Albendazole treatment and serological follow-up in hydatid disease of bone

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Summary. *Case histories of 9 patients with hydatid disease of bone are presented. All except one had undergone previous operations and had received oral albendazole (15 mg/kg/day) in 28 day cycles (6 to 18). The efficacy of chemotherapy was assessed by serological tests for circulating antigen, immunocomplexes and specific antibodies, and by radiography and CT scans. These methods helped to evaluate treatment and showed that the long term administration of albendazole was effective.*

Résumé. *Cet article présente les cas de neuf malades atteints de maladie hydatique osseuse. A l'exception d'un malade, tous ont un antécédent chirurgical, et ont reçu un traitement par l'albendazole par voie orale à la dose de 15 mg/kg/jour, administré par cycles de 28 jours, dont la durée varie de 6 à 18 cycles selon le cas. L'efficacité de la chimiothérapie a été évaluée en utilisant d'une part, des techniques sérologiques à la recherche d'antigènes circulants, de complexes immuns et d'anticorps; et d'autre part en utilisant des moyens d'imagerie dont la radiologie et la tomographie. Il est à souligner, dans l'hydatidose osseuse, l'efficacité de la chimiothérapie à long terme par l'albendazole de même que la recherche d'antigènes circulants comme moyen indirect permettant, avec les moyens classiques d'imagerie, d'évaluer le suivi thérapeutique.*

Introduction

Hydatid disease, or human cystic echinococcosis, is caused by *Echinococcus granulosus* and is a public health problem in Uruguay [12, 15]; some reports indicate a prevalence higher than 1% in the human rural population [2, 13, 14].

Hydatid disease in bone is rare in relation to the infestation of other organs, occurring in approximately 2% [1, 11]. Radiographs usually do not show typical changes, and CT scanning may not be helpful in diagnosis. Pain and pathological fractures frequently occur in long bones, and neurological symptoms such as paraplegia may accompany vertebral lesions. Surgical treatment alone may not be successful because of the difficulty of total excision, and may increase the risk of dissemination. Recently a combination of chemotherapy with albendazole and operation has had encouraging results [20].

Evaluation of treatment in the short term is complicated, and a follow-up of more than 2 years is needed because of the sluggish growth of the metacestode.

Detection of circulating antigen (CAG) and immune complexes (CIC) has been reported and their value in the follow-up of patients with hydatid disease has been suggested [3, 5].

We present the case histories of 9 patients with cystic hydatid bone disease for whom we determined (a) the effectiveness of prolonged albendazole therapy, and (b) the benefit of CAG detection as a means of evaluating the results of treatment.

Table 1. Salient clinical features of the nine patients with hydatid bone disease

Case	Age/sex (years)	Location of the lesion	Length of the disease (years)	Previous surgery	Albendazole courses (no.)	Re-treated by chemotherapy ^a	Follow-up (months)	Outcome
1	61/F	Tibia	12	yes	7	ABZ(12)+PZQ(3) ^b	60	improvement
2	31/F	Humerus	4	yes	6	no	48	success
3	28/F	Ilium	0	no ^c	6	no	60	success
4	45/M	Tibia	4	yes	6	no	36	success
5	71/F	Femoral	2	yes	6	no	48	improvement
6	51/F	Humerus	16	yes	6	no	60	success
7	38/M	Spine	10	yes	11	ABZ(18)+PZQ(7)	68	failure
8	50/F	Spine	0	yes	10	no	36	improvement
9	50/F	Spine	0	yes	12	ABZ(4)+PZQ(5)	60	improvement

^a Albendazole (ABZ), Praziquantel (PZQ), number of courses in brackets

^b Biltricide, USA – 40 mg/k, numbers in parenthesis: months

^c One course of ABZ was given previous to surgery

Patients and methods

Nine patients with primary cystic hydatid disease of bone, confirmed by biopsy, who came from rural areas of Uruguay were treated with albendazole (SmithKline Beecham, Welwyn Garden City, England). Two were men and 7 women; their ages ranged from 28 to 71 years. Three had combined chemotherapy and operation; the other 6, who had operations from 2 to 16 years previously, were treated by albendazole alone (Table 1).

Chemotherapy

Albendazole was given at 15 mg/kg body weight daily with meals for 28 days for 6 to 18 courses (mean 11) with an interval of 14 days between them. Praziquantel was given at 40 mg/kg once a week for 3 to 7 months to the 3 patients who had a bad response to albendazole alone.

Clinical follow-up

Clinical examination and laboratory tests (SGOT, SGPT, alkaline phosphatase, blood count and urinalysis) were carried out during each course of albendazole treatment to assess possible side effects.

Radiographs were taken and CT scanning done before treatment started and during its course. Imaging criteria indicating improvement were a reduction in size of the initial lesion with bony reaction, or no enlargement of the lesion after a follow up of at least 3 years.

Serum samples were collected before and during each cycle of treatment, aliquoted and stored at –20 °C until tested. The serum concentration of albendazole sulphoxide was analysed by HPLC. The mean follow-up period was 4.4 years (range 3 to 5.8 years).

