

THE IMPORTANCE OF DRUG THERAPY IN LUNG MULTIFOCAL HYDATIDOSIS

CLAUDIU NISTOR^{1*}, ADRIAN CIUCHE¹, DANIEL PANTILE¹,
MIHNEA DAVIDESCU², AURELIAN-EMIL RANETTI³

¹*Department of Thoracic Surgery, "Dr. Carol Davila" Emergency University Military Central Hospital, Bucharest, Romania*

²*Clinic of Thoracic Surgery, "Alexandru Trestioreanu" Bucharest Oncologic Institute*

³*Department of Endocrinology, "Dr. Carol Davila" Emergency University Military Central Hospital, Bucharest, Romania*

*corresponding author: ncd58@yahoo.com

Abstract

Echinococcosis is a parasitic zoonosis caused in humans by the larval stage of the *Echinococcus granulosus*.

This zoonosis was first reported in ancient times (Hippocrates, fourth century BC); Rudolphi (1808) first used the term hydatid cyst to describe echinococcosis in humans.

Currently, it is considered one of the main parasitoses affecting animals bred for income and one of the most important parasitic zoonoses.

It has a wide geographic distribution and human might be infected incidentally as intermediate hosts in the parasite's life cycle.

We present the case of a 25 year-old girl referred to our unit with non-productive cough, dull chest pain and fever for the past few weeks. Examination revealed a patient with tachypnea and fever. After several investigations, multiple hydatidosis was identified and the proposed course of treatment was first surgery, followed by medical treatment. The surgical intervention was performed through a left axillary thoracotomy.

Cystic hydatid disease, caused by *Echinococcus granulosus*, is still an important public health problem in many parts of the world, including our country. Hydatid cysts can be managed either by operative or non-operative methods.

We consider that hydatid cysts with dimensions over 2 cm have to be surgically approached because we noticed the preoperative treatment with albendazole might produce, along with parasite's death, local infection with possible evolution to pulmonary abscess.

In conclusion, our experience suggests that the most effective therapy in treating cystic hydatidosis is the combination of surgery with chemotherapy. Albendazole given as described together with surgery is considered to have the highest success rate in treating cystic hydatidosis.

Rezumat

Echinococoza reprezintă o zoonoză a cărei cauză este stadiul larvar al parazitului *Echinococcus granulosus*.

Această zoonoză a fost raportată pentru prima dată în Grecia antică de Hipocrate (secolul IV înainte de Christos); Rudolphi în 1808 a utilizat pentru prima dată termenul de chist hidatic în descrierea echinococozei la om.

Acum este considerată una dintre cele mai importante parazitoze ce afectează animalele crescute în ferme, precum și una dintre cele mai importante zoonoze. Are o distribuție globală, iar omul este infectat accidental, ca și gazdă intermediară în ciclul de viață al parazitului.

Se prezintă cazul unei paciente de 25 de ani, ce s-a prezentat în serviciul nostru acuzând tuse seacă, dureri în piept și febră cu debut în urmă cu câteva săptămâni. Examenul clinic a prezentat o pacientă cu febră și tahipnee. În urma investigațiilor efectuate s-a stabilit diagnosticul hidatidoză multiplă, iar tratamentul propus a fost intervenția chirurgicală, urmată de tratament medicamentos. Intervenția chirurgicală pulmonară a fost efectuată prin toracotomie axilară stângă.

Boala hidatică, a cărei cauză este reprezentată de parazitul *Echinococcus granulosus*, reprezintă o problemă importantă de sănătate publică în multe zone ale lumii, inclusiv țara noastră. Chisturile hidatice pot fi abordate atât printr-o metodă mai conservatoare, medicamentoasă, cât și printr-o metodă mai agresivă, chirurgicală.

Noi considerăm chisturile hidatice cu dimensiuni peste 2 cm abordabile obligatoriu chirurgical deoarece am observat că tratamentul preoperator cu albendazol poate produce, pe lângă moartea parazitului, o serie de complicații importante, printre care și infecția locală cu evoluție posibilă spre abces pulmonar.

În concluzie, experiența noastră demonstrează că cel mai bun tratament al hidatidozei multiple îl reprezintă combinația chirurgiei cu tratamentul medicamentos. Albendazolul, prescris așa cum menționăm în text, împreună cu intervenția chirurgicală, are cea mai mare rată de succes în tratamentul bolii hidatice.

