Short Case Report

An unusual Jarisch-Herxheimer reaction

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The Jarisch-Herxheimer reaction was first described by Jarisch (1895) and the concept was elaborated by Herxheimer in 1902 (Stokes, Beerman, and Ingraham, 1944). The reaction was first observed after mercury inunctions; it can occur, mildly, after bismuth; it was a frequent sequel to the first injection of an organic arsenical, and it occurs in about 50 per cent. of cases of early syphilis after the first dose of penicillin. The reaction usually consists of a single episode starting some 2 to 12 hours after the beginning of therapy, and in cases of early syphilis a well marked general reaction presents with malaise, headache, flushing and sweating together with fever which may reach 104°F. Often there is an accompanying local response; a chancre may become swollen and painful; there may be the transient first appearance of a secondary rash, or a pre-existing rash may become more dense and florid. Most general reactions have passed off by the following day. Repeated systemic reactions have been evoked experimentally by giving successive small doses of penicillin (Farmer, 1948; Gudjonsson and Skog, 1968), but with doses of the usual therapeutic range a second reaction is undoubtedly a rare event. The purpose of this report is to describe such a case.

Case report

A 27-year-old Indian male, born in Kuala Lumpur, West Malaysia, was referred to the clinic with one month's history of penile irritation. He had had four sexual contacts during the previous 4 months. There was no past history of yaws or of sexually-transmitted disease.

Examination

There was maculopapular balanitis and a round indurated non-tender ulcer with a well-defined margin was present in the coronal sulcus. There was a discrete rubbery non-tender right inguinal lymph node.

Treponema pallidum was identified in serum expressed from the ulcer. The initial Venereal Diseases Reference Laboratory (VDRL) test and quantitative Reiter protein complement-fixation test were both reactive at a serum dilution of 1:32. A Gram-stained smear from the ulcer

showed no organisms resembling *Haemophilus ducreyi*, and acute and convalescent sera gave negative results to the lymphogranuloma venereum complement-fixation test. A subpreputial smear showed no fungal elements.

Treatment

The patient was admitted to hospital and started treatment with local saline washes and daily intramuscular injections of aqueous procaine penicillin 600,000 units. Within a few hours of the first injection he complained of malaise, headache, and generalized aching pains, and the temperature rose to 103.8°F. (Figure). There was now oedema around the penile ulcer but there was no rash or other apparent change.

The next morning he felt well, full examination showed no new abnormality, and darkground examination was negative for *T. pallidum*. He complained of the same symptoms a few hours after the second injection and his temperature gradually rose again to 103.4°F. (Figure).

FIGURE Temperature (°F.) and pulse rate/min. during the first 3 days of penicillin therapy

Another detailed physical examination directed to finding some other cause for the fever revealed nothing abnormal. A peripheral blood film at the second peak of fever showed no malarial parasites and a second film a few hours later was also negative. At this time the total white cell count was 6,000 per cu. mm. with a normal differential count, a mid-stream urine specimen was entirely normal, and the chest radiograph was clear.

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The next morning he again felt well and the temperature had fallen. Treatment was continued and the subsequent course was uneventful.

Result

The balanitis resolved in 5 days and the ulcer healed in 9 days. Penicillin was continued to a total of twelve injections and the VDRL test became negative 6 months later.

Discussion

The first febrile episode was considered to be a Jarisch-Herxheimer (JH) reaction but the second caused concern. At first this second bout was thought to be due to another infection exacerbated by the JH reaction, but the absence of appropriate clinical findings, the normal results of investigations, and the subsequent course indicated that no other infection was present. It is therefore suggested that the febrile episode following the second injection was a second JH reaction.

The mechanism of the JH reaction is not yet clearly understood. Farmer (1948) observed that very small doses of penicillin given to patients with early syphilis neither produced a JH reaction nor affected the treponemes in the lesions. Slightly larger doses (10 to 20 units/kg. body weight) produced febrile reactions but organisms were afterwards still present in the lesions. A dose of 2,000 to 4,000 units/kg. body weight given 24 hours later produced another febrile reaction, but within a few hours the treponemes had disappeared. If the initial dose was 2,000 or more units/kg. the organisms disappeared from the lesions and no reaction followed subsequent injections. Reactions do not occur in all patients and King (1964), reviewing the subject, suggested that a minimum number of treponemes must develop in the body before a reaction takes place, and that individual reactions to treponemidal activity vary.

The work of Farmer (1948) and of Heyman, Sheldon, and Evans (1952) and more recent studies, such as those of Viegas, Lisboa, and Aguiar (1969), indicate that the release of antigenic material by the sudden death of treponemes is an important part of the reaction. The fact that only one obvious generalized reaction usually occurs suggests that normally most of the treponemes are destroyed by the first dose, but because a single dose of 600,000 units procaine penicillin is insufficient to cure syphilis, viable organisms must persist after one such dose. A second injection presumably destroys more treponemes, so releasing more antigenic material which may again provoke a reaction. Response to this event

will vary from patient to patient, and in most cases it is probably mild and subclinical. In the case described above the reaction was marked. Another indication that the response of syphilis to penicillin may not be so straightforward as generally believed is that several groups of workers, reviewed by Dunlop (1970), have observed treponemes or treponeme-like forms persisting in cases of 'adequately' treated syphilis.

Another possible explanation is a reduced efficacy of penicillin in this case. The potency of this batch of penicillin was not formally tested, but there was no other indication of impairment. The patient weighed only 57 kg., so that low tissue levels of penicillin were unlikely, and there has been no evidence of a reduced sensitivity of *T. pallidum* to penicillin.

Summary

A case of acquired syphilis treated with daily injections of 600,000 units procaine penicillin is described, in which both the first and the second injections were followed by a febrile reaction. It is suggested that both were Jarisch-Herxheimer reactions. Possible explanations for this double reaction are briefly discussed.

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Une réaction de Jarisch-Herxheimer inhabituelle

SOMMAIRE

On décrit un cas de syphilis acquise traitée par des injections quotidiennes de 600.000 U de pénicilline-procaine et dans lequel, aussi bien la première que la seconde injection furent suivies d'une réaction fébrile. On pense que, les deux fois, il s'agissait de réactions de Jarisch-Herxheimer. On discute brièvement les explications possibles pour cette double réaction.