Table 2. Results of serological follow-up: before, during and after chemotherapy^a

Case	Before chemotherapy			During chemotherapy			After chemotherapy		
	CAG ^b	CIC ^c	Ab ^d	CAG	CIC	Ab	CAG	CIC	Ab
1	++++	0	+++	+/++++	0/+	+/++++	+++	++	++++
1 ^e	+++	+	++++	+/++++	0/+	+/++++	0	0	+
2	0	++++	0	0	+	+	0	0	0/+
3	++	0	++++	0	0	+/+++	0	0	0/+
4	+++	++++	++	+/++	0	+/+++	0	0	0/++
5	0	++++	+++	0	0	+/+++	0	0	+/++
6	++++	++	++	+/++	+	+/++	0	0	+
7	ND	ND	++++	+	+	+/+++	++++	++++	+/++++
7 ^f	++++	++++	+/+++	+/++++	+/++++	+/++++	0/++	0/+	+
8	++++	0	+++	0/++++	0/+	0/+++	0	0	+
9	+++	0	++++	0/+++	0	+/++++			
9 ^g	++	0	+/++++	0/++	0	+/+++	0	0	+

^a Albendazole (6 to 12 courses)

^b Circulating Antigen = CAG – Levels: ++++ = very high, +++ = high, ++ = medium, + = low, 0 = absent, ND = not done

^c Circulating Immune complexes = CIC

^d Antibodies = Ab

^e treated for second time with albendazole (12 courses) and praziquantel (3 months)

^f treated for second time with albendazole (18 courses) and praziquantel (7 months)

^g treated for second time with albendazole (4 courses) and praziquantel (5 months)

Fig. 1. Case 1. Radiographs of the left tibia. **a** before chemotherapy; **b** post 7 courses of albendazole

Immunodiagnosis

Anti-echinococcus antibodies were assayed in human sera using a peroxidase micro-ELISA (enzyme-linked immunosorbent assay) [4] and modified by us [2].

Circulating antigen (CAG) and immune complexes (CIC) were assayed in whole human sera using a capture antibody method [5]. All sera from individual patients were tested simultaneously and in duplicate. OD values were taken to calculate by linear regression the absolute concentration of the samples in each technique against the controls. The comparison of the measurement in 3 patterns was facilitated by classification into 5 levels: 1 = very high; 2 = high; 3 = medium; 4 = low, and 5 = absent.

Fig. 2. Serological follow-up of the nine patients with hydatid bone disease during and after chemotherapy. ■ = circulating antigen (CAG); □ = circulating immune complexes (CIC); ● = antibodies; ■ = albendazole; □ = albendazole (second time); ◇ = praziquantel

Results

Tolerance to albendazole was good in every patient, and there were no side effects. During chemotherapy, the clinical response, imaging techniques and serological response were monitored satisfactorily.

In case 1, the radiograph after treatment, compared with that taken before (Fig. 1a), showed bone reaction and reduction in size of the lesion (Fig. 1b). Case 9 showed a particularly good correlation between CAg levels and satisfactory treatment (Table 2, Fig. 2).

There was agreement between the results of imaging with diminution in size and healing of lesions, and decreasing levels of CAg (Figs. 2–5).

In patients 1 and 7 the levels of CAg became negative during the early courses of treatment, but increased between courses when albendazole was not given.

Discussion

Until recently the only treatment for hydatid disease of bone was by operation which was often unsatisfactory because of the difficulty of radical excision and the high rate of recurrence [17].

Since 1983, comparable data have been collected on the outcome of chemotherapy with benzimidazole carbamate (albendazole) and show encouraging results [7, 22]. Albendazole sulfoxide

Fig. 3a, b. Case 3. CT scan of pelvis. **a** showing lytic hydatid lesion of right ileum (arrow) before operation/chemotherapy. **b** 3 years later, after surgery and 6 courses of albendazole therapy

Fig. 4a, b. Case 4. Radiographs of right tibia. **a** showing pathological fracture and lytic lesions. **b** after 6 courses of albendazole therapy

Fig. 5a, b. Case 6. Radiographs of right humerus. **a** showing a large hydatid disease in the elbow. **b** an osseous reaction was observed after 6 courses of albendazole therapy

is better absorbed with higher levels of active metabolite in the cysts compared with other benzimidazoles [10]. The poorest response has, however, been in hydatid disease of bone, although Szypryt et al. have reported 5 patients treated successfully by a combination of albendazole and surgery, even though only one or two cycles of chemotherapy were given [20]. Other studies have confirmed the effect of albendazole on hydatid disease which correlated with the duration of treatment [22]. Our results have shown that 6 courses of albendazole are the minimum needed for CAg levels to become negative (cases 1, 4 and 7) which is an indicator of viability and biological activity of the parasite [5].

Our 9 cases of hydatid bone disease showed a good response to albendazole in cases 5 and 8, and cure in cases 2, 3, 4, 6, but cases 1, 7 and 9 were refractory. Cases 1 and 9 responded well when praziquantel was given at the same time. Cases 7 and 9 had extensive spinal hydatid disease which could explain the poor response to albendazole. Patients 1 and 7 showed a clear parasitostatic effect, since when albendazole was stopped the serological parameters increased. In these 2 cases, serum levels of albendazole sulphoxide were more than 100 µg/l which is the lower end of the effective concentration against *Echinococcus granulosus* in vitro and in vivo [19].

Praziquantel has not been rigorously assessed in the treatment of hydatid disease, but in experimental animals its effect is as good as that of albendazole [21]. Reports suggest that a synergistic effect may occur when albendazole and praziquantel are administered together in humans [8]. The evaluation of patients with hydatid disease who are treated with albendazole is difficult because of the long period needed to assess the outcome in this chronic disease. This is particularly so in bone disease as imaging studies needed to be carried out over a prolonged period. The results of the present study suggest that detection of circulating antigen associated with CIC formation may help to monitor the true state of the parasite, the course of the disease and the outcome.

Finally, in a long-term follow up of hydatid disease of bone, it is important to determine the real status of the cysts since recurrence is usually apparent within 2 or 3 years. Our results confirm that treatment with albendazole is effective, but one cycle should be given before operation and 6 or more courses afterwards. The combination of albendazole and praziquantel in 3 cases was more promising than albendazole alone.

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