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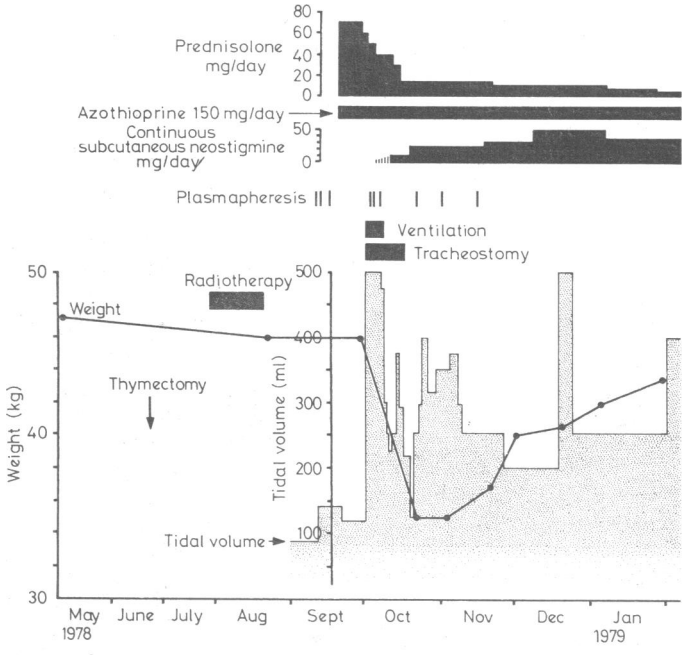
Continuous subcutaneous neostigmine in the management of severe myasthenia gravis

Oral anticholinesterase drugs are variably and incompletely absorbed and sometimes fail to maintain patients with myasthenia gravis independent of hospital care, even when combined with steroids and immunosuppressive agents. We describe such a patient and suggest a novel addition to the management of this problem.

Case report

In May 1978 a 27-year-old woman presented with an 18-month history of dysphagia and dysarthria. Examination showed that she had myasthenia gravis, which was confirmed by a Tensilon test, and investigation showed a thymic tumour. In June 1978 a thymic carcinoma affecting pleura and pericardium was removed as completely as possible; radiotherapy was given in July and August 1978 (see figure).

Before and after operation the myasthenia was controlled with neostigmine and pyridostigmine. After radiotherapy the patient's myasthenia worsened and affected her eyes, limbs, and respiratory muscles as well as swallowing. Because of severe weakness she was readmitted to hospital on 22 August 1978. Over the next month various combinations of neostigmine up to 300 mg/day, pyridostigmine up to 600 mg/day, and ambenonium 30 mg/day were given. A mild cholinergic crisis occurred once, but muscle weakness was often severe, causing problems with speech, breathing, and swallowing. The patient could not move far from her bed.



Course of myasthenia and treatment.

By 10 September 1978 breathing and swallowing were difficult and the tidal volume was only 90 ml. The patient could not lift her arms above her shoulders. Plasmapheresis was started, and after three exchanges over four days the tidal volume doubled, swallowing improved, and the patient could get out of bed. Within a few days she deteriorated, and prednisolone 75 mg/day and azothioprine 150 mg/day were added to the treatment. The patient's general condition did not improve over 12 days and her muscle weakness increased. Intubation and ventilation were started, followed by a tracheostomy. Three further plasmaphereses were done.

While the patient was being maintained on the ventilator and because we failed to control the myasthenia with oral neostigmine, we gave intermittent subcutaneous and intravenous injections of neostigmine in doses (up to 2 mg) recommended in *National Formulary*.

Ventilation was discontinued after a week, and as tidal volume was maintained at about 250 ml we increased the dose of subcutaneous neostigmine. The dose of prednisolone was slowly reduced to 15 mg/day as she showed no response to high doses and because of the severe catabolic state and repeated infection.

On 9 October 1978 we changed the subcutaneous neostigmine from intermittent to continuous administration, using an infusion pump. The daily dose was increased from 10 mg to 25 mg to control the muscle weakness as judged by tidal volume, speech, and power in the limbs. Swallowing, however, did not improve and nasogastric feeding was continued.

Two attempts to reduce the dose of neostigmine led immediately to severe myasthenia with respiratory embarrassment and inability to sit up. The patient's general condition then began to improve and for the first time in three months we considered discharging her.

