

## Serology in patients treated with albendazole for hydatid disease

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### Introduction

There are many difficulties concerning the diagnosis, treatment and subsequent follow up of hydatid disease<sup>1</sup>. Considerable advances have been made in the field of medical treatment, where albendazole has shown good results in *in vitro*, animal and human studies<sup>2-4</sup>. Success or failure of therapy has traditionally been monitored primarily by radiological means<sup>5,6</sup>. The serology of patients after surgical excision of hydatid cysts has been described<sup>7,8</sup>. There is little information, however, on the antibody responses in patients treated by chemotherapy, particularly with albendazole<sup>9,10</sup>.

### Method

Nineteen patients, mean age 43 years (range 13-77), with hydatid disease caused by *Echinococcus granulosus* were treated with albendazole, at a dosage of 10 mg/kg/day in divided doses for one or two months. Ten of the patients had cysts involving more than one organ. Clinical, radiological and serological follow-up was carried out for a mean 31 months (range 7-72). Five patients received albendazole after surgery and a further 7 had operations after chemotherapy<sup>11</sup>. One patient received albendazole only after failing to respond to one year's treatment with mebendazole<sup>12</sup>. Patients were closely monitored for signs of marrow, liver and renal toxicity. One patient received only 3 weeks' preoperative albendazole because of reversible abnormal liver function tests, and was then given praziquantel after surgery.

Serum samples were sent to the Liverpool School of Tropical Medicine where hydatid antibodies were assessed by both complement fixation test (CFT) and IgG specific enzyme-linked immunosorbent assay (ELISA) methods<sup>13</sup>. ELISA was only carried out on samples processed after 1983. Surgical specimens were analysed for cyst viability by warm microscopy, eosin exclusion test and inoculation into gerbil peritoneum<sup>14</sup>.

### Results

Serial CFT results are shown in Table 1.

To analyse the serology data four groups of patients were identified, according to treatment by surgery and/or albendazole, and whether or not relapse occurred (Figures 1-4).

#### *Albendazole and surgery - no relapse (patients 1,5,6,7,9,11,14)*

Patients 1,5,7,14 received albendazole before surgery and all had similar patterns of CFT results (Figure 1). A 4-fold or greater rise in complement fixing antibodies (CFA) occurred during or within 3 months of the end

of chemotherapy and was followed by subsequent fall. Proof of cyst death was obtained in each case by examination of surgical specimens. Three out of these 4 patients had no rise in CFA in response to surgery. In the remaining patient (patient 14) a marked rise in CFA occurred (1/8 to 1/256) after surgery to remove hydatid cyst debris causing cholangitis. This patient had previously failed to respond to mebendazole given for one year, and the rise and subsequent fall in CFA only occurred when albendazole was given.

Of the 3 patients given albendazole after surgery, 2 had marked initial rises in CFA after treatment, and later falls (patients 9,11). In both cases chemotherapy was started within 2 months of operation. Patient 6 had no initial rise in CFA but serology was not performed during the 5-month period in between operation and chemotherapy. Albendazole was given, although the CFA level had fallen, because of a residual cyst seen on liver scan. No rise in CFA was seen at this point.

ELISA results showed no clear pattern in this group of patients.

#### *Albendazole and surgery - relapse/insufficient chemotherapy (patients 2,3,4,8)*

Two of these received albendazole prior to surgery. One was given only 3 weeks' chemotherapy as surgery was indicated for neurological effects of spinal hydatid (patient 2). Viable cysts were found at operation. No rise in CFA was seen but levels fell post-treatment, apart from a small increase which coincided with a pronounced spike in ELISA values. Recurrent hydatid was found one year later at operation.

Patient 3 also received only 3 weeks' albendazole, because of disturbances in liver function test which later reversed. Again, viable cysts were found at operation. As above, no rise in CFT titres was seen. Postoperatively, praziquantel was given for 3 weeks and both CFT and ELISA results remained unchanged. This patient did not relapse as such and probably had insufficient albendazole prior to surgery.

