Short reports

Simultaneous onset of idiopathic dilated cardiomyopathy in identical middle-aged twins

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Summary

Idiopathic dilated cardiomyopathy is a primary myocardial disease which is characterised by left ventricular, or biventricular, dilatation and impaired contractility. The precise aetiology is unknown and the relative contribution of genetic and environmental factors is debated. We report two identical male twins of Caucasian origin with idiopathic dilated cardiomyopathy who presented within a few months of each other.

Keywords: idiopathic dilated cardiomyopathy; twins

Two identical male twins were born in 1937. Both had unremarkable medical histories, with the exception of a hemi-thyroidectomy performed in the younger twin (by 20 minutes) for benign nodular goitre. In particular, neither twin had a history of hypertension, rheumatic heart disease, diabetes mellitus or any neuromuscular disorder. Neither took excessive alcohol or smoked tobacco. At no stage had either twin experienced anginal-type chest pain. Neither twin had previously received treatment with any cardiotoxic chemotherapeutic agents. The older twin had worked in the building industry, but there was no history of prolonged exposure to industrial toxins. There was a weak family history of ischaemic heart disease but not of cardiomyopathy.

The older twin presented in May 1995 with a one-week history of paroxysmal nocturnal dyspnoea. He was admitted to hospital. The findings on physical examination were an irregularly irregular pulse with a rate of 110 beats/min and a blood pressure of 140/80 mmHg. The central venous pressure was elevated and auscultation revealed normal heart sounds with no gallop, a pansystolic murmur and bibasal inspiratory crepitations. Chest X-ray revealed a normal cardiac size without evidence of frank pulmonary oedema. The electrocardiograph confirmed atrial fibrillation with a ventricular rate of 113 and no evidence of ischaemia or prior myocardial infarction. Full blood count, thyroid function tests and biochemical profile, including cardiac enzymes, were normal. Serum ferritin was at the low end of the normal range. The patient was treated to good effect with digoxin, diuretics and warfarin. Subsequent echocardiography revealed mild dilatation of the left ventricle (end-systolic internal dimension 4.3 cm, normal range 2.5-4.1 cm; end-diastolic inter-

nal dimension 5.7 cm, normal range 3.5-5.6 cm), incomplete co-aptation of the mitral valve cusps with an eccentric regurgitant jet and a dilated left atrium (diameter 4.0 cm, normal 1.9-3.8 cm). The calculated left ventricular ejection fraction was 40%. The echocardiographic appearances of the mitral valve suggested regurgitation secondary to myocardial pathology rather than a primary valve disorder.

Despite the introduction of angiotensin-converting enzyme (ACE) inhibitors, the patient's symptoms worsened and he was referred to the regional centre for cardiac catheterisation. This revealed minor coronary artery disease, with a 50% lesion in the second obtuse marginal branch and 10% lesions in the mid-right coronary artery and mid-left anterior descending artery. There was grade III mitral regurgitation with a left ventricular ejection fraction of 40%, end-diastolic pressure 18 mmHg and aortic pressure of 98/66 mmHg, mean 82 mmHg. There was moderate pulmonary hypertension, pulmonary artery pressure 44/18 mmHg, mean 30 mmHg. Histological examination of biopsy material from the left ventricle revealed subendocardial fibrosis, variation in myocyte size with some central vacuolation and no evidence of glycogen or iron storage abnormalities (figure). The findings were consistent with dilated cardiomyopathy.

The second twin presented in January 1996 with a short history of nocturnal cough and wheeze. This was associated with at least one episode of confirmed atrial fibrillation. He was admitted to hospital for investigation and treatment. Serial electrocardiographs confirmed paroxysmal atrial fibrillation and suggested left atrial dilatation. Echocardiography revealed left ventricular dilatation (end-systolic internal dimension 4.7 cm, end-diastolic inter-

Figure Biopsy material from the left ventricle of the elder twin

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nal dimension 5.4 cm), mild mitral regurgitation with a normal mitral valve appearances and dilatation of the left atrium (diameter 4.0 cm). The calculated left ventricular ejection fraction was 32%. There was mild left ventricular hypertrophy. Biochemical profile, thyroid function tests and full blood count were normal. Serum ferritin was at the low end of the normal range. Treatment was commenced with warfarin, diuretics, amiodarone and an ACE-inhibitor. He was referred to the regional centre for cardiac catheterisation and left ventricular biopsy. This revealed normal coronary arteries, a left ventricular ejection fraction of 38%, end-diastolic pressure 2/12 mmHg and aortic pressure of 112/65 mmHg, mean 82 mmHg. Pulmonary artery pressure was 27/12 mmHg, mean 18 mmHg. Histological examination of a biopsy specimen from the left ventricle revealed fibrosis, variation in cell size and some cells with central degenerative vacuoles. The findings were consistent with dilated cardiomyopathy.

Discussion

Idiopathic dilated cardiomyopathy is not a rare condition. The estimated prevalence from studies in the US is 36.5 cases per 100 000 of the population¹ with males more commonly affected than females and Afro-Caribbeans more than Caucasians.² The reported 5-year survival rates are 50–80%, depending on the series.^{3–4} The condition is currently the most common indication worldwide for cardiac transplantation. Proposed pathogenetic mechanisms resulting in the disease include familial and genetic factors, chronic viral infection with resultant cardiac myocyte damage, and dysfunction of the immune system with autoimmune destruction of cardiac myocytes. It would seem likely that a number of factors combine to produce clinical disease in susceptible patients.

In recent years it has become apparent that familial disease is more important than was previously thought. Michels *et al*⁵ studied 315 relatives from the families of 59 index cases with dilated cardiomyopathy, finding that 20.3% of index cases had an affected relative. In addition, 9.2% of healthy relatives with nor-

mal left ventricular ejection fractions had increased left ventricular dimensions during systole or diastole. Keeling *et al*⁶ reported similar findings when studying 236 relatives from the families of 40 patients with dilated cardiomyopathy. In this study, 25 cases of dilated cardiomyopathy were identified among the relatives, of whom 22 were first degree relatives. The affected relatives all came from 10 (25%) of the 40 families screened. Amongst the apparently healthy relatives, 37 (18%) were found to have left ventricular enlargement.

The mode of inheritance in families with the condition is most commonly autosomal dominant. Genetic linkage analysis of a large family with familial dilated cardiomyopathy has indicated that the gene responsible for this condition is located on the long arm of chromosome 1 (1q32).⁷ However, four other specific gene loci for autosomal dominant dilated cardiomyopathy have also been described,^{8–11} indicating the genetically heterogeneous nature of the condition. Autosomal recessive,¹² X-linked recessive,¹³ and maternal inheritance through mitochondrial DNA have also been reported.¹⁴

To our knowledge, there has been only one published report of late-onset dilated cardiomyopathy in identical male twins.¹⁵ It is worth noting, however, that both these patients had maturity-onset non-insulin-dependent diabetes mellitus and one twin had hypertension.

The patients described here live close together in the same village. Therefore, it is possible that an environmental factor has played a part in the development of their similar cardiac conditions. In addition, the occurrence of dilated cardiomyopathy in members of the same family does not necessarily imply that the condition has a genetic basis. However, in the case of this pair of twins, the identical genetic profile and the onset of symptoms within a few months of each other would seem to imply that genetic factors in the aetiology of dilated cardiomyopathy are indeed more important than has been previously realised.

