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Alveolar Hydatid Disease

Review of the Surgical Experience in 42 Cases of Active Disease Among Alaskan Eskimos

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Objective
The authors reviewed the pathophysiology and clinical management of endemic alveolar hydatid disease in Alaskan Eskimos, incorporating recent developments in diagnosis and treatment.

Summary Background Data
Alveolar hydatid disease is a highly lethal zoonotic infection caused by the larval stage of *Echinococcus multilocularis*. This cestode is restricted geographically to northern climates, where foxes and small rodents represent the natural hosts. Domestic dogs also may serve as definitive hosts, and thus, transmit the parasite to humans. Human infection is characterized by the development of a cancer-like hepatic mass, which may extend to adjacent structures or metastasize to distant sites. If the infection goes untreated, mortality reaches 80%.

Methods
The medical records of all patients with alveolar hydatid disease diagnosed or treated at the Alaska Native Medical Center between 1951 and 1993 were reviewed. Forty-two cases of active disease are presented.

Results
Nine patients underwent resection of hepatic lesions with intent to cure, and each had a favorable result. Average post-diagnosis survival of those patients was 22 years; six still are living and free of disease. Partial resections or drainage procedures were performed in ten patients. Chemotherapy was used to augment the surgical treatment of eight patients, and four received chemotherapy alone, resulting in improved outcomes compared with historic controls. Late complications included hepatic abscess, biliary obstruction, and portal venous hypertension.

Conclusions
Whereas alveolar hydatid disease rarely is encountered in other areas of North America, the biologic potential for spread of the disease may be increasing because of illegal importation of infected foxes to the Eastern seaboard. Therefore, the surgical community should maintain an awareness of the diagnosis and management of this potentially devastating parasitic infection.

Of the four species of tapeworms of the genus *Echinococcus* which are pathogenic to man—*E. granulosus, E. oligarthrus, E. multilocularis,* and *E. vogeli*—two are of surgical importance in North America. Alveolar hydatid disease (AHD) is a zoonosis caused by infection with the larval stage of the cestode *E. multilocularis,* a small tapeworm of canine animals. The cestode has an extensive geographic range in the Northern Hemisphere, where it is perpetuated in nature by a cycle involving foxes and small rodents. Dogs (rarely cats) may replace foxes as the final host, and they evidently are the most important source of transmission to man. In Eurasia, it occurs from central Europe eastward to the Bering Strait and northern Japan, and southward to northern and northwestern China and northern India. Cystic echinococcosis, caused by infection by *E. granulosus,* has a worldwide distribution and is carried by canine primary hosts (dogs and wolves) and herbivore intermediate hosts, usually sheep, cattle, moose, and caribou.

In the Western Hemisphere, *E. multilocularis* was first identified on St. Lawrence Island, in the Bering Sea,[2] and subsequently was determined to occur in the zone of tundra as far as the western shores of Hudson Bay and some islands off the Canadian Arctic Archipelago.[3] Spread in natural hosts has resulted in its occurrence in 11 contiguous states in the United States, and in three adjacent provinces of Canada[4] (Fig. 1). Strong indications exist that it might have become established in the southeastern coastal states as a result of introductions of red foxes from the endemic region of the Northwest. From a sample of 44 red foxes illegally imported into South Carolina, 3 (7%) harbored *E. multilocularis.*[1] Because thousands of such imported foxes have been released into hunting enclosures in the southeastern United States during the past 20 years, there is concern that the parasite may have become established in indigenous mammals, although thus far, it has not been identified in local rodents that could serve as intermediate host.[5]

Since the mid 1940s, 44 cases of active, locally acquired AHD have been diagnosed in North America. James et al. reported a fatal case in a resident of Winnipeg, Manitoba,[6] and the first autochthonous case in the contiguous United States involved a woman residing in a rural area of Minnesota.[7] With the exception of these two patients, all locally acquired cases of AHD in North America have occurred in Eskimos from a small hyperendemic area in western Alaska. The incidence of AHD is much higher in Eurasia and is a cause of significant morbidity and mortality in extensive regions of central Europe, much of Russia, northern Japan (Hokkaido), and northern and western China.