In early December 1978, to increase the patient's mobility, we obtained a small battery-operated infusion pump (Syringe Driver Type MS-Pye Dynamics Ltd) to administer the contents of a 10 ml syringe; this was connected to the patient with 90 cm of fine plastic tubing and a butterfly cannula inserted into a subcutaneous site on the abdomen. The pump was carried in a shoulder holster and permitted full activity. The rate of infusion could be varied by the doctor or patient. Since then she has taken 36 to 60 mg of neostigmine daily. The cannula site has been changed every two weeks. The syringe has to be filled twice daily because of the strength of neostigmine solution (2·5 g/l) available. The patient manages the syringe herself.

With continuous subcutaneous neostigmine the patient has been able to go home and to do light housework, go shopping, and drive a car. Her weight has slowly increased towards normal (see figure), and swallowing has recently improved so that she can now eat normally. Steroids and azathioprine are gradually being withdrawn.

Comment

Continuous subcutaneous neostigmine may have a place in the management of severe myasthenia gravis in the short or medium term. Subcutaneous absorption seems to be reliable and there have so far been no local reactions to continuous subcutaneous administration. The dose, up to 50 mg/day, differs considerably from that normally recommended. The syringe driver seems to be reliable, needing new batteries every six weeks, and can be managed by the patient with infrequent visits to her doctor or the hospital.

We thank Dr Angela Robinson and colleagues for carrying out the plasmapheresis.

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Monocyte maturation and prognosis in primary breast cancer

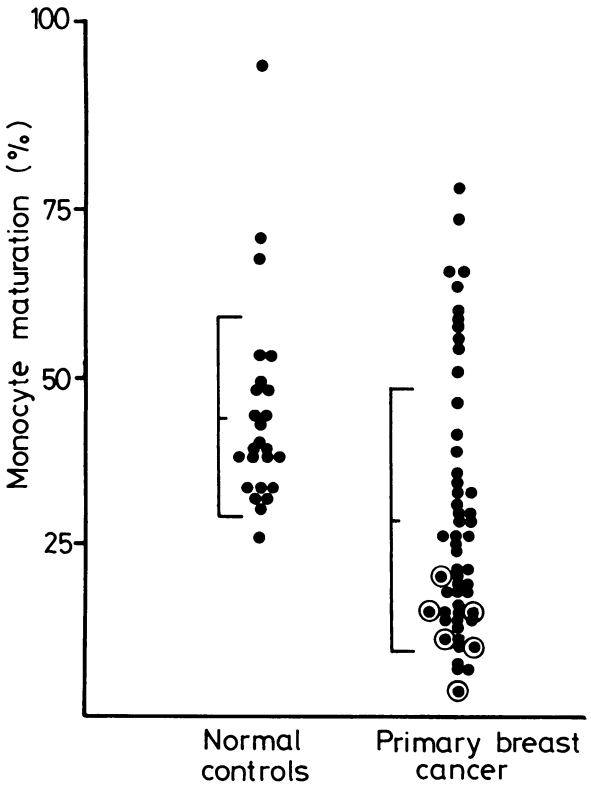
Patients with cancer show many functional abnormalities in the mononuclear phagocyte system. Dizon and Southam[1] found that patients with malignant disease have an impaired ability to mobilise macrophages. Studies in malignant melanoma[2] show that monocytes from patients with disseminated disease are unable to differentiate into macrophages in tissue culture.

Patients, methods, and results

Blood samples for assays of monocyte function were taken before surgery from 125 women presenting to a breast clinic and the assays performed in ignorance of their clinical condition. Benign lesions were subsequently found in 36 patients and operable primary breast carcinoma in 54. None of these 54 women showed any evidence of distant metastases at the time of primary surgery. Preoperative assessment included full blood count; liver function tests; serum calcium, phosphate, and alkaline phosphatase estimations; chest radiography; skeletal survey; liver and bone scans; hepatic ultrasonography; and bone-marrow examination. A further 35 patients with overt disease, either local or distant, were examined. Age-matched normal healthy women served as controls.

In-vitro maturation of monocytes was assayed as described.[2] Briefly, defibrinated venous blood was layered on to Lymphoprep (Nyegaard) and centrifuged. Washed mononuclear cells were counted, made up to 2×10^9/l in 50% fresh autologous serum, and cultured as described. A drop of the cell suspension was also stained for non-specific esterase (NSE)[3] and the proportion of NSE-positive cells counted. Maturation was expressed as the yield of attached macrophages assayed after seven days of incubation as a percentage of the number of monocytes added (NSE positivity being used as a monocyte marker).