Keywords: hydatid cyst, multiple hydatidosis, *Echinococcus granulosus*, albendazole.

Introduction

Echinococcosis is a disease recognized by humans for centuries. Its first mention is in the Talmud; later ancient scholars such as Hippocrates, Aretaeus, Galen and Rhazes also recognized it. Although echinococcosis has been well known for the past two millennia, it was not until the past couple of hundred years that real progress was made in determining and describing its parasitic origin. In the 17th century, Francesco Redi stated that the hydatid cysts of echinococcosis were of "animal" origin. Almost one hundred years later, in 1766, Pierre Simon Pallas predicted that these hydatid cysts, found in infected humans, were actually larval stages of tapeworms. A few decades afterwards, in 1782, Goeze accurately described the cysts and the tapeworm heads, while in 1786 *E. granulosus* was accurately described by Batsch. Half a century later, during the 1850s, Karl von Siebold showed through a series of experiments that *Echinococcus* cysts did cause adult tapeworms in dogs. Shortly after this, in 1863, Rudolf Leuckart identified *E. multilocularis*. Then, during the early to mid-1900s, the more distinct features of *E. granulosus* and *E. multilocularis*, their life cycles and how they cause disease were almost fully described as more and

more people began researching and performing experiments and studies [1,2,3].

We report a case of multifocal lung hydatidosis with excellent response to the combination of operative and non-operative treatment.

Materials and Methods

A 25 year-old girl was referred to our unit with non-productive cough, dull chest pain and fever for the past few weeks. Examination revealed a patient with tachypnea and fever. On chest examination, the left side moved less with impaired percussion note and diminished air entry. There were coarse crackles all over the chest. The liver was not palpable and other systems were normal. Her chest X-ray showed multiple opacities, especially in the left lung (figures 1 and 2), with an irregular air/fluid level in the left lung (the “water-lily” sign).

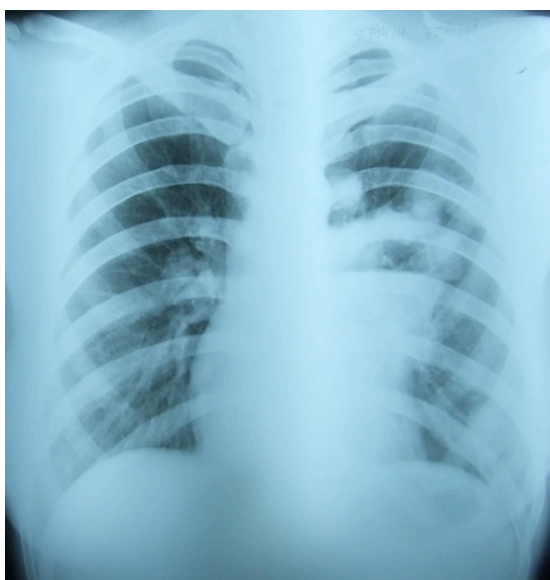


Figure 1

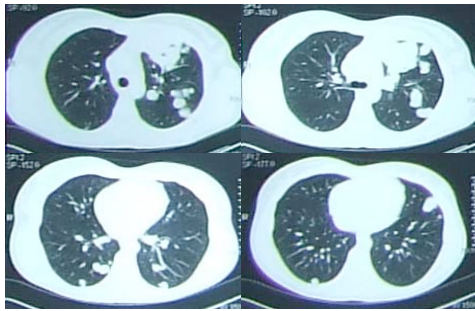
Chest X-ray showing multiple opacities, especially in the left lung, anterior view



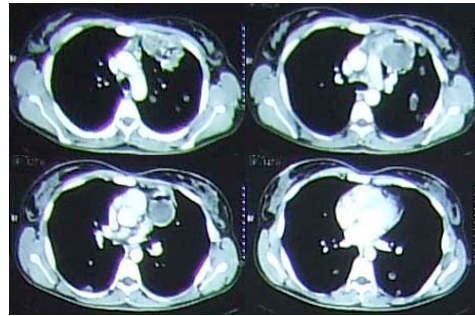
Figure 2

Chest X-ray showing multiple opacities, especially in the left lung, lateral view.

Computed tomography (CT) of the chest reported a cystic lesion of 5.5 cm with a hydro-aeric level in the anterior segment of the left upper lobe, surrounded by several small cysts, along with multiple other cysts with sizes between 1 and 2 cm in both lungs (figures 3 and 4).