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- Codd MB, Sugrue DD, Gersh BJ, Melton LJ 3rd. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975–1984. *Circulation* 1989;80:564–72.
- Coughlin SS, Szlo M, Baughman K, Pearson TA. The epidemiology of idiopathic dilated cardiomyopathy in a biracial community. *Am J Epidemiol* 1990;131:48–56.
- Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;47:525–31.
- Sugrue DD, Rodeheffer RJ, Codd MB, Ballard DJ, Fuster V, Gersh BJ. The clinical course of idiopathic dilated cardiomyopathy. A population-based study. *Ann Intern Med* 1992;117:117–23.
- Michels VV, Moll PP, Miller FA, *et al*. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. *N Engl J Med* 1992;326:77–82.
- Keeling PJ, Gang Y, Smith G, *et al*. Familial dilated cardiomyopathy in the United Kingdom. *Br Heart J* 1995;73:417–21.
- Durand J, Bachinski L, Bieling L, *et al*. Localization of a gene responsible for familial dilated cardiomyopathy to chromosome 1q32. *Circulation* 1995;92:3387–9.
- Kass S, MacRae C, Graber HL, *et al*. A gene defect that causes conduction system disease and dilated cardiomyopathy maps to chromosome 1p1–1q1. *Nat Genet* 1994;7:546–51.
- Krajinovic M, Pinamonti B, Sinagra G, *et al*. Linkage of familial dilated cardiomyopathy to chromosome 9. Heart Muscle Disease Study Group. *Am J Genet* 1995;57:846–52.
- Olson TM, Keating MT. Mapping a cardiomyopathy locus to chromosome 3p22–p25. *J Clin Invest* 1996;97:528–32.
- Bowles KR, Gajarski R, Porter P, *et al*. Gene mapping of familial autosomal dominant dilated cardiomyopathy to chromosome 10q21–23. *J Clin Invest* 1996;98:1355–60.
- Mestroni L, Miani D, Di Lenarda A, *et al*. Clinical and pathologic study of familial dilated cardiomyopathy. *Am J Cardiol* 1990;65:1449–53.
- Berko BM, Swift M. X-linked cardiomyopathy. *N Engl J Med* 1987;316:1186–9.
- Zeviani M, Gellera C, Antozzi C, *et al*. Maternally inherited myopathy and cardiomyopathy: association with mutation in mitochondrial DNA tRNA (Leu)(UUR). *Lancet* 1991;338:143–7.
- Twidale N, Kipperman RM, Whitehead AW, Blaker AM, Galichia JP. Late-onset idiopathic dilated cardiomyopathy in identical twins. *Am J Cardiol* 1994;128:839–41.

Hepatitis G virus infection as a possible causative agent of community-acquired hepatitis and associated aplastic anaemia

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Summary

Aplastic anaemia complicating hepatitis is a rare but well-documented phenomenon; however in many patients the cause remains unknown. We present a 24-year-old man with a well-defined community-acquired hepatitis, probably due to hepatitis G virus (HGV), who developed severe aplastic anaemia. In this case, the absence of other agents likely to cause the clinical manifestations, and the detection of HGV RNA at the time of illness, clearly point to this agent as being responsible for both the hepatitis and the aplastic anaemia. Further studies in serial serum samples and meticulous evaluation of the disorders associated with the infection will be needed to prove or dispute a causal association of HGV and aplastic anaemia.

Keywords: hepatitis G virus; aplastic anaemia

Aplastic anaemia complicating hepatitis is a rare but well-documented phenomenon. The mechanisms leading to marrow failure remain unclear.^{1,2} The recent identification of the hepatitis G virus (HGV) has opened the field to the study of disease association with these new agents.^{3,4} HGV-RNA has been reported in sera from patients with acute, chronic, and fulminant hepatitis who lacked evidence of infection with known hepatitis viruses.^{3,4} Of interest is an apparent link between HGV infection and cases of aplastic anaemia.^{5,6}

Case report

On 10 July 1992, a previously healthy white 24-year-old heterosexual man presented with 5 weeks of malaise and 3 weeks of jaundice. The patient had had no exposure to industrial chemicals or to any proprietary or non-proprietary drugs. He denied use of any medications, intravenous drug abuse, blood transfusion, or alcohol ingestion. On examination, the patient was alert with minimal scleral icterus and without stigmata of chronic liver disease. Serologic markers for HAV, HBV, HCV, HEV, and HIV were repeatedly negative. HBV and HCV testing by polymerase chain reaction (PCR) did not detect HBV-DNA or HCV-RNA. Virological and microbiological tests, including cytomegalovirus, Parvovirus B-19 (IgG and IgM), toxoplasma, Epstein-Barr virus, herpes simplex virus, coxiella, and leptospira, were all negative. Antinuclear antibodies, anti-smooth muscle antibody, antimitochondrial antibody, and screen for Wilson's disease and haemochromatosis were also negative. Chest X-ray and ultrasound examination of the abdomen were normal. His clinical state improved over the next 10 weeks; liver function tests returned to normal levels by week 12. On 5 August 1993 he was admitted to our hospital for evaluation of nose and gum bleeding and multiple haematomata. Examination revealed purpura of his oral mucosa and multiple petechiae. Virological and microbiological tests were again negative. Bone marrow biopsy showed a severely hypoplastic marrow and this, together with his low platelet and white cell counts, satisfied the criteria for severe aplastic anaemia. Over the following 2 weeks, he became progressively more pancytopenic and his aspartate transaminase and alanine transaminase returned to near normal ranges. On 25 August 1993 he received an allogeneic bone marrow transplant. He has remained well for more than 2 years after transplantation. The laboratory results are summarised in table 1.

HCV-RNA was investigated by PCR amplification of the 5' NCR as described previously.⁷ No cross-reactivity with HGV-RNA was found. HGV-RNA was investigated by PCR amplification of the 5' NCR as described previously.⁸ Briefly, nucleic acids were extracted from 100 µl of serum using extraction columns (Quiagen, Hilden, Germany). RNA was transcribed into cDNA with M-MLV retrotranscriptase. The primers were NCRI:

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Table 1 The haematological, biochemical, serological, and virological course of the community-acquired hepatitis and associated aplastic anaemia

Variable	July 1992	Sep 1992	Aug 1993	July 1994	Dec 1994
Hemoglobin (g/l)	151	145	100	135	137
White cells ($\times 10^9/l$)	6.1	7.35	1.3	5.45	6.7
Platelets ($\times 10^9/l$)	310	254	10	221	236
^a PI (%)	100	100	80	100	100
^b AST (IU/l)	941	40	451	51	35
^c ALT (IU/l)	1812	45	1344	70	38
^d AP (IU/l)	190	83	185	95	75
^e GGT (IU/l)	364	45	218	40	45
^f TB (μ mol/l)	51.3	22	55.3	27.2	31.2
^g HGV-RNA	Positive	Positive	Positive	Negative	Negative

^aPI: Prothrombin index (normal value 70–100%); ^bAST: aspartate transaminase (normal value 10–40 IU/l); ^cALT: alanine transaminase (10–40 IU/l); ^dAP: alkaline phosphatase (40–120 IU/l); ^eGGT: gamma-glutamyltranspeptidase (10–50 IU/l); ^fTB: total bilirubin (3.42–17.1 μ mol/l); ^gHGV-RNA detected by polymerase chain reaction.

