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Case Report: Nitazoxanide for Treatment of Refractory Bony Hydatid Disease

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Abstract. Although nitazoxanide has been shown to have activity against *Echinococcus multilocularis* in animal studies and against *E. granulosus in vitro*, its use in treatment of human cystic echinococcosis has not been reported. We report a case of progressive bony hydatid disease treated with nitazoxanide that showed a clinical and radiologic response. The patient had a 40-year history of hydatid disease involving the left hip. Despite prolonged courses of albendazole and praziquantel, she had progressive disease with extensive involvement of the left hemipelvis and adjacent soft tissue cysts. She was treated with nitazoxanide, 500 mg twice a day for 3 months in combination with albendazole. The clinical response was supported by imaging showing marked improvement in the soft tissue cysts, with stable disease in the bony pelvis. Although further studies are required, this case suggests that nitazoxanide may be an effective treatment option in hydatid disease, particularly in patients with progressive disease who are receiving conventional therapy.

CASE REPORT

The patient was born in 1938 and spent her early childhood on a sheep farm in Queensland, Australia. Pain developed in her legs in the early 1960s. Cystic changes were noted on a radiograph of her left femur, and a biopsy specimen indicated hydatid disease. She underwent a femoral head excision with good results.

In 1975, she had recurrent disease; over the next 13 years she had multiple excisions and aspirations of cysts involving the left femur, pelvis, and surrounding soft tissue. She was seen by an infectious diseases physician during this time and received intermittent courses of mebendazole.

In 1988 she began treatment with long-term albendazole at a dose of 400 mg twice a day in a 4-week on 2-week off cycling regimen. Her condition appeared to stabilize for a time with lessening of pain and stable disease as determined by serial computed tomography scans.

She was referred back to the infectious diseases clinic in 2004 with increasing pain and spontaneous discharge from the left hip. Praziquantel was prescribed, to be taken at a dose of 600 mg three times a day on the first day of each albendazole cycle.

When seen again in the infectious diseases clinic in late 2006, she reported worsening hip pain. Examination showed fluctuant masses at the left hip and the right iliac fossa and a discharging sinus at the left hip. Magnetic resonance imaging scans showed new multiloculated cysts in the right rectus abdominis muscle and lateral to the left iliac wing, together with almost complete replacement of the left hemipelvis with disease (Figure 1A and B).

The left hip cyst was aspirated resulting in symptomatic relief. A secondary group G streptococcal infection developed in her chronic hip sinus and was treated with ceftriaxone, followed by long-term oral amoxillin. Treatment with nitazoxanide was begun at a dose of 500 mg twice a day in combination with albendazole, 400 mg twice a day. The nitazoxanide was continued for three months after which time she remained on albendazole alone. Treatment was well tolerated.

After the course of nitazoxanide, repeat imaging demonstrated significant regression of the soft tissue cysts in the abdominal wall and lateral to the left iliac wing, with stable bony disease (Figure 1C and D). Although the reduction in size of the cysts adjacent to the left iliac wing may have been due in part to aspiration and spontaneous drainage, the right abdominal wall cysts had not been aspirated. She was reviewed in the clinic and reported lessening of hip pain and swelling. She had a persisting sinus over the left hip but the discharge was diminished. An additional one-month course of nitazoxanide was dispensed.

Unfortunately, she was readmitted to hospital after completion of the second course of nitazoxanide with septic shock thought to be caused by a secondary bacterial infection of the hip sinus. She initially responded well to treatment, however, on day 5 of the admission she had a massive left intracerebral hemorrhage and died. Although she had no history of cerebrovascular disease, she had risk factors of hypertension and mild coagulopathy attributed to sepsis, and had received aspirin and heparin for deep venous thrombosis prophylaxis. An autopsy was not conducted.

DISCUSSION

Treatment options for cystic echinococcosis include surgical excision; puncture, aspiration, injection of protoscolicidal agent, and reaspiration (PAIR); and chemotherapy.[1,2] Radical resection with wide margins has been recommended for treatment of bony disease. Disease involving the pelvis and spine is particularly difficult to treat because complete resection is often not possible, and the outcome for such patients is often poor.[3,4] Chemotherapy may be used alone or in combination with surgery and PAIR. Albendazole, a benzimidazole, is the agent of choice. In patients with hepatic echinococcosis, albendazole therapy has been reported to cause sterilization of the cyst in up to 30% of patients, reduction in size in 30–50% and no improvement in 20–40%.[2,5] Bony disease responds less well to chemotherapy.[6] Praziquantel, an isoquinolone, has been shown to have antiprotoscolicidal activity and has been reported to improve efficacy when used in combination with albendazole, perhaps because of a pharmacokinetic interaction resulting in increased albendazole levels.[2] Although albendazole is generally well tolerated, hepatotoxicity occur in 1–5%