**Figure 3**

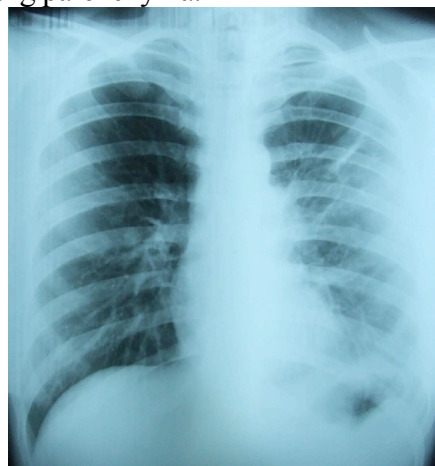
Chest CT showing multiple lesions, especially in the left lung, lung window

**Figure 4**

Chest CT showing multiple lesions, especially in the left lung, chest window

Fiberbronchoscopy was also performed and it revealed normal endobronchial aspects. Abdominal ultrasound was within normal limits.

The proposed course of treatment was first surgery, followed by medical treatment. The surgical intervention was performed through a left axillary thoracotomy. After opening the patient, we observed a 6/5 cm, partially evacuated, suppurated cystic mass placed in the anterior segment of the left upper lobe, surrounded by multiple smaller cysts; approximately 40 cysts were found in the parenchyma of the left lung with sizes between 0.5 cm and 3 cm. The surgical treatment applied for the large, complicated hydatid cyst found in the left upper lobe was the enucleation of the cyst, closing the bronchial leakage and padding the pericystic area. The other cysts were treated, according to their location and size by enucleation, pericystectomy or lung wedge resections, with maximal sparing of lung parenchyma.

**Figure 5**

X-ray showing complete resolution of the hydatid cysts.

After surgery, the patient had an uneventful recovery. Chemotherapy with albendazole started after surgery in the Department of Parasitology, considering the remaining cysts inside the right lung. Three 28-day cycles of therapy with 10 mg/kg b.w./day of albendazole, in divided doses separated by 2-week intervals were given to the patient. The X-ray after the albendazole therapy finalized revealed a complete resolution of the hydatid cysts in both lungs (Figure 5).

Results and Discussion

Cystic hydatid disease, caused by *Echinococcus granulosus*, is still an important public health problem in many parts of the world, including our country. Hydatid cysts can be managed either by operative or non-operative methods.

Until 1970s, the accepted treatment of hydatid disease was some form of surgical drainage and removal of the cyst. Surgery was not always possible, for example when the cysts are multiple or inaccessible. Furthermore, surgical intervention in malignant hydatid disease (caused by *Echinococcus multilocularis*), in which small cysts were disseminated, was rarely possible and had a high death rate [4].

The discovery of an effective medication, able to destroy the parasite and sterilize the cyst, for use either alone or in conjunction with surgery, has long been a cherished hope, and the introduction of mebendazole in the late 1970s was a huge step towards this. This synthetic benzimidazole derivative, related to the veterinary anthelmintic thiabendazole and cambendazole, is effective against several intestinal nematodes and cestodes. Nowadays non-operative methods include chemotherapy and percutaneous treatment. Benzimidazole carbamates (mebendazole and albendazole) are anthelmintic drugs that inhibit the assembly of tubulin into microtubules, thus impairing uptake of glucose and interfering with the homeostasis of the parasite.

Surgery is considered the standard treatment for cystic echinococcosis. However, surgery is not without risks and there is a high incidence of dissemination, infection and recurrence of 2% to 25%, with morbidity of 0.5% to 4% [5 - 10].

Hydatid cyst of the thoracic cavity often remains asymptomatic for many years [11]. Symptoms arise due to pressure effects on adjacent structures (lung parenchyma, heart, thoracic blood vessels), or when a complication occurs (spontaneous bronchial drainage of the hydatid cyst, infection, anaphylactic shock, allergy). Commonly, the patient presents with cough, dyspnea and fever, as it happened in our case study.

We decided to perform left thoracotomy because on this side, apart from multiple cysts with dimensions between 0.5 – 3 cm was also a cystic lesion with clinical and radiological characteristics of complicated, suppurated hydatid cyst with indication of surgical approach.

We consider that hydatid cysts with dimensions over 2 cm have to be surgically removed because we noticed the preoperative treatment with albendazole might produce, along with parasite's death, local infections with possible evolution to pulmonary abscess. Unlike liver hydatidosis, in lungs the risk of infection is greater because of micro fistulae at the level of the pericystic cavity.

