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doi:10.1093/qjmed/hcm102

Antibiotic hypersensitivity mimicking recurrent endocarditis—identifying the culprit with the *in vitro* lymphocyte transformation test

Sir,

The drug hypersensitivity syndrome is characterized by fever and systemic abnormalities including lymphopenia, lymphadenopathy, skin and visceral involvement mimicking systemic sepsis. The following case illustrates how the *in vitro* lymphocyte transformation test can be used to confirm drug hypersensitivity in this scenario, differentiating it from deteriorating infective endocarditis, hence avoiding progression to inappropriate interventions.

A 62-year-old man was admitted as a result of his cardiac resynchronization pacemaker generator eroding through the skin. On admission he was systemically well, and blood cultures were sterile; treatment with intravenous flucloxacillin 1 g qds was commenced empirically. A transoesophageal echocardiogram showed two vegetations; on the tricuspid valve and the right ventricular pacing lead. The pacemaker was extracted and culture of the leads grew *Staphylococcus aureus*. Intravenous flucloxacillin was changed to gentamycin 80 mg and intravenous teicoplanin 400 mg once daily. Ten days later, the patient became systemically unwell with pyrexia; the C-reactive protein became

raised together with lymphopenia and mild eosinophilia. There was concern that endocarditis had recurred despite appropriate antibiotics and sterile blood cultures. However, the alternative diagnosis of teicoplanin hypersensitivity was also considered; teicoplanin was changed to vancomycin, and the patient monitored closely. Within twenty-four hours, he felt better and the fever settled. A repeat transoesophageal echocardiogram showed no evidence of new infection. No further episodes of fever occurred following discontinuation of teicoplanin. A cardiac resynchronization pacemaker with defibrillator back up was implanted. Twelve months later the patient remains well.

The presence of hypersensitivity to teicoplanin was investigated. Epicutaneous patch tests with teicoplanin were negative, probably because teicoplanin (a complex mix of six compounds with molecular weights between 1584 and 1894 kDa) is too big to pass through the epidermal barrier. However, peripheral blood mononuclear cells (centrifuged isolated lymphocytes and monocytes) cultured with various concentrations of teicoplanin (0–1000 µM) for 6 days, showed significant dose-related lymphocyte proliferation. Proliferation was quantified by measurement of [³H]-thymidine incorporation, and expressed as the stimulation index (SI = counts per minute in presence of drug—c.p.m. in drug-free control cultures/c.p.m. in control cultures) (Figure 1a). Labelling cells with the fluorescent dye carboxyfluorescein succinimidyl ester showed that the proliferating teicoplanin-specific lymphocytes were exclusively CD4⁺ as reflected by dilution of the carboxyfluorescein succinimidyl ester in this cell population (Figure 1b). Supernatants that were collected from the peripheral blood mononuclear cell cultures on day 5, and analysed with a flow cytometry-based bead enzyme linked immunosorbent assay (Cytometric Bead Array Kit; BD Biosciences) contained high levels of interferon-γ, interleukin-5 and tumour necrosis factor-α, indicating a Th0 lymphocyte response. These results thus confirmed the presence of teicoplanin sensitivity mediated by T lymphocytes.

Antibiotic-induced hypersensitivity may give a similar clinical picture to systemic sepsis. Laboratory markers such as C-reactive protein and liver enzymes may be abnormal and eosinophilia is a helpful clue. The hypersensitivity results from T-cell sensitization and develops 10–14 days after exposure to the drug.

Hypersensitivity syndrome is most commonly reported with anticonvulsants and sulphonamides, but has been reported in association with teicoplanin frequently with associated pyrexia.^{1,2} Peripheral blood mononuclear cells cultures, also

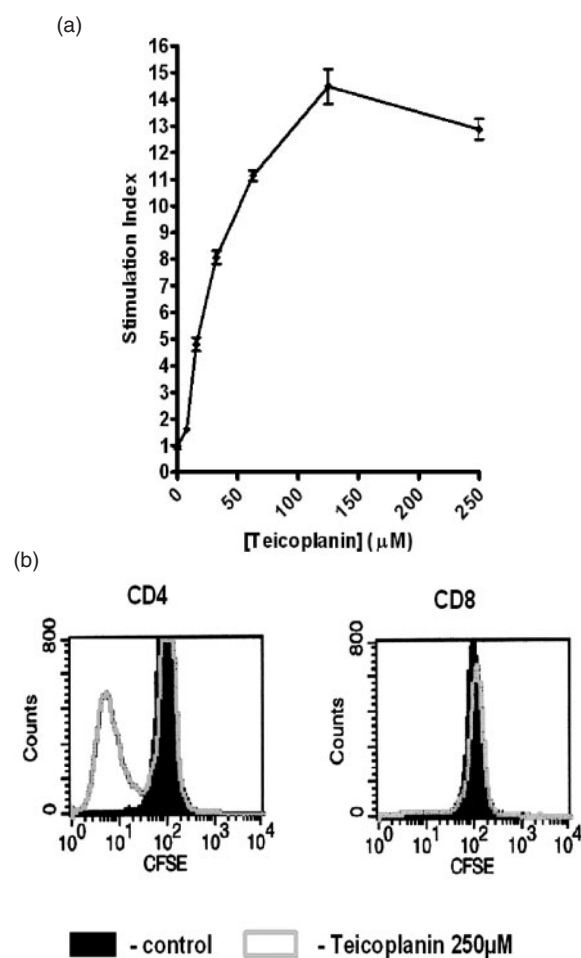


Figure 1. (a) Response of patient's peripheral blood mononuclear cell to dose range of Teicoplanin. (b) Flow cytometry histograms of CD4 and CD8 labelled lymphocyte populations—shift of open grey curve to the left represents dilution of CFSE within proliferating cells; this is seen only within CD4⁺ population on exposure to teicoplanin. CFSE—carboxyfluorescein succinimidyl ester.

known as the lymphocyte transformation test,³ implicated CD4⁺ lymphocytes with a Th0 cytokine profile in the pathology of this condition. In this case, the lymphocyte transformation test proved invaluable in confirming the clinical diagnosis of teicoplanin hypersensitivity.

H.L. Cooper

C. Pickard

E. Healy

P.S. Friedmann

Dermatopharmacology Unit

University of Southampton

Southampton General Hospital

Tremona Road, Southampton

UK

email: hywel1@soton.ac.uk

P.W.X. Foley

J.M. Morgan

Wessex Cardiac Centre

Southampton University Hospitals Trust

Southampton General Hospital

Tremona Road, Southampton

UK

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doi:10.1093/qjmed/hcm107