The other 2 patients in this group had postoperative albendazole. Serology results in both cases varied widely. Patient 4 initially had very high ELISA values but a CFT titre of < 1/2. After treatment serial values in these tests moved in opposite directions, CFA peaking before recurrence was diagnosed. Patient 8 had falling CFA and ELISA values post-treatment despite later proven recurrence (Figure 2).

*Albendazole only - no relapse (patients 10,12,13,15,16)*  
Patients 12,15,16 had an initial rise in CFA occurring within 3 months of the end of chemotherapy (2 patients >4-fold increase, one patient a 2-fold increase). Later

Table 1. Serial complement fixation test results●

Patient												
1	1	1 (x)	4 (y)	4	1							
2	32 (x,y)	16	8	1	16	8 (y,x)	4	1	4			
3	32 (x,y)	16	16	16 (y)	16 (x)							
4	1 (y)	1 (x)	32	4 (y)	1							
5	128	32 (x)	64	256	128 (y)	256	128 (y)	128	32	64	16	4
6	128 (y)	128	64 (x)	32	32	32						
7	32	64 (x)	128	256	128 (y)	128						
8	16 (y)	32 (x)	32	16	8	8	8 (x,y)	4	4			
9	2 (y,x)	512	128	8	1	4	2	2	2	8		
10	256	32 (x)	8	1								
11	8 (y,x)	256	32	2	1	1 (y,x)	2					
12	256	128	64	64	64 (x)	64	128	256	32	64	16	
13	1	64	1 (x)	32	16							
14	16 (x)	32	128	128	32	32	8 (y)	32	256	32	16	
15	128	32 (x)	32	64	32	64	8	32	8			
16	16	2	2 (x)	8	16	8	16	8	1	4	1	
17	32	32 (x)	16	8	4	32	64	64 (x)	64	32	32	
18	32	32 (x)	8	8	16 (x)	32	64	128	128	32	16	
19	64	16	8 (x)	16	64							

●: Results are expressed as reciprocals of titres  
 (x), Course of treatment with albendazole  
 (y), Surgical treatment of hydatid disease