Mebendazole, a benzimidazole, was the first compound assessed in the treatment of human hydatid disease [12]. It was found to interfere with the mechanisms of glucose absorption that takes place in the wall of the hydatid parasite, subsequently causing cell autolysis [13]. Mebendazole, however, has a very poor absorption rate and does not reach high concentration levels in the cyst wall [14]. Advances in drug therapy were influenced by the introduction of albendazole, another benzimidazole, that was found to have much better absorption achieving higher blood, cyst wall and cyst fluid concentrations [15]. Although albendazole sulphoxide, the active metabolite reaches predictable levels in the serum after a single oral dose, cyst fluid levels are slow to reach therapeutic levels and are less predictable [16], thus requiring prolonged periods of treatment. The drug treatment protocol we used was based on previous studies [17].

Praziquantel is another agent used in the treatment of hydatid disease. However, some researchers think that at doses that can be used in humans it does not produce adequate serum levels to kill the germinal membrane and also does not enhance the effect of albendazole on the germinal membrane [18]. For these reasons, the use of praziquantel has been limited to patients who developed severe adverse reactions to albendazole [19]. Others say that 40-60 mg/kg b.w./day of praziquantel in divided doses is the most active and rapid scolicalidal agent [20]. Praziquantel is probably an ideal agent for prophylaxis in the preoperative and postoperative settings to prevent implantation of protoscolecs and subsequent recurrence [17, 21].

Albendazole given postoperative in a dose of 10 mg/kg b.w./day for one month kills most of the protoscoleces within the hydatid cyst [22]. Other authors say that better results have been reported after three months of uninterrupted therapy with albendazole [20].

Other drugs active against *Echinococcus granulosus* include oxfendazole and fenbendazole. Both of them are still being studied, none of them has been used in humans. However, the preliminary trials of

oxfendazole given to goats, twice weekly show similar results with the administration of a single daily dose of albendazole. Oxfendazole given with a lower frequency than albendazole, virtually, eliminated all protoscolices in both lung and liver cysts [23].

Fenbendazole is a broad spectrum benzimidazole anthelmintic used against gastrointestinal parasites (roundworms, hookworms, whipworms, the taenia species of tapeworms, pinworms, aelurostrongylus, paragonimiasis, strongyles and strongyloides) and can be administered to sheep, cattle, horses, fish, dogs, cats, rabbits and seals [24]. No experience is noted for fenbendazole on humans.

The most frequent side effects of albendazole and other anthelmintic benzimidazole drugs include nausea, vomiting, abdominal pain, headache, or temporary hair loss. Many people using this medication do not have serious side effects. Unlikely but serious side effects that may occur are vision disorders, jaundice, severe stomach/abdominal pain, dark urine. Very rare but very serious side effects that may occur: unusual tiredness, easy bruising/bleeding, signs of infection (e.g., fever, persistent sore throat), severe/persistent headache, seizures, confusion, very stiff neck. A very serious allergic reaction to this drug is rare.

Precautions before starting anthelmintic treatment include known allergies to benzimidazole anthelmintic drugs, liver disease, biliary tract problems or blood/bone marrow disorders.

Conclusions

In our department of thoracic surgery, we have approached multiple cases of hydatid cysts, Romania being considered one of the endemic areas for this condition. We have surgically approached single organ hydatid cysts (lung, pleura, liver), as well as multivisceral hydatidosis (lung and liver hydatidosis). Some of these hydatid cysts were uncomplicated, other presented complications as pulmonary abscess, liver abscess, bilio-bronchial fistula, etc.

In conclusion, our experience suggests that the most effective therapy in treating cystic hydatidosis is the combination of surgery with chemotherapy. Albendazole given as described together with surgery is considered to have the highest success rate in treating cystic hydatidosis.

References

1. Tappe, Dennis, August Stich, and Matthias Frosch. "Emergence of Polycystic Neotropical Echinococcosis." *Emerging Infectious Disease* 14.2 (2008): 292-97. Web. 21 February 2010.
2. Howorth, MB. "Echinococcosis Of Bone." *Journal of Bone and Joint Surgery* 27. (1945): 401-11. Web. 21 February 2010.