5'-CGGCCAAAAGGTGGTGGATG-3' and NCR2: 5'-CGACGAGCCTGACGTC GGG-3'. Amplified cDNA sequences were detected by agarose gel electrophoresis with ethidium bromide staining. The specificity of the amplified bands was confirmed by an electro-immunoassay procedure (PCR ELISA (Dig detection, Boehringer Mannheim, Germany). Sera obtained before any blood products were given and throughout the clinical course, were positive for HGV. Similarly, serum obtained on presentation with aplastic anaemia was positive for HGV. Unfortunately, fresh bone marrow aspirates were not available to show whether HGV RNA was present in bone marrow. Sera obtained in July and December 1994, were negative for HGV.

Discussion

Hepatitis-associated aplastic anaemia (HAAA) is a severe disorder with a high mortality; the responsible agent for most cases of HAAA has not been identified, although it is presumed to be viral. HGV has been postulated as the aetiological agent of acute hepatitis, chronic liver disease of unknown aetiology, fulminant hepatitis, and HAAA.^{3,4} In our patient, we were able to detect HGV-RNA in the serum repeatedly before any blood transfusion. In this case, the HGV infection was demonstrated coincident with the two flares of hepatic necrosis, and for this reason a causative association can be inferred. The role of HGV in non-A-E community-acquired hepatitis is under investigation.⁹⁻¹¹ Published case series have claimed an association between HGV and acute liver diseases, but case-control studies are required to confirm whether or not HGV is an aetiological agent of viral hepatitis.⁹ The negative HGV RNA by PCR in the post-bone marrow transplant serum suggests HGV clearance in this patient. Few reports have analysed the role of HGV in the development of HAAA (table 2); however, the high prevalence of HGV in these cases may arise from disease treatment rather than from HGV being a causative agent of aplastic anaemia.

Table 2 Cases reported of possible HGV infection as a causative agent of hepatitis-associated aplastic anaemia

Reference	n patients	HGV-RNA positive (%)
1	10	3 (30)
3	1	1 (100)
5	1	1 (100)
6	1	1 (100)
10	4	4 (100)
present case	1	1 (100)

The patient with HGV hepatitis we report here followed a pattern noted to be typical of HAAA. Moreover, after the bone marrow transplant, there was no further evidence of chronic hepatitis or HGV infection. Although the detection of HGV RNA at the time of illness, in the absence of other agents likely to cause the clinical manifestations, clearly points to this agent as being responsible for both the hepatitis and the aplastic anaemia, controversial issues should be addressed. First, the clinical significance of HGV remains uncertain.⁸⁻¹⁰ Second, neither a specific location nor replication in the liver has yet been verified and HGV RNA has not been documented in fresh marrow aspirates. Third, we cannot exclude that our patient with HGV infection may have simultaneously acquired another unidentified agent(s) which might have caused the rise in liver enzymes and/or the aplastic anaemia. Fourth, several features of the HAAA suggest that it is mediated by immunopathologic mechanisms; for this reason, the causative agent of this syndrome may not be an infectious agent.¹⁻²

In summary, in this case the absence of other agents likely to cause the clinical manifestations, and the detection of HGV RNA at the time of illness, clearly point to this agent as being responsible for both the hepatitis and the aplastic anaemia.

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- 1 Brown KE, Tisdale J, Barrett J, Dunbar CE, Young NS. Hepatitis-associated aplastic anemia. *N Engl J Med* 1997;336:1059-64.
- 2 Kojima S, Matsuyama K, Koderia Y, Okada J. Circulating activated suppressor T lymphocytes in hepatitis-associated aplastic anemia. *Br J Haematol* 1989;71:147-51.
- 3 Simons JN, Leary TP, Dawson GJ, et al. Isolation of novel virus-like sequences associated with human hepatitis. *Nat Med* 1995;1:564-9.
- 4 Linnen J, Wages J Jr, Zhang-Keck ZY, et al. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. *Science* 1996;271:505-8.
- 5 Zaidi Y, Chapman CS, Myint S. Aplastic anaemia after HGV infection. *Lancet* 1996;348:471-2.
- 6 Byrnes JJ, Banks AT, Piatak M, Kim JP. Hepatitis G-associated aplastic anaemia. *Lancet* 1996;348:472.
- 7 Crespo J, Carte B, Lozano JL, et al. Hepatitis C virus (HCV) recurrence after liver transplantation: Relationship to anti-HCV core IgM, genotype, and level of viremia. *Am J Gastroenterol* 1997;92:1458-62.
- 8 Leary TP, Muerhoff AS, Simons JN, et al. Consensus oligonucleotide primers for the detection of GB virus C in human cryptogenic hepatitis. *J Virol Meth* 1996;56:119-21.
- 9 Alter MJ, Gallagher M, Morris TT, et al. Acute Non-A-E hepatitis in the United States and the role of hepatitis G virus infection. *N Engl J Med* 1997;336:741-6.
- 10 Kao J-H, Chen P-J, Hsiang S-C, et al. Phylogenetic analysis of GB virus C: comparison of isolates from Africa, North America and Taiwan. *J Infect Dis* 1996;174:410-3.
- 11 Alter HJ, Nakatsuji Y, Melpolder J, et al. The incidence of transfusion-associated hepatitis G virus infection and its relation to liver disease. *N Engl J Med* 1997;336:747-54.

Primary antibody deficiency and Crohn's disease

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Summary

Five patients with primary antibody deficiency were investigated because of intermittent but persistent diarrhoea of several years duration despite immunoglobulin replacement therapy. We found no evidence of *Giardia lamblia* or other intestinal pathogens to explain their gastrointestinal symptoms. All five had definite radiological evidence of small bowel Crohn's disease and three had histological specimens available with abnormalities consistent with Crohn's disease. One patient had a non-caseating granuloma in an oral ulcer. A second patient with stricturing disease in the small bowel had a mucosal inflammatory infiltrate with non-caseating granulomas. A third had transmural inflammation but no granulomas. All five patients were diagnosed as having Crohn's disease and have responded symptomatically to steroid therapy.

Keywords: antibody deficiency; Crohn's disease

Some patients with primary antibody deficiency have an enteropathy. Infection is common and although immunoglobulin replacement therapy seems to have reduced the incidence of some bowel pathogens such as *Giardia*, *Salmonella* and *Campylobacter*, 10% have diarrhoea, abdominal pain or weight loss which defies explanation.¹

There is a broad spectrum of histological abnormality in these patients. In the stomach there is a high frequency of gastric atrophy and a predisposition to gastric carcinoma,²⁻⁴ whilst in the small bowel, lymphoid nodular hyperplasia is common.²⁻⁵ In those with common variable immunodeficiency, there are well-documented cases of jejunal villous atrophy which may or may not respond to gluten withdrawal; however, the diagnosis of coeliac disease has only been reliably proved in one patient after gluten withdrawal and challenge.⁶

There have been several case reports showing radiological appearances compatible with Crohn's disease in patients who have presented with diarrhoea and intestinal strictures, although the histology has generally not shown granulomas or transmural inflammation.⁷⁻¹¹ Teahon and Webster,¹¹ in their series of patients with primary antibody deficiency, proposed the existence of an enteropathy distinct from Crohn's disease. The radiology was consistent

with Crohn's disease but the histology was apparently distinctive with the presence of microscopic colitis, increased intra-epithelial lymphocytes and an intact crypt architecture in the colon. Any inflammation in the small bowel was not transmural and there were no granulomas.

We investigated the cause of diarrhoea in five patients with primary antibody deficiency who were referred with refractory diarrhoea.