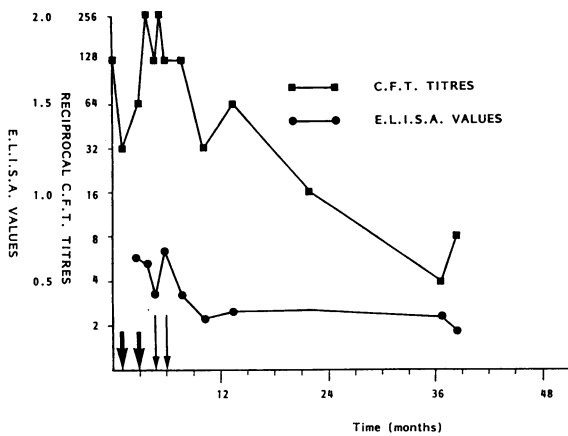


Figure 1. Albendazole given prior to surgery - no relapse

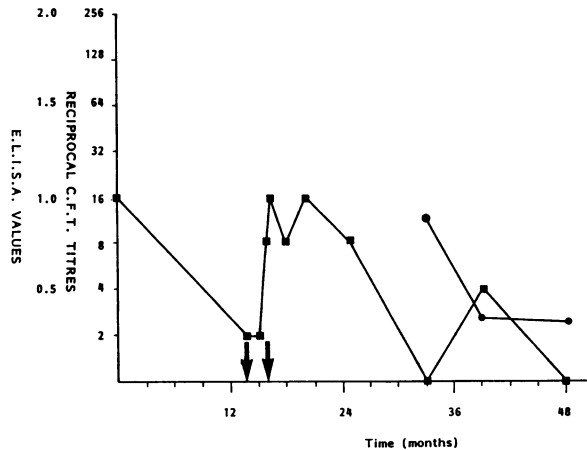


Figure 3. Albendazole only - no relapse

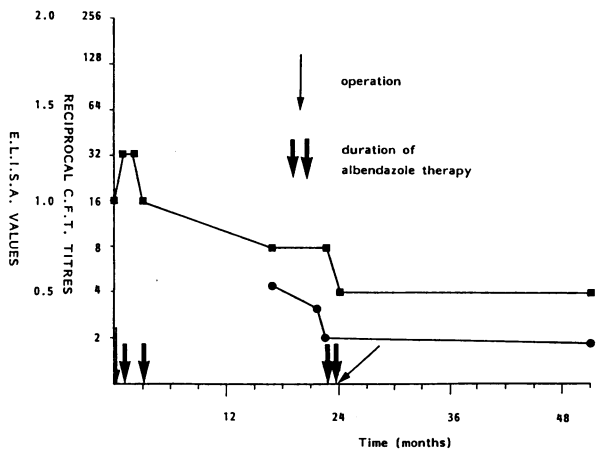


Figure 2. Albendazole given after surgery - relapse requiring further surgery and chemotherapy

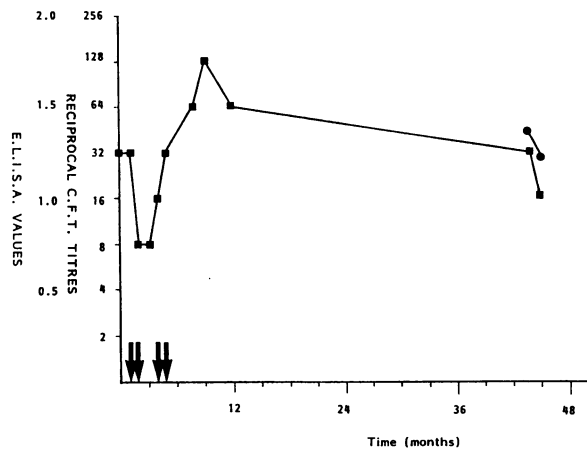


Figure 4. Albendazole only - failure of initial treatment, but success after second course of chemotherapy

falls in CFA were noted and the patients remain well (Figure 3). Patient 10 had falling CFA levels but no serology was performed in the 5-month period after albendazole therapy.

Patient 13 was incidentally found to have a calcified hydatid cyst on liver scan. CFT results varied from  $<1/2$  to  $1/64$  before any treatment was initiated. Titres continued to fluctuate after a one-month course of albendazole but the patient remains well.

#### *Albendazole only - relapse (patients 17,18,19)*

Patients 17 and 18 had initial falls in CFA when albendazole was given, and later rises to higher than previously. Patient 18 was rechallenged with albendazole soon after the first course, because of poor clinical response. On this occasion a rise in CFA occurred initially and then subsequent fall (Figure 4). The patient remains well. The other patient was given a second course of chemotherapy after 2 years because of suspected relapse. CFA levels then fell by half but no further results are presently available.

The remaining patient included in this group is mentioned here because she was thought to have had a ruptured hepatic hydatid cyst after albendazole therapy (patient 19). Unfortunately, we have no serology results to cover this event. CFA measured beforehand showed a  $>4$  fold rise with treatment.

#### **Discussion**

The increasing knowledge of the results with albendazole in the treatment of hydatid disease suggests a definite place for chemotherapy in this condition. Follow-up of patients can be both long and expensive because of the reliance on costly radiological assessment of disease state. A relatively inexpensive and simple means of monitoring hydatid disease would be valuable, particularly in poorer countries where the condition is endemic<sup>15</sup>. Unfortunately, the serology of hydatid disease is an extremely complex field and the reliability of many tests has been called into question<sup>16</sup>. Despite this, however, we are encouraged by our results showing a recurring pattern of serology in patients treated with albendazole.

