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

A G C Sutton, U Somasundram, J A Hall

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 internal dimension 5.7 cm, normal range 3.5–5.6 cm), incomplete coaptation 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-
nal left ventricular ejection fractions had increased left ventricular diameters during systole or diastole. Keeling et al. reported similar findings when studying 236 relatives of 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). However, four other specific gene loci for autosomal dominant dilated cardiomyopathy have also been described, indicating the genetically heterogeneous nature of the condition. Autosomal recessive, X-linked recessive, and maternal inheritance through mitochondrial DNA have also been reported.

To our knowledge, there has been only one published report of late-onset dilated cardiomyopathy in identical male twins. 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.

The authors acknowledge the assistance of Dr C Ritchie, Consultant Pathologist, Middlesbrough General Hospital, Middlesbrough.

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 population with males more commonly affected than females and Afro-Caribbeans more than Caucasians. The reported 5-year survival rates are 50–80%, depending on the series. 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. 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 normal left ventricular ejection fractions had increased left ventricular diameters during systole or diastole. Keeling et al. reported similar findings when studying 236 relatives of 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.

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

J Crespo, B de las Heras, M Rivero, J L Lozano, E Fábrega, F Pons-Romero

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. The recent identification of the hepatitis G virus (HGV) has opened the field to the study of disease association with these new agents. HGV-RNA has been reported in sera from patients with acute, chronic, and fulminating hepatitis who lacked evidence of infection with known hepatitis viruses. Of interest is an apparent link between HGV infection and cases of aplastic anaemia.

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, coxliella, 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 haematoma. 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 allogenic 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. No cross-reactivity with HGV-RNA was found. HGV-RNA was investigated by PCR amplification of the 5’ NCR as described previously. 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 NCR1:

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

<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin (g/l)</td>
<td>151</td>
<td>145</td>
<td>100</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td>White cells (× 10^3/l)</td>
<td>6.1</td>
<td>7.35</td>
<td>1.3</td>
<td>5.45</td>
<td>6.7</td>
</tr>
<tr>
<td>Platelets (× 10^9/l)</td>
<td>310</td>
<td>254</td>
<td>10</td>
<td>221</td>
<td>236</td>
</tr>
<tr>
<td>aPI (%)</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>941</td>
<td>40</td>
<td>451</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>1812</td>
<td>45</td>
<td>1344</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>GGT (IU/l)</td>
<td>364</td>
<td>45</td>
<td>218</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>TB (µmol/l)</td>
<td>51.3</td>
<td>22</td>
<td>55.3</td>
<td>27.2</td>
<td>31.2</td>
</tr>
<tr>
<td>HGV-RNA</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*PI: Protrombim index (normal value 70–100%); aAST: aspartate transaminase (normal value 10–40 IU/l); ALT: alanine transaminase (10–40 IU/l); aAP: alkaline phosphatase (40–120 IU/l); GGT: gamma-glutamyltranspeptidase (10–50 IU/l); TB: total bilirubin (3.42–17.1 µmol/l); aHGV-RNA detected by polymerase chain reaction.
Cases reported of possible HGV infection as a causative agent of hepatitis-associated aplastic anaemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>n patients</th>
<th>HGV-RNA positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3 (30)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>4 (100)</td>
</tr>
<tr>
<td>present case</td>
<td>1</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

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.7

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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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 strictureing 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 but whilst in the small bowel, lymphoid nodular hyperplasia is common.3 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.4

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.5 6 Teahan and Webster,7 8 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 in 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 strictureing disease in the duodenum and small bowel (figure 3). Patient 3 had a stenotic lesion in the terminal
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 cryptitis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation</th>
<th>Radiological abnormalities</th>
<th>Histological abnormalities</th>
<th>Other features</th>
<th>Other sites of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>M</td>
<td>Weight loss, loss of appetite, abdominal pain</td>
<td>Jejunum, ileum = nodular thickening</td>
<td>Mouth-granulomas, non-caseating</td>
<td>Has developed a protein losing enteropathy</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>Oral ulcers, abdominal pains, weight loss</td>
<td>Duodenum, jejunum, ileum = stricturing 2nd &amp; 4th parts of the duodenum &amp; mid small bowel</td>
<td>S - not done</td>
<td>Strictures disease in mid small bowel requiring resection</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>M</td>
<td>Diarrhoea, abdominal pain</td>
<td>Terminal ileum = skip lesions &amp; ulceration with stenotic lesions</td>
<td>C - not done</td>
<td>Has developed spondyloarthropathy affecting large joints</td>
<td>One episode of meningitis</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>M</td>
<td>Diarrhoea, right iliac fossa pain</td>
<td>Terminal ileum = oedematous, with rose thorn ulcerations</td>
<td>S - normal</td>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>F</td>
<td>Bloating, diarrhoea, abdominal pain</td>
<td>Terminal ileum = ulceration and stricturing disease</td>
<td>S - gastritis, no atrophy</td>
<td></td>
<td>Recurrent chest infection</td>
</tr>
</tbody>
</table>

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

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.
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. 

