Octreotide treatment had no notable effects in patients 4, 5, and 6, but in patients 1, 2, 3, and 7 it was associated with rapid and pronounced decrease in the size of pseudocysts (average reduction after 2 weeks' treatment 42%, range 29–52%, as measured by ultrasonography) and a complete cessation of pain (within 3–5 days of the start of treatment). Fig 1 illustrates a representative patient (number 2). In patient 3 the cyst regrew and pain reappeared after the first treatment; a second more prolonged course of octreotide caused complete disappearance of the cyst and pain (fig 2). The only changes seen at the last follow-up visit were a slight increase in the size of pseudocysts in patients 2 (after 4 months) and 4 (after 2 months), and complete disappearance of the extrapancreatic cyst in patient 7 (after 3 months). Octreotide caused no untoward effects other than mild transient pain at the injection site in most patients and a mild diarrhoea in patient 3.

Our study shows that suppression of pancreatic secretion with octreotide can influence favourably the course of pseudocysts complicating chronic pancreatitis. The pseudocysts of four of the seven patients decreased in size during octreotide treatment, and in the patient who had 4 weeks of treatment the cyst disappeared completely. It is worth stressing that, in these four patients, the decrease in size of pseudocysts was accompanied by complete disappearance of pain, even when it had been severe. Similar pain relief is seen when cysts are successfully drained by surgery or other invasive procedures.^{2–5}

It is not clear why some pseudocysts appeared to respond to octreotide while others did not. The pseudocysts which decreased in size with treatment were large, tense, and extrapancreatic (three of four) with no ultrasonographic evidence of a thick wall. Thus, it is possible that pseudocysts with these features are the most amenable to octreotide treatment.

Though the follow-up of our patients has been short, the effects of octreotide treatment seem to persist for some months at least. Clearly, further studies are necessary to better define the role of octreotide in the management of pancreatic pseudocysts.

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REFERENCES

1. Gullo L, Costa PL, Labò G. Chronic pancreatitis in Italy. Aetiological, clinical and histological observations based on 253 cases. *Rendic Gastroenterol* 1977; 9: 97–104.
2. Bradley EL, Clements JL, Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. *Am J Surg* 1979; 137: 135–39.
3. Van Sonnenberg E, Ferrucci J, Mueller P, Wittomberg J, Simeone J. Percutaneous drainage of abscesses and fluid collections: technique, results and applications. *Radiology* 1982; 142: 1–10.
4. Sahel J, Bastid C, Pellat B, Schurgers P, Sarles H. Endoscopic cystoduodenostomy of cysts of chronic calcifying pancreatitis: a report of 20 cases. *Pancreas* 1987; 2: 447–53.
5. Cremer M, Deviere J, Engelholm L. Endoscopic management of cysts and pseudocysts in chronic pancreatitis: long-term follow-up after 7 years of experience. *Gastrointest Endosc* 1989; 35: 1–9.
6. Creutzfeldt W, Lembcke B, Folsch UR, Schleser S. Effect of somatostatin analogue (SMS 201-995, Sandostatin) on pancreatic secretion in humans. *Am J Med* 1987; 82 (suppl 5B): 49–54.
7. Gullo L, Biliotti G, Pezzilli R, Di Stefano M, Ancona D. Effect of octreotide (SMS 201-995) on meal-stimulated pancreatic secretion in three patients with external pancreatic fistula. *Am J Gastroenterol* (in press).

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Reversible thyroid dysfunction during treatment with GM-CSF

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To investigate whether autoimmunity against thyroid antigens is induced or exacerbated by granulocyte-macrophage colony-stimulating factor, thyroid function and thyroid autoantibodies were studied in 14 patients with advanced breast cancer and 11 with soft-tissue sarcoma who received several cycles of doxorubicin and cyclophosphamide plus GM-CSF 250 µg/m² intravenously daily for 10 days in every 21 day cycle. All patients had normal thyroid function before treatment. In 2 patients with pre-existing thyroid antibodies, thyroid dysfunction developed but disappeared after cessation of GM-CSF. No other autoimmune abnormalities appeared. Stimulation of antigen-presenting cells by GM-CSF may bring about this phenomenon.