3. Vifor Berteșteanu ȘG, Popescu CR, Popescu B, Popa F, Purcarea VL, The role of topic corticoids in rhinosinusal pathology management, *Farmacia*, 2011, 59(5), 729-736
4. Safta AN, Constantin VD, Socea LI, Socea B, The efficiency of low molecular wight heparins in the prophylaxis of venous thromboembolic complications in general surgery, *Farmacia*, 2012, 60(1), 127-137
5. Balasegaram M, Kong LF. Surgical treatment of hydatid disease of the liver. *Trop Gastroenterol* 1982; 3: 194-200
6. Karavias DD, Vagianos CE, Bouboulis N, Rathosis S, Androulakis J. Improved techniques in the surgical treatment of hepatic hydatidosis. *Surg Gynecol Obstet* 1992; 174: 176-180
7. Sayek I, Yalin R, Sanaç Y. Surgical treatment of hydatid disease of the liver. *Arch Surg* 1980; 115: 847-850
8. Ekrami Y. Surgical treatment of hydatid disease of the liver. *Arch Surg* 1976; 111: 1350-1352
9. Ammori BJ, Jenkins BL, Lim PC, Prasad KR, Pollard SG, Lodge JP. Surgical strategy for cystic diseases of the liver in a western hepatobiliary center. *World J Surg* 2002; 26: 462-469
10. Langer JC, Rose DB, Keystone JS, Taylor BR, Langer B. Diagnosis and management of hydatid disease of the liver. A 15-year North American experience. *Ann Surg* 1984; 199: 412-417
11. P Aggarwal, J P Wali. Albendazole in the treatment of pulmonary echinococcosis. *Thorax* 1991;46:599-600
12. Gil-Grande LA, Boixeda D, Gracia-Hoz, *et al.*, Treatment of liver hydatid disease with mebendazole: A prospective study of 13 cases. *Am J Gastroenterol* 1983;78:584-588.
13. Khuroo MS, Dar MY, Yattoo GN, *et al*: Percutaneous drainage versus albendazole therapy in hepatic hydatidosis: A prospective, randomized study. *Gastroenterology* 1993;104:1452-1459.
14. Morris DL, Gould S: Serum and cyst concentrations of mebendazole and flubendazole in hydatid disease. *Br Med J* 1982; 285:175-177.
15. Saimot AG, Meulemans A, Cremieux AC, *et al.*, Albendazole as a potential treatment for human hydatodoses. *Lancet* 1983;ii:652-656.
16. Morris DL, Chinnery JB, Georgiou G, *et al.*, Penetration of albendazole sulphoxide into hydatid cysts. *Gut* 1987;28:75-80.
17. Horton RJ: Chemotherapy of Echinococcus infection in man with albendazole. *Trans R Soc Trop Med Hyg* 1989;83:97-102.
18. Taylor DH, Morris DL, Richards KS: Echinococcus granulosus: *In vitro* maintenance of whole cysts and assessment of the effects of albendazole sulphoxide and praziquantel on the germinal layer. *Trans R Soc Trop Med Hyg* 1989;88:535-538.
19. M.A. Silva D.F. Mirza S.R. Bramhall A.D. Mayer P. McMaster J.A.C. Buckels: Treatment of Hydatid Disease of the Liver. *Dig Surg* 2004;21:227-234
20. Shams-Ul-Bari, Sajad Hussain Arif, Ajaz A. Malik, Abdul Rouf Khaja, Tufale A. Dass, and Zahoor A. Naikoo: Role of Albendazole in the Management of Hydatid Cyst Liver. *Saudi J Gastroenterol*. 2011 Sep-Oct; 17(5): 343-347.
21. Arif SH, Shams-Ul-Bari, Wani NA, Zargar SA, Wani MA, Tabassum R, *et al.*, Albendazole as an adjuvant to the standard surgical management of hydatid cyst liver. *Int J surg*. 2008;6:448-51.
22. Chinnery J JB, Morris DL. Effect of albendazole on viability of hydatid protoscolesces. *Trans R Soc Trop Med Hyg*. 1986;80:815-17.
23. Ronald E. Blanton, Timothy M. Wachira, Eberhard E. Zeyhle, Ernest M. Njoroge, Japheth K. Magambo, Peter M. Schantz: Oxfendazole Treatment for Cystic Hydatid Disease in Naturally Infected Animals. *Antimicrob Agents Chemother*. 1998; 42(3): 601-605
24. Plumb's Veterinary Drug Handbook, Fifth Edition, 2005.