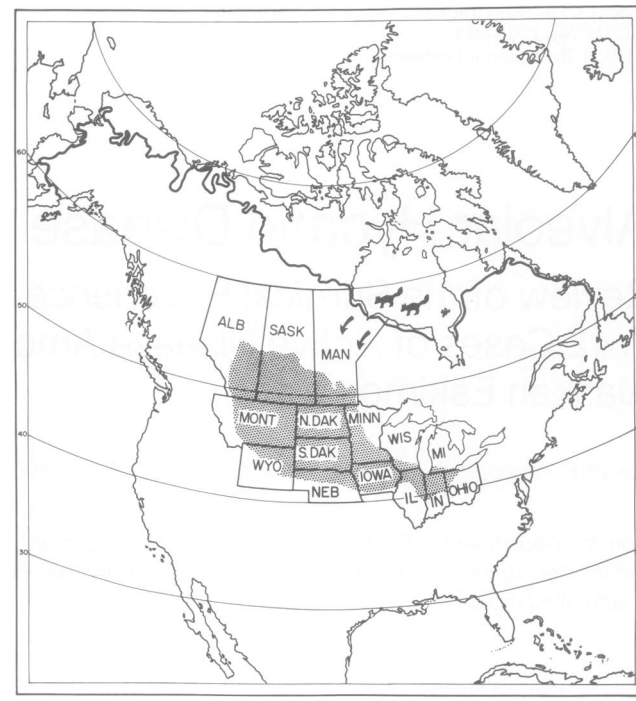

Figure 1. The approximate distribution of *Echinococcus multilocularis* in central North America. The geographic range of the cestode, in addition to three provinces of Canada, currently encompasses at least 11 contiguous states as a result of dispersal in natural hosts since it was first recorded in North Dakota in 1964. In additon, extensive introductions and possible establishment of the cestode in indigenous mammals along the Eastern seaboard has occurred through importation of foxes from endemic areas to Eastern states.

PATHOPHYSIOLOGY

Alveolar hydatid disease is a devastating disease that takes a malignant clinical course characterized by an indolent morbidity and a high mortality. When accidentally ingested, the egg of *E. multilocularis* releases the embryo (oncosphere) in the small intestine; the embryo then enters a capillary and is carried to the liver, where it localizes, and development of the larval stage begins. In humans, this lesion does not appear as a cyst, but as a firm, white-to-yellowish, solid, cancer-like mass that always is primary in the liver (Fig. 2). Single or multiple foci may be present. Typically, numerous microcysts, 1 to 3 mm in diameter, are observed scattered in a dense stroma of fibrous tissue (Fig. 3). In the natural hosts (voles or lemmings), such cysts are uniform in size and are filled with protoscolices, but in humans, biologically poor hosts, the microcysts are irregular, vary greatly in size, and only rarely contain protoscolices. The term "alveolar" hydatid disease stems from this alveolar pattern

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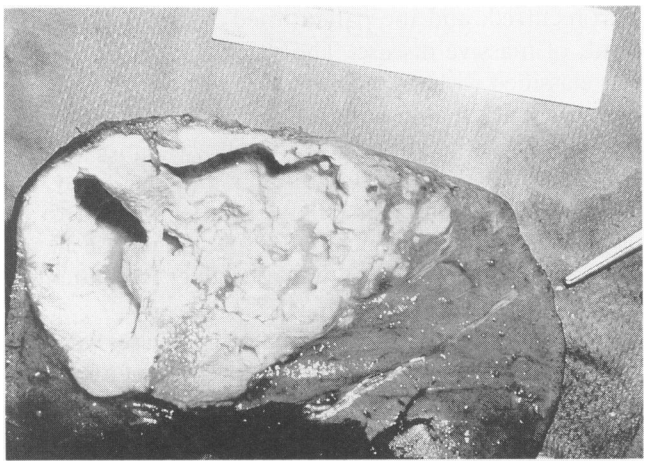