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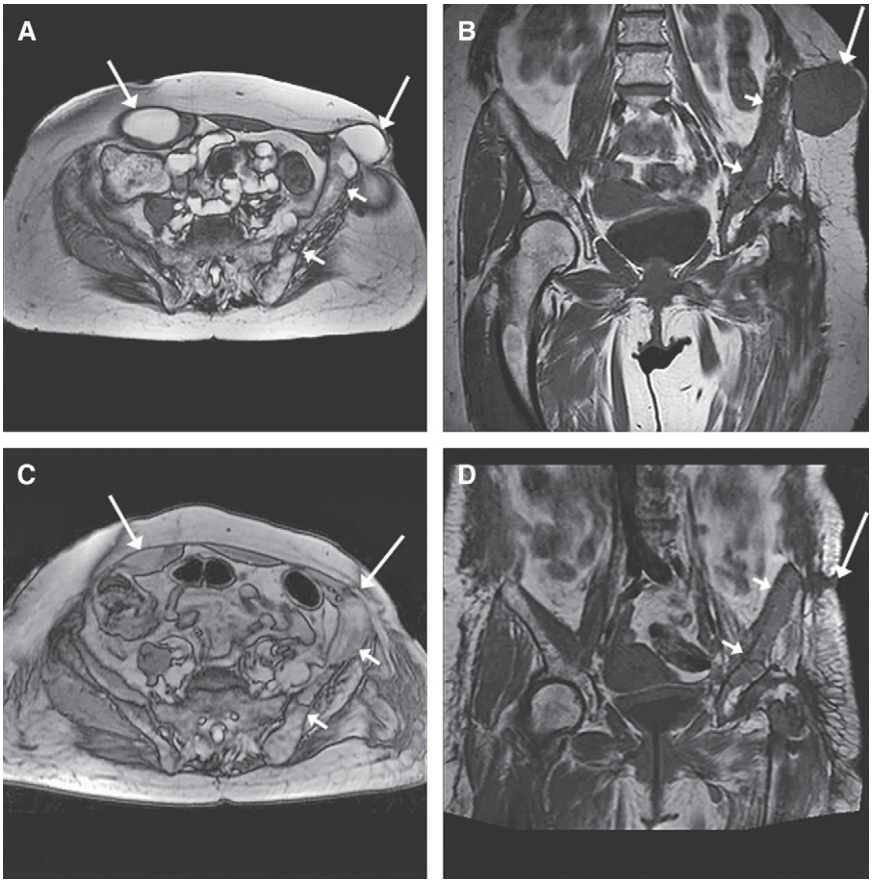

FIGURE 1. **A** and **B**, Magnetic resonance imaging (MRI) scans of the patient showing new multiloculated cysts in the right rectus abdominis muscle and lateral to the left iliac wing (large arrows), together with almost complete replacement of the left hemipelvis with disease (small arrows). **C** and **D**, MRI scans showing significant regression of soft tissue cysts in the abdominal wall and lateral to the left iliac wing (large arrows), with stable bony disease (small arrows).

of patients and reversible leukopenia and hair loss occur in less than 1%.[2,5] Alternative treatment options would be useful for patients in whom albendazole therapy is contraindicated, not tolerated, or ineffective.

Nitazoxanide, 2-acetyloxy-N-(5-nitro-2-thiazolyl) benzamide, is the prototype compound of the thiazolide class of drugs. It was initially developed as a veterinary antihelminthic agent against intestinal cestodes but has since been shown to have activity against a wide range of protozoa and helminths in humans.[7,8] It also has activity against a large number of anaerobic and microaerophilic bacteria including *Clostridium difficile* and *Helicobacter pylori*, and has recently been found to be active against hepatitis C.[7–9] In protozoa and anaerobic bacteria nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase, an enzyme involved in anaerobic energy metabolism. However, its mechanism of action against helminths is unknown. The U.S. Food and Drug Administration has approved the use of nitazoxanide for diarrhea caused by *Cryptosporidium* spp. and *Giardia* spp.[7]

Although use of nitazoxanide for treatment of echinococcosis in humans has not been reported, it has been studied *in vitro* against *E. granulosis*[5] and *E. multilocularis*,[10,11] and in a mouse model against *E. multilocularis*.[12] The *in vitro* activity of nitazoxanide against *E. granulosus* protoscoleces and metacestodes was reported by Walker et al.[5] Dose-dependent protoscolex death was seen within a few days of nitazoxanide treatment, with subsequent *in vitro* culture confirming non-viability. Progressive distortion of nitazoxanide treated metacestodes was seen by electron microscopy, with complete destruction of all parasitic tissue by day 7 of treatment. Metacestodes treated with albendazole showed similar morphologic changes to those treated with nitazoxanide.[5] Nitazoxanide therapy against *E. multilocularis* was studied in an experimental mouse model by Stettler et al.[12] Mice were infected by intraperitoneal injection of metacestodes and treated with nitazoxanide, albendazole, or combined therapy. Combination treatment was the most effective, resulting in the greatest reduction in parasite weight and the most severe ultrastructural changes when viewed by transmission electron microscopy. Nitazoxanide and albendazole alone induced inconsistent ultrastructural changes, with some metacestodes remaining intact and others showing severe destruction. Combination therapy resulted in a 2–4-fold increase in levels of albendazole-sulfoxide, an observation that may have contributed to the improved efficacy of the combined treatment.[12]

Nitazoxanide is generally well tolerated and no significant adverse events have been noted in more than 2,000 patients in clinical trials.[7,8] There have been no reports of an increased risk of bleeding with nitazoxanide therapy.

Our patient had a long history of extensive bony and soft tissue pelvic hydatid disease that was progressing while she was taking albendazole and praziquantel. The addition of

nitazoxanide in combination with albendazole resulted in a significant improvement in the soft tissue cystic disease, with stable disease in the bony pelvis. Radiologic evidence of response after successful therapy of pyogenic osteomyelitis can be delayed. It is possible that a pharmacokinetic interaction resulting in higher levels of albendazole, as noted in the mouse model,[12] contributed to the response seen in our patient.

Use of nitazoxanide for treatment of cystic echinococcosis has not been previously reported in humans or in animal studies. This case suggests it may represent a treatment option in patients with progressive disease who are receiving conventional therapy.

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