Of 19 patients, 9 were given albendazole either alone or prior to surgery and have remained well since. Seven out of 9 of these had a pattern of rising CFA initially, and later falls correlating with clinical and radiological improvement (patients 1,5,7,12,14,15,16). Antibody titres increased at least 4 times in all except one (patient 15), and the rise occurred either during or within 3 months of the end of chemotherapy. One further patient had no serology performed in the period after albendazole was given and we suspect that we may have missed the initial rise in antibody levels (patient 10). The confirmation of cyst non-viability in 4 of these patients who later had surgery is encouraging.

Patients 2 and 3 were given albendazole before surgery and were later shown to have viable cysts. Both received only 3 weeks' treatment which is almost certainly too short a period to achieve cyst death<sup>11</sup>. Neither patient had the initial rise in CFA seen in successfully treated cases. Patients 17 and 18 received albendazole alone and later relapsed. Neither showed an initial antibody increase, but instead falls. One of these when rechallenged with albendazole showed a rise and then later a fall in CFA and now remains well (patient 18).

It is likely that the early rise in CFA occurring with albendazole therapy is due to cyst leakage. High levels of albendazole in cyst fluid have been demonstrated and may well cause damage to the germinal laminated membranes with consequent leaking<sup>4,17</sup>. The observation of a halo effect around the cysts on ultrasound scanning, would support this<sup>2</sup>. The one patient whose cyst ruptured after a course of albendazole showed at least an 8-fold increase in CFA before this event (patient 19). If albendazole damage to the cyst wall renders it more permeable, then the release of fluid and, therefore, antigenic material might well be expected to produce a rising antibody titre. Hence, the appearance of a rise in CFA could be a good indication that albendazole has caused damage to the cyst.

The ELISA results were disappointing considering the relative optimism with which this test has been received<sup>18</sup>. This may be because it was measuring IgG levels. Previously it has been shown that IgM levels may rise and remain elevated after surgery, so indicating possible recurrence<sup>7,8</sup>. Fissured or ruptured hepatic hydatid cysts were also shown to be associated with raised IgM as the major subclass of antibody<sup>19</sup>. Complement fixing antibodies are known to include both IgG and IgM subclasses and it might, therefore, be expected that the CFT would be more useful in this setting. It is difficult to explain why we sometimes observed a large disparity between ELISA and CFT serial values. Measurements of levels of hydatid antigen and immune complexes may be helpful here<sup>16</sup>. We have not attempted to define cut-off points at which a test result becomes positive or negative. Patients with hydatid disease may retain low levels of antibody for many years even after 'cure'. The trend of serology values may be more helpful than absolute levels.

Serology results in those patients who had operations was more varied. Interpreting antibody measurements after surgery is difficult because of the many factors involved. Patients with prolonged debility and poor nutritional status after extensive surgery might be expected to have impaired immune response (patient 4, for example). Later rises or falls in serology are probably easier to interpret<sup>7</sup>. Interestingly, however, in 4 patients treated initially with albendazole, later surgery in 3 of these was not associated with rising CFA. In each case non-viability of cysts was demonstrated (patients 1,5,7). In patient 14, however, CFA rose from  $1/8$  to  $1/256$  after operation. Large amounts of cyst debris had to be cleared in this patient, who had been having recurrent episodes of cholangitis. Spillage of cyst contents during surgery might be expected to result in raised antibody levels post-operatively. The varying results seen in our patient with a calcified hepatic hydatid cyst might be a reflection of cyst status in the absence of treatment.

In conclusion, it seems that in patients treated with albendazole for hydatid disease, an initial rise in CFA and later falling values correlate with good response. Out of 19 patients, none showed this early rise with albendazole therapy and subsequently relapsed. Conversely, an initial fall in CFA appears not to be a good sign. The potential benefits of such findings include simpler and less expensive means of follow-up of hydatid disease treatment. Serology interpretation can be difficult, however, and further elucidation of the observed changes is needed.

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