Figure 2. Surgical specimen of a 10 × 16-cm lesion, case 27, resected by radical right lobectomy, 1960. A 2 × 4-cm local recurrence was resected in 1979, which retrospectively, is believed to have died spontaneously without benefit of chemotherapy. Patient is living and well 33 years after resection and has been consistantly seronegative since 1979.

seen in the natural host and in some human specimens. The lesion enlarges progressively, with extension into vital structures, and often with distant metastases. A fatal outcome results in approximately 80% of untreated cases. As the mass enlarges, dense scar tissue causes central, avascular necrosis, and a sterile abscess often develops within the lesion. Such an abscess may become very large, 7 to 8 liters of semifluid content having been present in one Alaska case.[8]

In contrast to AHD, cystic echinoccosis is characterized by the development of a fluid-filled cyst that develops after implantation of larvae carried in the blood stream. Although the liver and lungs are the most common sites for these cysts, almost any tissue or organ may be involved. The cysts are lined by germinal epithelium and contain numerous protoscolices, elements that often develop into new cysts if disseminated by accidental spillage, but they do not metastasize. Alveolar hydatid disease, on the other hand, always is primary in the liver, then spreads by direct extension, lymphatic or hematologic metastasis, or by peritoneal seeding.

Clinical Management

Until recently, the only useful treatment for echinococcosis was surgical resection. Since the report of Heath and Chevis,[9] there has been worldwide interest in the benzimidazole compounds for treatment of hydatid disease. Many clinical trials have been reported on the use of both mebendazole (MBZ) and albendazole (ALBZ). Although early findings were controversial, the majority of recent reports have presented good therapeutic results.[8,10–34] Most investigators have concluded that these drugs primarily offer palliation and should be considered to be only parasitostatic.[13,19,23] However, our experience in Alaska has been more favorable,[33] indicating that chemotherapy has been successful in killing *E. multilocularis*. This report summarizes the surgical experience with this disease in Alaska and outlines some recent developments in its diagnosis and management.

METHODS

The medical records of all patients with AHD diagnosed or treated at the Alaska Native Medical Center were reviewed. Initially, patients were evaluated by physical examination, serological data, and chest and abdominal x-rays. Later, computed tomography (CT) and ultrasound became available and have become the primary means of assessing and monitoring the disease. Serologic surveys, using the indirect hemagglutination method, were employed early in this experience. An improved serologic technique using a specific *E. multilocularis* antigen (Em2 ELISA) was introduced in 1985[35]; in 1989, annual screening surveys using a portable ultrasound unit were begun in four villages.

Clinical chemotherapy trials were initiated in 1975 using MBZ, 40 mg/kg/day.[8,10,11,16,33] In 1985, trials with ALBZ were started with a dose of 400 mg orally twice daily with meals, following a protocol involving 28 days of therapy alternating with 14-day drug-free intervals.[17,33] That period of 42 days is considered one cycle of therapy (sometimes referred to as 1 month of therapy). The efficacy of therapy was assessed by an *in vivo* viability assay based on the intraperitoneal inoculation of red-backed voles with larval membranes from lesions. The technique used, the importance of obtaining *in vivo*

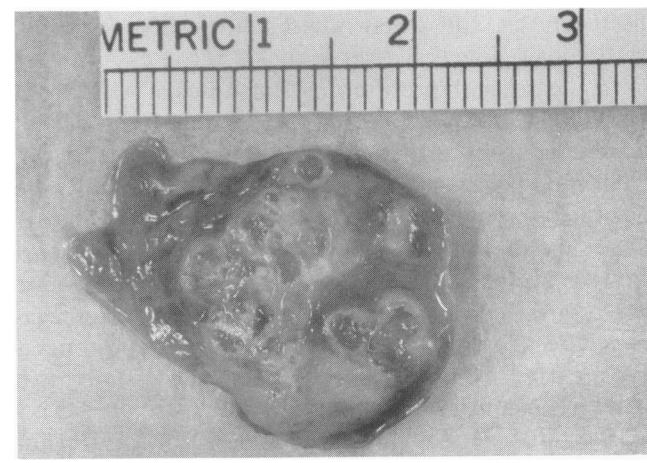

Figure 3. A surgical biopsy specimen, showing appropriate size and an adequate number of microcysts in the specimen for vole-injection viability assay.