Methods

We investigated five patients who were referred with intermittent but persistent diarrhoea of several years duration from a cohort of 100 patients with primary antibody deficiency from the Department of Immunology at Hope Hospital in Manchester over a period of 8 years. There were four men (19–65 years) and one woman (54 years). One had X-linked agammaglobulinaemia (Bruton's disease), the others had common variable immunodeficiency. All five patients had been shown to have a primary immunological deficiency by their repeated failure to generate responses to common antigens such as pneumococcus, tetanus and pokeweed nitrogen. All were on regular immunoglobulin replacement therapy with Sandoglobulin (Sandoz Pharmaceuticals) at a dose of 0.3–0.4 g/kg/month with regular assessment of their immunoglobulin trough levels.

Two sets of three fresh stool specimens from each patient were examined for evidence of parasitic involvement or other pathogens. Each patient had a gastroscopy with duodenal biopsy, full colonoscopy and a small bowel enema. The specimens obtained were examined histologically for parasites.

Patients were commenced on steroid therapy and their response assessed according to improvements in their symptoms. They were then followed up over a 5-year period.

Results

The main findings are shown the table. No pathogens were identified from several stool examinations specifically looking for *Salmonella*, *Shigella*, *Campylobacter*, ova and cysts. All of the patients had radiological evidence of small bowel abnormalities compatible with Crohn's disease. Patient 1 had nodular thickening throughout the jejunum and ileum (figures 1 and 2). Patient 2 showed stricturing disease in the duodenum and small bowel (figure 3). Patient 3 had a stenotic lesion in the terminal

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Table 1

Patient	Age	Sex	Presentation	Radiological abnormalities	Histological abnormalities	Other features	Other sites of infection	
1	X-linked agammaglobulinaemia	19	M	Weight loss, loss of appetite, abdominal pain	Jejunum, ileum = nodular thickening	Mouth-granulomas, non-caseating S - not done D - duodenitis, no atrophy SB - none available C - normal	Has developed a protein losing enteropathy	Bronchiectasis
2	CVID	60	M	Oral ulcers, abdominal pains, weight loss	Duodenum, jejunum, ileum = stricturing 2nd & 4th parts of the duodenum & mid small bowel	S - not done D - not done SB - granulomas, inflammatory infiltrate, not transmural C - not done	Stricturing disease in mid small bowel requiring resection	Nil
3	CVID	36	M	Diarrhoea, abdominal pain	Terminal ileum = skip lesions & ulceration with stenotic lesions	S - normal D - total villous atrophy, crypt hyperplasia, intraepithelial lymphocytes SB - none available C = non-specific inflammation	Has developed spondyloarthopathy affecting large joints	One episode of meningitis
4	CVID	33	M	Diarrhoea, right iliac fossa pain	Terminal ileum = oedematous, with rose thorn ulcerations	S - normal D - normal SB - none available C - non-specific inflammation		Bronchiectasis
5	CVID	52	F	Bloating, diarrhoea, abdominal pain	Terminal ileum = ulceration and stricturing disease	S - gastritis, no atrophy D - not done SB - mild transmural inflammation, patchy inflammatory cells, no granulomas C - normal	Required terminal ileum resection	Recurrent chest infection

CVID = common variable immunodeficiency, S = stomach, D = duodenum, SB = small bowel, C = colon.

ileum with skip lesions and ulceration. Patient 4 had rosethorn ulceration of the terminal ileum. Patient 5 also had stricturing disease in the terminal ileum (figure 4).
There was a wide spectrum of histological abnormality. Patient 1 had granulomatous ulceration in the mouth and duodenitis. Patient 3 had total villous atrophy on duodenal biopsy with increased intra-epithelial lymphocytes and crypt hyperplasia. Patient 5 had gastritis. Patients 2 and 5 needed resections for obstructive symptoms. One resected terminal ileal

specimen revealed an inflammatory non-transmural lymphocytic infiltrate, fibrosis and two non-caseating granulomas. The other resected ileal specimen showed transmural lymphocytic inflammation without granulomas. In the colon of patients 3 and 4 the specimens demonstrated a mild non-specific inflammation restricted to the mucosa which was mainly lymphocytic with some neutrophils, infiltration, no crypt abscesses, and without

Figure 1 Film on barium follow-through study (patient 1). There is mild thickening and nodularity of the jejunum. In addition in this case more diseased loops of bowel are seen within the pelvis where the nodularity is more marked (open white arrow) and there is associated luminal narrowing with bowel loop separation (black arrow)

Figure 2 Film from small bowel enema (patient 2). Note the small bowel enema tip in third part of duodenum. Strictures are evident: the first (white arrow) is at the junction of the second and third part of the duodenum. A second stricture is seen in the region of the DJ flexure (curved open arrow). This is causing pre-stenotic dilatation of the third part of the duodenum which contains a filling defect/food residue. Contrast has, however, passed beyond this point into the proximal jejunum

Figure 3 Film from small bowel follow-through series (patient 2). There is mild, diffuse nodular thickening of the jejunum and proximal ileum. No structuring disease is identified. The appearances are non-specific but can be seen in diffuse Crohn's jejunal ileitis as well as many other conditions such as Giardiasis.

Figure 4 Cone view of right iliac fossa during small bowel enema (patient 5). The distal terminal ileum shows stricturing in several places (white arrows). The folds are thickened and there is nodularity with several adverse ulcers. These are most prominent between the two labelled strictures.

intra-epithelial lymphocytes. There was no evidence of parasites in any of the specimens examined.

Patients 1 and 3 who had particularly severe symptoms were treated with budesonide but did not respond and were controlled on regular prednisolone. The other three patients responded to short courses of prednisolone following commencement of steroids, a clinical improvement was documented by a significant reduction in stool frequency.

Discussion

The five patients described had Crohn's disease. We found no evidence to support the existence of a separate enteropathy associated with primary antibody deficiency. One might have expected that infection would explain these patients relapsing and remitting gastrointestinal symptoms. After all, the majority had

evidence of infection in other body systems, but despite looking for pathogens in stools and histological specimens none was ever implicated. It could be argued that we did not look aggressively enough for micro-organisms. *Microporida* and *Cyclospora* are difficult to detect on haematoxylin and eosin sections; electron micrographs would perhaps have been preferable. It is also difficult to attain a perfect plateau of immunoglobulin replacement, even with frequent monitoring of trough levels, and Sandoglobulin contains predominantly IgG with only small amounts of IgA, the principal bowel immunoglobulin.

All of our patients had radiological evidence of small bowel involvement varying from stricturing disease requiring surgical resection in two patients to nodular thickening in the jejunum and ileum or rosethorn ulceration. The histological abnormalities were very diverse. Two patients had non-caseating granulomas; in one, this was present in a lesion in the mouth and the other in a resected terminal ileal specimen. This latter patient, however, had a predominantly mucosal rather than transmural lymphocytic infiltrate. The other patient who needed a terminal ileal resection for stricturing disease had a mild transmural lymphocytic infiltrate without granulomas.

Total villous atrophy with increased intra-epithelial lymphocyte infiltration was found in one patient on duodenal biopsy but he showed no improvement in histological appearance with gluten withdrawal. Another had lymphocytic infiltration in the duodenum but no other abnormalities. In colonic specimens, two patients had mild inflammation restricted to the mucosa, with an intact crypt architecture and no increase in intra-epithelial lymphocytes.

We would argue that the pattern of histological and radiological findings demonstrate these patients to have Crohn's disease rather than belonging to a different grouping as originally proposed by Teahon and Webster.¹¹

Patients 2 and 5 needed small bowel resections for stricturing disease in the early part of their clinical course; their subsequent gastrointestinal symptoms have responded well to short courses of prednisolone, as have those of patient 4. Two other patients (1 and 3) were tried on 9 mg of budesonide but did not respond and have better disease control on regular prednisolone therapy, with one of these also tolerating and responding to an elemental diet. Patient 1 with x-linked agammaglobulinaemia has recently developed a protein-losing enteropathy initially suggested by rising requirements for immunoglobulin therapy. Interestingly, this problem appears to have been controlled with steroid therapy.