Microsporidia 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 stricture 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 stricture 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 Teahan and Webster. Patients 2 and 5 needed small bowel resections for stricture 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 phagocytose and in chemotaxis on ‘skin

Figure 3 Film from small bowel follow-through series (patient 2). There is mild, diffuse nodular thickening of the jejunum and proximal ileum. No stricture 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 stricture 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.

Antibody deficiency and Crohn’s disease
Brain parenchymal, subarachnoid racemose, and intraventricular cysticercosis in an Indian man

D Ghosh, T N Dubey, S Prabhakar

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 *Tena solium*. The most common manifestation of neurocysticercosis is seizure due to brain parenchymal cysts at various stages of evolution. Subarachnoid and intraventricular cysts are rarely seen in India. In Mexicans, however, they are more common (up to 10% of all cases). 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, depending 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, nonthrobbing 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 steroid therapy.

Primary antibody deficiency who also have Crohn's disease defined radiologically and histologically, and whose symptoms are controlled on steroid therapy.


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 T1- becoming hyperintense on T2- 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. 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. Subarachnoid cysticercosis can cause specific neurologic syndromes when large lesions are located in the cerebellopontine angle, sylvian fissure, or the convexity. Intraventricular cysts are frequently found in association with subarachnoid cysts. The fourth ventricle is the most common site. 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.

The racemose form of neurocysticercosis is a collection of transient membranes forming a cluster like a bunch of grapes, thought to be a forme fruste of cysticercus cellulosae. Supratentorial racemose cysts are usually found in the sulci. When vesicles break down, an intense inflammatory reaction may occur in the
ependymitis, and perivascular cuffing. As the lining is lost, with subependymal gliosis, granulomatous inflammation. The ependymal intraventricular cysts there is more intense typical budding of the vesicular wall. In inspection than by microscopy, as they show cysts are more easily diagnosed by gross 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 glial, ependymitis, and perivascular cuffing. As the cyst degenerates, granulomatous ependymitis and glialosis are the only residual histological findings.

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

**CT scan in subarachnoid cysticercosis most commonly shows hydrocephalus, which may be communicating or non-communicating.** There may be contrast enhancement of tentorium and basilar cistern secondary to arachnoiditis and fibrosis. The vessel involvement can lead to infarction. Intraventricular cisticercus 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.

**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 cysternal cysts. *T* images are better for delineating cisternal wall while *T* -weighted images are better in detecting oedema and arachnoiditis. Gadolinium-DTPA contrast in *T* images enhances leptomeninges, suggesting inflammation. Racemose cysts have a similar signal intensity to that of CSF. Intraventricular neurocysticercosis must be suspected when hydrocephalus is present. MRI is superior to CT scan in detection of intraventricular cyst. Proton density images may better delineate the cyst from the CSF around the cyst, as shown in the present case.

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

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

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**CT criteria to differentiate between cellulose and racemose cysts**

- Cellulose cysts are usually located intra-axially, i.e., 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.

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

Sandeep Gujral, Richard Bell, Julian Kabala, Rajendra Persad

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, irrigation with alum solution, and instillation of formalin, and may finally culminate in open surgical techniques ranging from simple packing of the bladder to cystectomy and urinary diversion. 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. 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...
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.

Complications arising from the procedure are uncommon and include sepsis, gluteal pain, gait disturbances and, very rarely, bladder necrosis.

This case report illustrates the value of the procedure in the acute transurethral perioperative phase, when haemostasis is proving to be difficult to achieve. Previous reports 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.

**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

Good prognosis in thyroid cancer found incidentally at surgery for thyrotoxicosis

Louiza Vini, Stephen Hyer, Brenda Pratt, Clive Harmer

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. 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. Other investigators 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 clinical 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
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 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 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. 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.

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.


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

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

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