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Haemopoietic growth factors are being increasingly used to accelerate myeloid recovery after chemotherapy and bone-marrow transplantation. Granulocyte-macrophage colony-stimulating factor (GM-CSF) not only stimulates the growth and differentiation of precursors of granulocytes and monocytes/macrophages, but also affects the biological activity of their mature offspring.^{1,2} GM-CSF causes aggravation of idiopathic thrombocytopenia³ and seropositive arthritis.⁴ We have investigated whether autoimmunity against thyroid antigens was induced or exacerbated in a group of 25 patients with breast cancer or soft-tissue sarcoma who received chemotherapy plus GM-CSF.

The median age of the 14 women with advanced breast cancer and 11 patients (6 men, 5 women) with soft-tissue sarcoma was 50 years (range 36–68). The patients with breast cancer were treated with doxorubicin 90 mg/m² plus cyclophosphamide 1000 mg/m² intravenously and the sarcoma patients with doxorubicin 90 or 110 mg/m² intravenously every 3 weeks.

The *Escherichia coli* derived non-glycosylated recombinant human GM-CSF (Behringwerke AG, Marburg, Germany) was given by continuous infusion from day 2 to day 12 of each cycle at 250 µg/m² daily. Thyroid function and thyrotropin assays were carried out every 3 weeks ('Simultrac', Becton Dickinson, New York, USA). Titres of antibodies to thyroglobulin and thyroid peroxidase (thyroid microsomes) were measured by a haemagglutination assay ('Thymune', Wellcome Diagnostics, Dartford, UK) before and after treatment; in positive patients tests were repeated every 3 weeks. Thyrotropin-receptor antibodies were measured by inhibition of iodine-125-labelled thyrotropin binding to thyroid membranes ('TRAK'-assay, Henning, Berlin, Germany). Antibodies against nuclear factors, n-DNA, pancreas, stomach, and adrenal gland were assayed by indirect immunofluorescence on frozen tissue sections. Rheumatoid factors were measured by an enzyme-linked immunosorbent assay with aggregated rabbit IgG as antigen.

All 25 patients had normal thyroid function and size at the start of treatment. 2 patients with breast cancer had antibodies to thyroid peroxidase; in both, thyroid function

THYROID FUNCTION AND THYROID ANTIBODIES IN PATIENTS WITH HYPOTHYROIDISM

	Free T4 (pmol/l)*	TSH (mU/l)†	Antibody titres to	
			Thyroid peroxidase‡	Thyrotropin receptor§
Patient 1				
Pre-treatment	15.4	3.0	400	—ve
Cycle 2	13.8	6.5	6400	—ve
Cycle 3	14.3	5.4	6400	—ve
Cycle 4	7.8	42.0	1600	—ve
Post-treatment	23.0	2.3	1600	ND
Patient 2				
Pre-treatment	16.8	5.9	6400	1.6%
Cycle 2	29.5	<0.2	1600	5.6%
Cycle 3	4.2	13.0	1600	10.8%
Cycle 4	2.0	>50.0	400	14.5%
Cycle 5	5.6	>50.0	400	9.2%
Cycle 6¶	15.0	7.9	400	10.1%
Post-treatment	13.0	4.0	100	6.0%

*Normal range 11–23 pmol/l. †Normal range <6.0 mU/l.

‡Reciprocal titre. §% of inhibition of thyrotropin binding.

¶With thyroxine supplementation.

ND = not done.

Measurements done on day 1 of each treatment cycle; post-treatment = 8 wk after stopping thyroxine.

abnormalities developed and the gland enlarged (table). In the 23 patients without pre-existing thyroid antibodies, thyroid function and thyrotropin concentrations remained normal.

In patient 1 a goitre developed, the titre of thyroid peroxidase antibodies rose, and hypothyroidism was clinically apparent after three cycles of therapy. No antibodies to thyroglobulin or thyrotropin receptor were ever found. Patient 2 became mildly hyperthyroid after the first cycle of GM-CSF. A slightly enlarged thyroid gland developed and she became clinically hypothyroid at the end of the second cycle. Antibodies to thyroglobulin were transiently present (titre 320 cycle 2, 80 cycle 3) and antibodies against the thyrotropin receptor were found and apparently increased during treatment. It is, however, possible that this increase was due to the high concentrations of thyrotropin which can interfere with the assay. Both patients required thyroxine therapy for 2 months. In both patients thyroid function returned to normal within 8 weeks of the last dose of GM-CSF.

In the 2 patients with autoimmune thyroiditis there was no evidence of other organ-specific (stomach, pancreas, adrenal gland) or non-organ-specific autoimmunity. Patient 1 had a persistently low titre of antinuclear factors. 2 other patients had antibodies to nuclear factors and the titre fell during treatment.