The aetiology of Crohn's disease is still unknown. A variety of hypotheses exist but none have been proved. Immune function has been extensively tested in Crohn's patients. There have been studies suggesting mild defects in neutrophil functions, both in ability to phagocytose¹² and in chemotaxis on skin

windows¹³ (serum-filled perspex windows placed over abraded skin). Others, however, have shown normal neutrophil oxidative ability^{14 15} and normal chemotaxis in vitro. All in all, these probably add up to mild defects in phagocyte function. Lymphocyte function is thought to be normal in Crohn's disease; although there is a specific increase in IgG2

immunocytes.¹⁶ It is not known how many patients with Crohn's have primary antibody deficiency.

In conclusion, we report five patients with primary antibody deficiency who also have Crohn's disease defined radiologically and histologically, and whose symptoms are controlled on steroid therapy.

- 1 Webster ADB. Immune deficiency syndrome and the gut. In: Peters TJ, ed. *The cell biology of inflammation in the gastrointestinal tract*. Hull: Corners Publication, 1990; pp 231-48.
- 2 Ament ME. Immunodeficiency symptoms and the gut. *Scand J Gastroenterol* 1985;20:127-35.
- 3 Hermans PE, Diaz-Buxo JA, Stobo JD. Idiopathic late onset immunoglobulin deficiency. Clinical observations in 50 patients. *Am J Med* 1976;61:221-37.
- 4 Hermans PE, Huizenga KA. Association of gastric cancer with idiopathic late immunoglobulin deficiency. *Ann Intern Med* 1972;76:605-9.
- 5 Hermans PE, Huizenga KA, Hoffman HN, Brown AL, Marcowitz H. Dysgammaglobinaemia associated with nodular lymphoid hyperplasia of small intestine. *Am J Med* 1966;40:78-89.
- 6 Webster ADB, Slavin G, Shiner M, Platts-Mills TAE, Asherson GL. Coeliac disease with severe hypogammaglobinaemia. *Gut* 1981;22:153-7.
- 7 Soltot J, Petersen L, Kruse P. Immunoglobulin deficiency and regional enteritis. *Scand J Gastroenterol* 1972;7:233-6.
- 8 Strauss RG, Chisan F, Mitros F, et al. Rectosigmoid colitis in common variable immunodeficiency. *Dig Dis Sci* 1980;25:798-801.
- 9 Fillit H, Bernstein L, Davidson M, Brandt L, Bezahler G, Cohen M. Primary acquired hypogammaglobinaemia and regional enteritis. *Arch Intern Med* 1977;137:1252-4.
- 10 Mir-Madjlessi SH, Tavassolie H, Kamalian N. Malakoplakia of the colon and recurrent colonic strictures in a patient with primary hypogammaglobinaemia. *Dis Colon Rectum* 1982;25:723-7.
- 11 Teahon K, Webster AD, Price AB, Weston J, Bjarnason I. Studies on the enteropathy associated with primary hypogammaglobulinaemia. *Gut* 1994;35:1244-9.
- 12 Nielsen OH, Elmgreen J, Thomson BS, Ahnfelt-Ronne I, Wilk A. Release of leukotriene B4 and 5-hydroxyicosotetraenoic acid during phagocytosis of artificial complexes by peripheral neutrophils in chronic inflammatory bowel disease. *Clin Exp Immunol* 1986;65:465-71.
- 13 Segal AW, Loewi G. Neutrophil dysfunction in Crohn's disease. *Lancet* 1976;2:219.
- 14 Koldkjaer O, Klitgaard NA, Schmidt KG. Cellular and humoral indices of disease activity in inflammatory bowel disease. *Digestion* 1978;17:387.
- 15 Ward M, Eastwood MA. The nitroblue tetrazolium test in Crohn's disease and ulcerative colitis. *Digestion* 1979;14:179.
- 16 Kett K, Rognum TO, Brandtzaeg P. Mucosal subclass distribution of IgG producing cells is different in ulcerative colitis and Crohn's disease of the colon. *Gastroenterology* 1987;93:919-24.

Brain parenchymal, subarachnoid racemose, and intraventricular cysticercosis in an Indian man

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Summary

The coexistence of brain parenchymal cysts at various stages of evolution, both intraventricular and subarachnoid racemose, is reported in a patient with neurocysticercosis. The condition has a variety of presentations, depending on the location of the cyst. This case is of particular interest because of the rarity of this condition in India.

Keywords: brain parenchymal cyst; cysticercosis; albendazole

Cysticercosis is caused by cysticercus larvae of *Tenia solium*. The most common manifestation of neurocysticercosis is seizure due to brain parenchymal cysts at various stages of evolution.¹ Subarachnoid and intraventricular cysts are rarely seen in India. In Mexicans, however, they are more common (up to 10% of all cases).² Subarachnoid cysts are of the racemose type, as are the majority of intraventricular ones. A combination of cysticercus cysts in these locations is rather uncommon, especially in the Asian subcontinent. Considering the varied presentations of neurocysticercosis, de-

pending on the location of the cysts, it was felt to be worthwhile reporting this case. Some of the varied presentations and their pathogenesis are also discussed.

Case report

A 50-year-old man presented to the neurology out-patient department with history of left-sided sensorimotor seizures for the last 3 years with a frequency of once every one or two months. There was secondary generalisation at times. There was also a history of complex partial seizures for the last 6 months. These were characterised by episodic altered behaviour, aimless running around, and complete amnesia for the events. He had suffered from recurrent, nonthrobbed left parieto-occipital headaches, each lasting for a few hours, for the last 18 months. Accompanying the headache, he experienced tinnitus in both ears and vertigo, but there was no vomiting or visual symptoms. He gave a history of pork ingestion. He was on a maintenance of dose of phenytoin. He had received albendazole for a month in November 1994.

His general examination was normal. Systemic examination was unremarkable. The

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fundus did not show any papilloedema. There was no neurodeficit or meningeal signs. The haemogram was normal and biochemical parameters were within normal limits. Cerebrospinal fluid (CSF) analysis showed 55 cells (all lymphocytes) with protein 2 g/l, sugar 0.2 g/l (corresponding blood sugar 1.1 g/l), Gram stain was negative and culture sterile. Cysticercus serology (IHA) in blood and CSF was 1:8 (not suggestive). Contrast-enhanced computed tomography (CT) scan of the head showed multiple active parenchymal cysts and an enlarged left sylvian fissure (figure 1). Magnetic resonance imaging (MRI) of the brain showed multiple hypointense lesions on T_1 -becoming hyperintense on T_2 -weighted image, with multiple cysts in the left sylvian fissure with septations (figure 2A and B). No scolex was seen within the racemose cyst. There was an intraventricular cyst in the right posterior horn, seen more clearly on proton density imaging (figure 2C).

In summary, this patient had multiple cysts (cysticercus) in the brain parenchyma, intraventricular region, and a racemose cyst in the left sylvian fissure. In the absence of any acute neurological signs, it was decided to try medical therapy for one month and then re-evaluate the situation.

