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Cutaneous necrotising vasculitis induced by levamisole

The anthelmintic agent levamisole has immunostimulant properties in patients with defective cell-mediated immune responses. We are assessing the drug in patients with breast cancer to see whether it can maintain surgically induced remission. One such patient developed a severe cutaneous necrotising vasculitis, which disappeared once the drug was withdrawn.

Case report

A 59-year-old woman had been receiving thrice-weekly levamisole 150 mg/day for three months, when in May 1975 she developed fever and a severe rash. Cutaneous necrotising vasculitis was diagnosed. Biopsy of one of the lesions showed intense neutrophil and eosinophil infiltration of the vessel wall with obliteration of the lumen. There were no other physical abnormalities, and no sign of the original disease was noted. She had not been taking any other drugs.

Haemoglobin was 13 g/dl and white cell count $3{\cdot}0 \times 10^9$/l (3000/mm^3; 30% segmented neutrophils, 8% eosinophils, 10% monocytes, 52% lymphocytes). Results of complement studies were within normal limits, and other immunological and biochemical values were normal. A bone-marrow aspirate showed a normal distribution of white and red cells but a moderate increase in eosinophils. A chest radiograph was normal.

Levamisole was discontinued and the patient given a short course of prednisone 40 mg daily. After two weeks the clinical picture returned to normal, and three months later the skin lesions showed no signs of recurrence and the white cell count was normal.

Comment

Levamisole-induced vasculitis has not been reported, despite wide use of the drug in various conditions, including malignant and rheumatic diseases.[1-3] The pathogenesis of our patient's skin reaction is unknown, though histologically it was similar to an Arthus-type reaction, in which immune-complex formation or complement activation is usually implicated. We found no complement abnormalities in our patient, but the tests did not exclude a local type III reaction.

The peripheral blood neutropenia in our patient also implicates levamisole as the causal agent, since neutropenia and agranulocytosis are associated with levamisole treatment.[3] The exact mechanism of this reaction is unknown, but the peripheral and central eosinophilia suggest a hypersensitivity reaction. Although we did not challenge the patient (for ethical reasons) we think that levamisole was the likely cause of the vasculitis.

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SHORT REPORTS

Toxicity of oral adjuvant chemotherapy in breast cancer

The results of management of "early" breast cancer will be improved only by systemic treatment, since the disease should be regarded as systemic in many patients at the time of initial treatment.[1] We report the preliminary results of a trial of oral adjuvant chemotherapy with two drugs in 202 patients over 18 months. The aims of the study were, firstly, to observe the incidence and degree of toxicity, which must be acceptable to patients and clinicians; and, secondly, to establish the ease of administration—that is, the treatment should be within the capability of any hospital in Britain.

Trial design and results

The regimen is on trial in 70 centres in the UK and Ireland. Women are treated as outpatients in either surgical or chemotherapy clinics. Primary treatment is at the discretion of the surgeon, who has the option of either simple mastectomy and "watch" policy or simple mastectomy and radiotherapy or radical mastectomy. Patients under 70 with histologically evident spread to lymph nodes and in stage I or II are randomly allocated to chemotherapy or no chemotherapy.

Two oral drugs were chosen to try to maximise acceptability to patients and clinicians while retaining the advantages of multiple-drug treatment.[2 3] Melphalan 10 mg is given on five consecutive days together with methotrexate 15 mg on the first day. This is repeated every six weeks for two years and should be started within four weeks after surgery. Patients under 50 kg receive melphalan 7·5 mg and methotrexate 10 mg. Should marrow depression occur (white cell count (WBC) $< 4 \times 10^9$/l; platelets $< 100 \times 10^9$/l) the dosages are halved. A course is omitted when the WBC falls below $2{\cdot}5 \times 10^9$/l and platelets below 75×10^9/l or if liver function deteriorates. Methotrexate is withheld if oral ulceration occurs. When marrow or liver function returns to normal treatment is restarted. Nausea and vomiting may be controlled with antiemetics at the discretion of the clinician in charge.

The end-point is disease recurrence or death. Full clinical details at times of entry and follow-up are recorded by the central secretariat for computer processing. Emphasis is placed on obtaining toxicity records after each course.

So far 484 courses have been given to 102 patients; their primary treatment was as follows (controls in parentheses): simple mastectomy 43 (57), simple mastectomy and radiotherapy 17 (13), and radical mastectomy 42 (32). Two patients refused oral treatment, and one stopped treatment after experiencing nausea with one tablet. In 68 (14%) the dosage had to be halved temporarily because of transient toxicity (table), usually in the first few courses. No patient needed a wig.

Comment

Three years after adjuvant chemotherapy for early breast cancer an appreciable reduction in distant metastases[2] and improvement in survival[3] occur, predominantly in premenopausal women. Uncertainty remains, however, about the most appropriate chemotherapy for distant micrometastases; appropriate regimens may well prove to vary with individual patients.[2 3] The toxicity of chemotherapy must be acceptable to both patient and clinician. Ease of administration is also important. When considering the facilities available in the UK the regimens must be practicable. The 70 centres contributing to the study confirm that this two-drug regimen fulfils these requirements.

The therapeutic efficacy of adjuvant chemotherapy must await results at three, five, and ten years after initial treatment. Melphalan alone results in improvement at three years[2] and is less toxic than more powerful multiple-drug regimens.[3] The preliminary results on