-mediated immune response which occurred, producing a primary chancre with marked fibrous infiltration and sclerosing lymphangitis locally; the amount of fibrous tissue possibly allowed an area of tissue to be incompletely penetrated by treponemacidal penicillin levels. Indeed, the patient stated that although the surface had almost healed by the end of the initial treatment the area remained

very swollen and hard, and this area subsequently broke down to produce the relapsed lesion.

Failure to cure syphilis with routine penicillin treatment has been reported before in a case of congenital syphilis (Hardy *et al.*, 1970). This is the first report, however, of an almost unequivocal treatment failure in primary syphilis with a generally acceptable treatment regimen.

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