Discussion

The clinical manifestations of neurocysticercosis are determined by the load of organisms, location of cysts, whether the cyst is dead or alive, and the response of the host.¹ Parenchymal neurocysticercosis occurs most commonly at grey-white matter junctions. Neurocysticercosis is a common cause of late-onset seizure in countries where it is prevalent. Focal seizures are most common, but generalised tonic-clonic seizures are also observed. While parenchymal neurocysticercosis presents with seizures, subarachnoid neurocysticercosis usually presents with meningitis and raised intracranial pressure. Cysticercosis of the basal cistern is severe and frequently fatal. This variant is caused by a racemose form of cysticercosis which may cause obstruction to 4th ventricular outflow.³ Subarachnoid cysticercosis can cause specific neurologic syndromes when large lesions are located in the cerebellopontine angle, sylvian fissure,⁴ or the convexity. Intraventricular cysts are frequently found in association with subarachnoid cysts. The fourth ventricle is the most common site.⁵ They usually present as a syndrome of hydrocephalus and increased intracranial pressure. Free floating cysts in ventricles can cause Brun's syndrome, characterised by intermittent foramen obstruction causing episodic recurrent headaches, vertigo, ataxia and drop attacks.⁵

The racemose form of neurocysticercosis is a collection of transient membranes forming a cluster like a bunch of grapes,⁶ thought to be a forme fruste of cysticercus cellulosae.⁷ Supratentorial racemose cysts are usually found in the sulci. When vesicles break down, an intense inflammatory reaction may occur in the

Figure 1 Contrast-enhanced CT scan of the head showing large CSF density lesion in the left sylvian fissure with incomplete septation. Multiple parenchymal cysts can be seen, some with visible scolexes

Figure 2 Brain MRI scans. (A) T_1 -weighted image, showing the left sylvian fissure containing multiple thin-walled large racemose cysts along with many parenchymal cysts. The lesions are hypointense; (B) T_2 -weighted image showing hyperintensity of the cyst fluid at the left sylvian fissure and multiple parenchymal cysts, some with perifocal oedema; (C) proton density MRI showing right posterior horn of lateral ventricle containing an intraventricular cyst

subarachnoid space, causing arachnoiditis and hydrocephalus.

Cysticercus racemose was first described by Virchow in 1860. It is found in serious cases of cerebral cysticercosis and is characterised by larger size (4–12 cm), absence of scolex and a variable appearance. The coexistence of racemose and cellulosa is rare in Asian countries but not uncommon in Mexico (found in 10% of cases).² The racemose type is more common in the suprasellar area, the cerebellopontine angle and sylvian fissure. The proliferating connective tissue encircles the characteristic bladder wall of the parasite.

Subarachnoid and intraventricular racemose cysts are more easily diagnosed by gross inspection than by microscopy, as they show typical budding of the vesicular wall. In intraventricular cysts there is more intense granulomatous inflammation. The ependymal lining is lost, with subependymal gliosis, ependymitis, and perivascular cuffing.⁸ As the cyst degenerates, granulomatous ependymitis and gliosis are the only residual histological findings.

According to some authors, *cysticercus racemose* may actually be due to a different variety of cestode, including *Tenia solium*, *Tenia multiceps*, and *Tenia serialis*.⁹ In few specimens degenerated scolices have been found, suggesting *T. solium* as the aetiological agent.¹¹

CT scan in subarachnoid cysticercosis most commonly shows hydrocephalus, which may be communicating or non-communicating.¹² There may be contrast enhancement of tentorium and basilar cistern secondary to arachnoiditis and fibrosis. The vessel involvement can lead to infarction. Intraventricular cysticercosis is difficult to diagnose by CT scan alone. Obstructive hydrocephalus in the presence of a low-density intraventricular lesion may give a clue. The cysts enhance with contrast.

CT criteria to differentiate between cellulosa and racemose cysts

- cellulosa cysts are usually located intra-axially, ie, in brain tissue, while racemose cysts are frequently seen in basal cisterns, particularly the suprasellar area and cerebellopontine angle
- racemose cysts are usually bigger, appear as multiloculated cysts resembling 'bunches of grapes', elicit a more intense inflammatory reaction and frequently act as a space-occupying lesion
- in racemose varieties, no scolex is found

MRI is currently the most useful imaging tool for neurocysticercosis. Subarachnoid neurocysticercosis is better seen on MRI than on CT. Similarly, MRI is better for detection of cisternal cysts.¹³ T₁-Weighted images are better for delineating cisternal wall while T₂-weighted images are better in detecting oedema and arachnoiditis. Gadolinium-DTPA contrast in T₁ images enhances leptomeninges, suggesting inflammation. Racemose cysts have a similar signal intensity to that of CSF.¹⁴ Intraventricular neurocysticercosis must be suspected when hydrocephalus is present. MRI is superior to CT scan in detection of intraventricular cyst.¹⁴ Proton density images may better delineate the cyst from the CSF around the cyst,¹³ as shown in the present case.

Ventricular shunting is indicated for hydrocephalus.¹² Cyst extirpation and drainage is indicated for racemose cysticercosis. Intraventricular neurocysticercosis also needs extirpation and/or surgical drainage. A few cases have been treated successfully by albendazole alone.¹⁵

Subarachnoid, intraventricular, spinal and mixed types of neurocysticercosis may behave in a malignant way with worse outcome.¹²

1 Del Bruto OH, Garcia E, Talamas O, Sotelo J. Sex related severity of inflammation in parenchymal brain cysticercosis. *Arch Intern Med* 1988;148:544–6.

2 Rabiela-Cerrantos MR, Rivas-Hernandez A, Rodrigues-Ilbara J, Castillo Medina S, Cacino FM. *Anatomical pathological aspects of human brain cysticercosis*. New York: Academic Press, 1982; pp 179–99.

3 McCormick GF. Cysticercosis - review of 230 patients. *Bull Clin Neurosci* 1985;50:76–101.

4 Martinez-Lopez M, Ferrari FQY. Cysticercosis. *J Clin Neurol Ophthalmol* 1985;5:127–43.

5 Sotelo J, Guerrero V, Rubio F. Neurocysticercosis : a new classification based on active and inactive forms. *Arch Intern Med* 1985;145:442–5.

6 Escobar A. The pathology of neurocysticercosis. In : Palacios E, Rodrigues-Carbajal J, Taveras JM, eds. *Cysticercosis of the central nervous system*. Springfield IL: Charles C Thomas, 1983; pp 27–54.

7 Gutierrez Y. Cysticercosis, coenurosis and sparganosis. In: *Diagnostic pathology of parasitic infections with clinical correlations*. Philadelphia: Lea and Febiger, 1990; pp 432–59.

8 Itabashi HH. Pathology of CNS cysticercosis. *Bull Clin Neurosci* 1983;48:6–17.

9 Jung RC, Rodrigues A, Beaver PC, Schenthal JE, Levy RW. Racemose cysticercus in human brain. A case report. *Am J Trop Med Hyg* 1981;30:620–4.

10 Escobar A. The pathology of neurocysticercosis. In: Palacios E, Rodrigues-Carbajal J, Taveras JM, eds. *Cysticercosis of the central nervous system*. Springfield IL: Charles C Thomas, 1983; pp 27–54.

11 Berman JD, Beaver PC, Cheever AW, Quindlen EA. Cysticercus of 60 milliliter volume in human brain. *Am J Trop Med Hyg* 1981;30:616–9.

12 Sotelo J, Marin C. Hydrocephalus secondary to cysticercotic arachnoiditis. A long term follow up review of 92 cases. *J Neurosurg* 1987;66:686–9.