GM-CSF induced reversible thyroid dysfunction in 2 patients with pre-existing antibodies to thyroid peroxidase. The pattern of development of thyroid dysfunction differed, however. The pattern in patient 2 strongly suggests silent thyroiditis.

Autoimmune thyroiditis has been observed after treatment with interferon- α^5 and interleukin-2⁶ in patients both with and without pre-existing thyroid antibodies. In our study thyroid abnormalities occurred during GM-CSF treatment only in patients with pre-existing thyroid antibodies. It has been postulated that interferon- γ has an important role in both sporadic and cytokine-induced thyroid dysfunction through its ability to induce the expression of HLA class II antigens⁷ and adhesion molecules on thyrocytes,⁸ which allows these cells to present

their thyroid antigens to T lymphocytes effectively. Paradoxically, long-term interferon- γ treatment did not result in the development of thyroid abnormalities.⁹

Another hypothesis can be proposed based on our finding that GM-CSF can also cause thyroid dysfunction and the fact that GM-CSF is produced in vivo after interleukin-2 treatment. GM-CSF increases the number of monocytes and macrophages and enhances their expression of HLA class II antigens and their production of interleukin-1.¹ These factors are necessary for the activation of and presentation of antigen to T lymphocytes. Moreover, GM-CSF is unique in its ability to stimulate the viability and differentiation of dendritic cells,² which are efficient antigen-presenting cells. The thyroid gland affected by autoimmune thyroiditis shows an accumulation of dendritic cells in close contact with T and B lymphocytes, and this infiltrate precedes the appearance of class II positive thyrocytes.¹⁰ These findings suggest that GM-CSF has a key role in priming antigen-presenting cells to a state in which they can activate auto-aggressive T cell clones and which ultimately leads to the induction of thyroid (and other) autoimmunity.

Patients receiving GM-CSF must be screened for autoimmunity and their clinical condition carefully followed during the administration of this cytokine.

REFERENCES

- Smith PD, Lamerson CL, Wong HL, Wahl LM, Wahl SM. Granulocyte-macrophage colony-stimulating factor stimulates human monocyte accessory cell function. *J Immunol* 1990; 144: 3829–34.
- Markowicz S, Engleman EG. Granulocyte-macrophage colony-stimulating factor promotes differentiation and survival of human peripheral blood dendritic cells in vitro. *J Clin Invest* 1990; 85: 955–61.
- Lieschke GJ, Mahler D, Cebon J, et al. Effects of bacterially synthesized recombinant human granulocyte-macrophage colony-stimulating factor in patients with advanced malignancy. *Ann Intern Med* 1989; 110: 357–64.
- Hazenber BPC, van Leeuwen MA, van Rijswijk MH, Stern AC, Vellenga E. Correction of granulocytopenia in Felty's syndrome by granulocyte-macrophage colony-stimulating factor. Simultaneous induction of interleukin-6 release and flare up of the arthritis. *Blood* 1989; 74: 2769–70.
- Burman P, Tötterman TH, Öberg K, Karlsson FA. Thyroid autoimmunity in patients on long term therapy with leukocyte-derived interferon. *J Clin Endocrinol Metab* 1986; 63: 1086–90.
- Atkins MB, Mier JW, Parkinson DR, Gould JA, Berلمان EM, Kaplan MM. Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; 318: 1557–63.
- Weetman AP, Volkman DJ, Burman KD, Gerrard TL, Fauci AS. The *in vitro* regulation of human thyrocyte HLA-DR antigen expression. *J Clin Endocrinol Metab* 1985; 61: 817–24.
- Martin A, Huber GK, Davies TF. Induction of human thyroid cell ICAM-1 (CD54) antigen expression and ICAM-1-mediated lymphocyte binding. *Endocrinology* 1990; 127: 651–57.
- Kung AWC, Jones BM, Lai CL. Effects of interferon- γ therapy on thyroid function, T-lymphocyte subpopulations and induction of autoantibodies. *J Endocrinol Metab* 1990; 71: 1230–34.
- Voorbij HAM, Kabel PJ, de Haan M, et al. Dendritic cells and class II MHC expression on thyrocytes during the autoimmune thyroid disease of the BB rat. *Clin Immunol Immunopathol* 1990; 55: 9–22.

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