Thrombophlebitis migrans following co-trimoxazole therapy

J. Verne-Pignatelli, G.P. Spickett, A.G. Dalglish and A.M. Denman

Division of Immunological Medicine, Clinical Research Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, UK.

Summary: We report an unusual and severe vasculitic disorder following co-trimoxazole, given orally for a urinary tract infection. The vasculitis was manifest solely as thrombophlebitis migrans and involving only veins without evidence of polyarteritis nodosa, or underlying malignancy.

Introduction

Since the introduction of co-trimoxazole, a combination of trimethoprim and sulphamethoxazole, in 1968, numerous adverse reactions have been reported. Serious toxicity is rare, but usually causes skin lesions or blood dyscrasias. The most common forms of skin eruption are toxic erythema (1–4%), erythema nodosum and fixed drug eruptions.¹ Vasculitis is rare. We present a case of thrombophlebitis migrans occurring following co-trimoxazole therapy.

Case report

A 59 year old Greek Cypriot was admitted with high fever and widespread painful inflammation of the superficial veins of both forearms, hands and lower legs. Two weeks prior to admission, he had been prescribed co-trimoxazole for dysuria and haematuria. Three days later he was admitted to another hospital with high fever and pain and itching in the forearms and lower legs. Blood and urine cultures were negative; intravenous pyelography and renal ultrasound demonstrated a left renal calculus and benign right renal cyst. He remained pyrexial, and after one week of co-trimoxazole, he was started on cefuroxime and metronidazole. His fever did not settle, and the pain in his arms and legs localized to the superficial veins. He was discharged on no antibiotics, taking chlorpheniramine. He was then admitted to Northwick Park Hospital with rigors, sweats, anorexia and weight loss. On examination his temperature was 38.5°C, and there was a florid superficial thrombophlebitis, involving the veins of the arms to above the antecubital fossa and of the legs to the groin. The white cell count was elevated, with

increased lymphocytes ($5.5 \times 10^9/l$) and neutrophils ($10.6 \times 10^9/l$); the haemoglobin was 9.5 g/dl and the platelet count was elevated at $510 \times 10^9/l$. The ESR was 90 mm/h. Total globulin was elevated at 46 g/l and there was a polyclonal increase in gammaglobulin. Complement studies and C-reactive protein were normal; anti-nuclear factor and latex test for rheumatoid factor were both negative. Blood and urine cultures were sterile. Pending culture results, he was started on intravenous heparin, and flucloxacillin, without effect on temperature or phlebitis which continued to spread. After 24 hours, when the negative culture results were available, he was commenced on prednisolone 60 mg/day, and a biopsy performed of his affected right long saphenous vein. This showed florid internal thickening with fibrosis, elastosis and inflammatory cell infiltrate throughout the vessel wall. Typical features of polyarteritis nodosa were not seen. He was negative for hepatitis B surface antigen. His temperature settled within 12 hours of starting steroids, and his ESR, white cell count and haemoglobin returned to normal over the following week. Computed tomographic scan of the pancreas has not demonstrated evidence of pancreatic malignancy. Electrocardiogram, chest X-ray and tests of renal function were all normal.

While the steroid dose was being reduced, he returned to Cyprus, where a doctor advised him to abruptly cease his steroids and go on a diet of grape juice. He had a profound relapse with generalized venous involvement, fever and profound weight loss. On return to this country, 4 months after his initial presentation, he was re-admitted. The findings were similar to the initial admission, but on this occasion the thrombophlebitis was relatively resistant to steroids, and addition of cyclosporin conferred no therapeutic benefit. He remained unwell with intermittent fever, erythematous skin rashes and thrombophlebitis mainly of the arms until intravenous cyclophosphamide, 200 mg intravenously on alternate days for 5

Correspondence and present address: G.P. Spickett, D.Phil, M.R.C.P., Department of Immunology, John Radcliffe Hospital, Oxford OX3 9DU, UK.

Accepted: 26 July 1988

doses, was administered. This produced a rapid resolution in symptoms, decline in ESR and rise in haemoglobin. He has since been commenced on maintenance cyclophosphamide, and steroids. At no time has there been hypertension or evidence of renal involvement, although his chest X-ray has shown evanescent interstitial shadowing at times of high fever, but no changes of infarction or infection. Computed tomographic scan of the lungs was unhelpful.

Discussion

Skin reactions to co-trimoxazole have been well-documented, and in one survey² were found to be the most frequent adverse reaction (3.3%) found in a population of 1,121 patients studied in the Boston Collaborative Drug Surveillance Programme. Vasculitis appears rare. In a case reported in 1976, Wahlin & Rosman³ describe a 69 year old male with a nodular cutaneous vasculitis, confirmed on biopsy to be affecting the small vessels of the dermis. This developed 4 days after commencing oral co-trimoxazole, and was accompanied by fever, leucocytosis and a raised ESR. However, in contrast to the case we report here, the skin lesions and fever resolved spontaneously over 3 weeks. These authors also state that they had observed seven other similar cases, although no clinical details are given of the remaining cases. The total number of reports to the Committee on Safety of Medicines in which vascular problems are mentioned is ten. Of these, one report relates to a deep venous thrombosis, one to superficial thrombophlebitis, although it is not clear whether this was related to intravenous co-trimoxazole, and two cases of thrombophlebitis of the leg.

References

1. Lawson, D.N. & Price, B.J. Adverse reactions to trimethoprim – sulphamethoxazole. *Rev Infect Dis* 1982, **4**: 429–433.
2. Jick, H. Adverse reactions to trimethoprim – sulphamethoxazole in hospitalized patients. *Rev Infect Dis* 1982, **4**: 426–428.
3. Wahlin, A. & Rosman, N. Skin manifestations with vasculitis due to co-trimoxazole. *Lancet* 1976, **iii**: 1415.

Sulphonamides have previously been incriminated in the genesis of polyarteritis nodosa, but review of the Committee on Safety of Medicines' data does not support this strongly. Symmers suggests that polyarteritis has become rarer as a pathological entity as the usage of sulphonamides has decreased and that of penicillins has increased.⁴ He also notes that generalized angitis may very rarely occur with penicillin, thiouracils, phenylbutazone, quinidine, promazine and hydantoins. He reviews eight cases of 'collagen diseases' associated with drugs, and of these, four were related to sulphonamide usage, two with polyarteritis (one death) on biopsy, and two with thrombotic purpura, although there were no features of angitis as such in these latter two cases. An earlier paper by van Rijssel & Meyler,⁵ discusses seven patients, although two are very poorly documented, in whom sulphonamide treatment led to a necrotizing vasculitis, but in all of these cases nephritis was a feature, and polyneuritis was present in 6 of the 7.

Our case had no evidence of nephritis, and the serum creatinine clearance remained normal throughout. The later chest X-ray changes were not accompanied by any respiratory symptoms, nor was the gas transfer factor deranged. There were no signs of polyneuritis, even when the thrombophlebitis was most active. There were no biopsy features suggestive of polyarteritis, and we conclude that this severe generalized thrombophlebitis was an unusual reaction to co-trimoxazole, as it developed within a week of commencing the drug in an otherwise healthy man.

Acknowledgements

We thank Angela Welby for secretarial assistance, and the CSM for permission to use their data.

4. Symmers, W.St.C. The occurrence of angitis and other generalised diseases of connective tissue as a consequence of the administration of drugs. *Proc R Soc Med* 1962, **55**: 20–28.
5. Van Rijssel, Th.G. & Meyler, L. Necrotizing generalized arteritis due to the use of sulphonamide drugs. *Acta Med Scand* 1948, **132**: 251–264.