13 Zee CS, Segall HD, Boswell W, Ahmadi J, Nelson M, Colleti P. MRI imaging of neurocysticercosis. *J Comput Assist Tomogr* 1988;12:927–34.

14 Suss RA, Maravilla KR, Thompson J. MR imaging of intracranial cysticercosis: comparison with CT and anatomopathologic features. *AJNR* 1986;7:235–42.

15 Del Bruto OH, Sotelo J. Albendazole therapy for subarachnoid and ventricular cysticercosis. Case report. *J Neurosurg* 1990;72:816–7.

Internal iliac artery embolisation for intractable bladder haemorrhage in the peri-operative phase

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Summary

Intractable haemorrhage from the bladder wall during transurethral resection of bladder tumour is uncommon but potentially catastrophic. Internal iliac artery embolisation is a minimally invasive technique, which is now widely practised to stop bleeding from branches of these arteries in situations including pelvic malignancy, obstetric and gynaecological emergencies and trauma. We report its successful use peri-operatively, in an unfit, elderly patient with uncontrolled bleeding.

Keywords: embolisation; internal iliac artery; transurethral resection of bladder tumour

Severe haemorrhage from the bladder wall during and following transurethral resection of bladder tumour (TURBT) can be life threatening. Methods of management for uncontrolled bladder bleeding include cystoscopic clot evacuation with cystodiathermy, Helmstein balloon compression,¹ irrigation with alum solution,² and instillation of formalin,³ and may finally culminate in open surgical techniques ranging from simple packing of the bladder to cystectomy and urinary diversion.⁴ Most patients in this situation are elderly and unfit and therefore unlikely to withstand these latter morbid procedures, especially as they require regional or general anaesthesia. Prolonged hypovolaemia and the associated massive blood transfusions that may be required are also poorly tolerated.

Internal iliac artery embolisation has been successfully used in controlling bladder haemorrhage from terminal pelvic malignancy for over 20 years.⁵⁻⁶ This case report illustrates its added value in the transurethral peri-operative phase.

Case report

A frail 79-year-old man with superficial, high-grade transitional cell carcinoma of the bladder (G3 pT1) kept on regular surveillance for 3 years, was admitted for transurethral resection under general anaesthesia of recurrent bladder tumour. There was no history of recent haematuria and his haemoglobin level was 10.2 g/dl. Clotting profile was normal.

Cystoscopy revealed an extensive tumour recurrence predominantly on the left side and occupying over 70% of the bladder surface

area. Resection of the tumour was difficult due to excessive bleeding. After 25 minutes, he became cardiovascularly unstable and was transfused with two units of blood. It was not

Figure 1 Pre-embolisation subtraction arteriogram showing selective contralateral catheterisation of the left internal iliac artery with significant vascular supply to the bladder wall tumour

Figure 2 Post-embolisation subtraction arteriogram showing occlusion coils bilaterally within the anterior divisions of the internal iliac arteries

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possible to control the bleeding endoscopically and he was deemed too unfit to undergo an open surgical procedure. Immediate transfer to the radiology suite was organised for bilateral internal iliac artery embolisation. A pelvic arteriogram was performed and the anterior division of the contralateral internal iliac artery supplying branches to the left bladder wall, was identified. This illustrated the significant vasculature supplying the tumour in the left bladder wall (figure 1). Embolisation of the anterior division of the left internal iliac artery was carried out using occlusion coils and repeated on the right side to prevent any collateral circulation (figure 2). Immediate control of the haemorrhage was achieved without complications. His haemoglobin level was 9.7 g/dl following two further units of blood and he made a full recovery. He declined any further surgical intervention, but was well at 3 months with no further haematuria.

Discussion

Internal iliac artery embolisation for the palliation of severe bladder haemorrhage in inoperable malignancy results in good initial control in 80–100% of patients. The duration of control is usually life long in these terminal cases.⁷ Complications arising from the procedure are uncommon and include sepsis, gluteal pain, gait disturbances and, very rarely, bladder necrosis.⁸

Summary points

- severe bladder haemorrhage from surgery or pelvic malignancy *per se*, can be difficult to control and is life threatening
- internal iliac artery embolisation is a minimally invasive technique which successfully stems intractable haemorrhage in the majority of cases
- early referral of suitable patients to the radiologist reduces morbidity related to prolonged hypovolaemia and associated blood transfusions and negates the need for more radical open surgical procedures

This case report illustrates the value of the procedure in the acute transurethral peri-operative phase, when haemostasis is proving to be difficult to achieve. Previous reports⁹ have shown the efficacy of embolisation in the early postoperative period but this was undertaken only after massive blood transfusions had been given for prolonged hypovolaemia, with the attendant risks including consumptive coagulopathy, multi-organ failure, transfusion reactions, and possible blood-borne infections. This case demonstrates that providing there is good liaison between urologist and radiologist, early peri-operative referral of an unfit patient for arterial embolisation results in minimal total blood loss and therefore avoids the morbidity of multiple blood transfusions. It also avoids the use of more invasive techniques to achieve haemostasis.

1 Holstein P, Jacobsen K, Pedersen JF, Sorensen JS. Intravesical hydrostatic pressure treatment: new method for control of bleeding from the bladder mucosa. *J Urol* 1973;109:234–6.

2 Kennedy C, Snell ME, Witherow RO. Use of alum to control intractable vesical haemorrhage. *Br J Urol* 1984;56:673–5.

3 Shrom SH, Donaldson MH, Duckett JW, Wein AJ. Formalin treatment for intractable haemorrhagic cystitis. A review of the literature with 16 additional cases. *Cancer* 1976;38:1785–9.

4 Pomer S, Karcher G, Simon W. Cutaneous ureterostomy as last resort treatment of intractable haemorrhagic cystitis following radiation. *Br J Urol* 1983;55:392–4.

5 Hald T, Mygind T. Control of life threatening vesical haemorrhage by unilateral hypogastric artery muscle embolisation. *J Urol* 1974;112:60–3.

6 Kobayashi T, Kusano S, Matsubayashi T, Uchida T. Selective embolisation of the vesical artery in the management of massive bladder haemorrhage. *Radiology* 1980;136:345–8.

7 Jenkins CNJ, McIvor J. Survival after embolisation of the internal iliac arteries in ten patients with severe haematuria due to recurrent pelvic carcinoma. *Clin Radiol* 1996;51:865–8.

8 Wells I. Internal iliac artery embolisation in the management of pelvic bleeding (Editorial). *Clin Radiol* 1996;51:825–7.

9 Appleton DS, Sibley GNA, Doyle PT. Internal iliac artery embolisation for the control of severe bladder and prostate haemorrhage. *Br J Urol* 1988;61:45–7.

Good prognosis in thyroid cancer found incidentally at surgery for thyrotoxicosis

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Summary

An analysis of the outcome of thyroid carcinoma incidentally discovered in patients undergoing surgery for hyperthyroidism is presented. Among 986 patients with differentiated thyroid cancer, 23 had presented with symptoms and signs of hyperthyroidism. Graves' disease was diagnosed in 11, multinodular goitre in eight and toxic adenoma in four. Following thyroidectomy, histology revealed papillary (18), follicular (four) and Hurthle cell (one) carcinoma. Tumour size ranged from 4 mm to 5.5 cm, multifocality was detected in three patients, and lymph node involvement in one. Two patients (one with associated Graves' disease, one with multinodular goitre) relapsed locally and required further surgery; one developed distant metastases and died 7 years after initial presentation. Two patients died of unrelated causes; the remaining 20 patients are alive and well with a median follow-up of 16 (1–34) years. Differentiated thyroid cancer found incidentally at surgery for hyperthyroidism has a good prognosis.