The figure gives the results. In normal donors the mean percentage maturation was 48·3±SD19·7 and in the patients with benign disease 45·31±9·0 (t±0·52; P>0·1). In the patients with primary breast cancer the mean maturation was 29·3±18·9%, whereas in the appropriate age-matched controls it was 44·3±14·8%; this difference was highly significant (t=3·42; P<0·001). At the time of writing, nine months after starting the study, six of the 54 patients with primary cancer had relapsed with overt recurrent disease. Their mean monocyte maturation (at presentation) was 12·6±5·0% —that is, all their values were extremely low. Furthermore, the 35 patients with overt dissemination also showed depressed maturation. Those with distant metastases (24) had a mean maturation 15·9±12·9%, whereas those with local spread (11) had a mean maturation of 28·8±16·3%. The overall group was significantly depressed (20·2±15·2%) when compared with age-matched normal women (t=6·07; P<0·001) and those with primary tumours (t=2·47; P<0·05), and the difference between women with distant and local spread was also significant (t=2·54; P<0·01).



In-vitro maturation of monocytes in 54 women with operable primary breast cancer and age-matched normal control donors. Six patients relapsed; their values at presentation are encircled. Bars are means ±1SD.

Maturation of monocytes correlated with the diameter of the primary tumour, the larger the tumour the greater the suppression (r=0·290; t=2·184; P<0·05). Nuclear grade 3 tumours were associated with significantly lower maturation than grade 1 (P<0·02). The presence of sinus histiocytosis in the axillary nodes was also associated with significantly higher monocyte maturation (t=2·31; P<0·05). There was, however, no correlation with axillary node state (t=0·276; P>0·1).

Comment

The use of tumour-product markers[4] and immunological state[5] has failed to provide assays suitable for detecting patients whose poor prognosis dictates the need for some form of adjuvant treatment. The suppression of in-vitro differentiation of monocytes has been described in patients with malignant melanoma[2] and is related to tumour burden. In our study of 54 women with primary breast cancer (with no evidence of distant metastases) the maturation of monocytes was significantly depressed when compared with that in normal women or those with benign breast disease. Monocyte maturation in half of the patients was lower than in the lowest normal control. The most startling finding was the prognostic significance of the in-vitro results. Out of 54 women presenting over nine months, six relapsed with overt metastatic disease. These six when first seen showed severely subnormal monocyte maturation in vitro. No patient relapsed who presented with normal maturation. The number of relapses was still small. We report the data at this stage, however, to encourage the evaluation of this observation in other laboratories.

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Small-bowel volvulus in association with progressive systemic sclerosis

Progressive systemic sclerosis (PSS) is a generalised disorder characterised by deposition of increased amounts of collagen in skin, heart, lung, gastrointestinal tract, and kidney. The small intestine is affected in some 50% of cases, and in about half of these small-bowel lesions cause symptoms. We describe a patient who presented with the hitherto unrecognised complication of small-intestinal obstruction as a result of volvulus.

Case report

A 69-year-old Caucasian man was admitted to hospital as an emergency case shortly after eating a large lunch. He complained of the sudden onset of dysphagia associated with upper abdominal pain, nausea, and vomiting. His history included Raynaud's phenomenon for four years. He was a thin man with telangiectasia on the arms and neck. His facial skin was smooth and flattened with lip puckering. The fingers were cold and cyanosed. There was proximal muscle wasting of the arms. Bilateral basal crepitations were heard in the chest. The upper abdomen was distended, tympanitic, and tender. Plain abdominal radiography showed eventration of the left hemidiaphragm and multiple dilated loops of small bowel with fluid levels in the erect film suggesting obstruction. Conservative treatment with analgesics, nasogastric intubation, and intravenous fluid replacement failed to alleviate the symptoms. At laparotomy eventration of the left hemidiaphragm was seen; the stomach was rotated in a ventroaxial direction; the small bowel, which showed massive dilatation throughout its length, had volvulated around the base of a thickened, foreshortened mesentery; the sigmoid colon was also dilated. The condition could not be treated surgically, so the