Keywords: thyroid neoplasms; thyrotoxicosis; thyroidectomy

Previous studies have suggested that thyroid cancer occurs more frequently in patients operated for hyperthyroidism than in euthyroid patients.^{1–4} The reported incidence of thyroid carcinoma found at surgery in hyperthyroid patients ranges from 0.21% to 8.7% depending on the criteria used to select patients for surgery, patient characteristics and history of previous neck irradiation. More recently, it has been suggested that thyroid cancer associated with Graves' disease is highly aggressive and should be treated vigorously.⁵ Other investigators⁶ have not confirmed this finding and the issue remains controversial. We report our experience in patients found to have differentiated thyroid cancer at thyroidectomy for hyperthyroidism.

Patients and methods

Between 1949 and 1997, 986 patients with differentiated thyroid cancer were treated at the Royal Marsden Hospital, which serves as a tertiary referral unit for patients with thyroid disease. Twenty-three patients (19 women, four

men, median age at diagnosis 35 years, range 21–78 years) had presented with clinical features of hyperthyroidism. The duration of hyperthyroidism ranged from 4 months to 13 years (median 3 years). Graves' disease was diagnosed in 11 patients based on clinical findings, the presence of circulating thyroid antibodies and a uniformly increased ¹³¹I thyroid uptake scan appearance.

Toxic multinodular goitre was diagnosed in eight patients and autonomously functioning thyroid adenoma in four patients based on clinical and scan appearances. Graves' disease with a palpable nodule was not diagnosed in this series.

Subtotal thyroidectomy was performed initially in all cases. Indications were: recurrent hyperthyroidism after medical treatment (7), physician preference (5), large goitre responding poorly to medical treatment (4), persistent drug effects (3), enlarging nodule (2) and patient preference (2). In 13 patients, total thyroidectomy was subsequently performed followed by 3 GBq of ¹³¹I to ablate residual tissue.

All patients were followed-up according to our thyroid cancer protocol at intervals increasing from 6 months to yearly. At each visit, patients were clinically assessed and serum thyroglobulin was estimated. Where whole body ¹³¹I scans demonstrated persistent uptake, further ablation with radioiodine was given.

Results

Eighteen papillary, four follicular and one Hurthle cell carcinoma were found incidentally in the thyroidectomy specimens. In three cases, more than one focus of cancer was identified. Tumour size ranged from 4 mm to 5.5 cm; 12 tumours were less than 1 cm (T1), five were 1–2 cm and five were over 2 cm in diameter. Five (45%) of the tumours in the Graves' patients, two (50%) in the toxic adenoma patients and four (57%) in the multinodular patients were over 1 cm in diameter. Only one patient had evidence of lymph node involvement at presentation.

Follow-up ranged from 1–34 years with a median of 16 years. Two patients suffered a local recurrence; one with associated Graves' disease, the other with an underlying multinodular goitre. A 2.5 cm follicular thyroid cancer was discovered at thyroidectomy in the Graves' patient. She underwent total thyroidectomy and received ablative radioiodine but despite this, developed lymph node recurrence 5 years after presentation. Block dissection of

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lymph nodes was performed but two years later she had developed brain metastases and died 7 years after initial diagnosis.

The patient with multinodular goitre and recurrent thyroid cancer had been found to have an 8 mm Hurthle cell carcinoma at the time of subtotal thyroidectomy. Ten years later a 1 cm palpable nodule was discovered in the thyroidectomy scar and was found to contain recurrent cancer. She underwent completion total thyroidectomy. She remained disease-free thereafter and died of heart disease 17 years after initial presentation with no evidence of recurrent thyroid cancer at death.

There was one further death in a patient with associated Graves' disease unrelated to thyroid cancer (gall bladder cancer). The remaining 20 patients are alive and well with no evidence of recurrent disease.

Discussion

In this series of patients with occult thyroid malignancy and hyperthyroidism, we have not found evidence of increased tumour aggressiveness over a long period of follow-up. Only two patients developed local recurrence and only one distant metastases. Tumours in patients with Graves' disease were no larger than in other hyperthyroid patients and behaved no differently from those in non-Graves' patients. These results contrast with those of Belfiore *et al*⁵ who reported a high incidence of local invasiveness, lymph node involvement and distant metastases in their patients with Graves' disease and thyroid cancer. However, all but two of their Graves' patients had palpable nodules in contrast to the present study (none had nodules) which could indicate that tumours in the previous study were detected later and hence had a poorer outcome.

Only three patients had evidence of multiple foci in histological specimens. A higher frequency may have been found if all patients had

Learning points

- tumours discovered incidentally at thyroidectomy in patients with thyrotoxicosis generally have a good prognosis
- occult thyroid tumours in patients with Graves' disease behaved no differently from those in non-Graves' patients

undergone total thyroidectomy. Similarly, elective node dissection on all patients may have detected a higher incidence of nodal involvement. Nevertheless, the prognosis of our patients remained good and certainly we would have expected to detect metastases during the long period of follow-up.

The good outcome of the patients in our series is similar to that found in previous studies.⁶⁻⁸ Possible factors contributing to the high survival and low incidence of recurrences include young age at presentation and more aggressive treatment. In this series, we treated patients with less favourable prognostic indicators (older patients, T2 and T3 tumours) with more radical surgery and ablative iodine. However, treatment alone does not explain the initial lack of invasiveness and metastases observed in this study.

Care is needed in interpreting histology as the diffusely hyperplastic gland of Graves' disease may simulate malignancy; the cases in this series were all diagnosed by experienced pathologists according to established criteria.⁹

In summary, our results do not suggest increased aggressiveness in incidentally discovered thyroid carcinomas associated with hyperthyroidism. Further work is needed to define the optimal treatment for this group of patients.

1 Sokal JE. Incidence of malignancy in toxic and nontoxic nodular goitre. *JAMA* 1954;154:1321-5.

2 Shapiro SJ, Friedman NB, Perzik SI, Caty B. Incidence of thyroid carcinoma in Graves' disease. *Cancer* 1970;26:1261-70.

3 Farbota LM, Calandra DB, Lawrence AM, Paloyan E. Thyroid carcinoma in Graves' disease. *Surgery* 1985;98:1148-53.

4 Pacini F, DiCoscio GC, Anelli S, *et al*. Thyroid carcinoma in thyrotoxicosis patients treated by surgery. *J Endocrinol Invest* 1988;11:107-12.

5 Belfiore A, Garofalo MR, Giuffrida D, *et al*. Increased aggressiveness of thyroid cancer in patients with Graves' disease. *J Clin Endocrinol Metab* 1990;70:830-5.

6 Hales IB, McElduff A, Crummer P, *et al*. Does Graves' disease or thyrotoxicosis affect the prognosis of thyroid cancer? *J Clin Endocrinol Metab* 1992;75:886-9.

7 Dobyns BM, Sheline GE, Workman JB, Tompkins EA, McConale WM, Becker DV. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism. *J Clin Endocrinol Metab* 1974;38:976-998.

8 Behar R, Arganini M, Wu TC, McCormick M, Straus FH, DeGroot LJ. Graves' disease and thyroid cancer. *Surgery* 1986;100:1121-7.

9 Rosai J, Carcangiu ML, Delellis RA. *Atlas of tumour pathology, 3rd series, Fascicle 5, Tumours of the thyroid gland*. Washington: Armed Forces Institute of Pathology, 1992; p 302.