viability assays, and other means of assessing the efficacy of chemotherapy have been summarized elsewhere.[36,33]

RESULTS

Forty-two cases of active AHD were diagnosed in Alaska between 1951 and 1993. The male:female ratio was 57%:43%, and the ages at the time of diagnosis ranged from 12 to 82 years, with a median of 53 years. Alveolar hydatid disease may reach an advanced stage before signs or symptoms are produced. Among 41 cases with sufficient clinical history for evaluation, 16 (39%) were asymptomatic at the time of diagnosis. Right upper quadrant pain (29%), palpable mass (27%), and an enlarged liver (24%) were the most common findings or complaints at diagnosis. Jaundice (12%) and central nervous system symptoms (7%) were less common features reported. The diagnosis initially was suspected as the result of a positive serology in nine cases (22%), and in an equal number of cases, a positive serology provided collaborative evidence for diagnosis (44%).

As a result of the improved diagnostic and screening methods introduced in 1989 and 1990, we began to identify small, calcified hepatic lesions which, on further study, proved to be inactive, burned-out larval *E. multilocularis* infections. In five of the early cases, the lesions were resected for diagnosis and viability studies.[33,37] Each case returned a negative vole viability assay. We have adopted the principle that small (usually less than 2 cm in diameter), totally calcified lesions in patients residing in the hyperendemic region of *E. multilocularis* can safely be considered to be nonviable. On the other hand, we believe that any lesion with definite mixed-density pattern on CT scan must be considered active. Thus far, 29 such inactive cases have been identified, diagnosed primarily by means of serologic and ultrasound surveys in the field.[37] Six had histologic confirmation of the diagnosis, and seven others had positive serology. Adding these inactive cases to the 42 active cases makes 71 total cases with presumptive diagnoses of AHD from Alaska. The group of 29 inactive cases is under study and is excluded from further consideration in this report.

All nine patients who underwent resections for cure eventually had good results (Table 1 and Fig. 2). The average survival time of these patients since diagnosis currently is 22 years, and six are living. Eight of these nine cases converted their serologies postoperatively to negative. Three (cases 27, 29, and 30[11]) developed postoperative recurrences, but each was treated successfully, two by resection and one by chemotherapy.[33]

Two other patients (cases 33 and 38) underwent incomplete resections. One patient (case 33) had an extended left hepatic resection, but the portal vein could not be cleared completely of the parasite tissue. The lesion recurred, and the patient died 3 years later as the result of massive disease. The second patient (case 38) was classified with an incomplete resection because one of two small satellite lesions could not be identified at the time a 4 × 5.7-cm primary lesion was removed. The patient died of cancer 2.3 years later, and at autopsy, the 0.5-cm satellite had not enlarged and appeared to be nonviable histopathologically. The patient in case 33 was seen before chemotherapy was available; the patient in case 38 also was treated with MBZ.

Early in this experience, the majority of cases were not resectable at the time of diagnosis because of a massive lesion or invasion of the inferior vena cava or porta hepatis. In eight patients, the following palliative procedures were employed: marsupialization of hepatic abscesses in two cases; a partial resection in one; and some type of drainage procedure in five (Table 1).

Five patients who developed metastases to the brain survived only 1 year, on average, after diagnosis. Before chemotherapy was available, two of these patients underwent craniotomy, but neither benefited from surgery. However, neurosurgical successes have been reported by surgery alone[38] or in combination with chemotherapy.[39] Only six patients with active disease did not require surgical intervention. Twenty patients required abdominal operations, and two had thoracic procedures for diagnosis or staging. No operative or perioperative mortality occurred as a result of the 43 operations, and two percutaneous drainage procedures were required in the treatment of 36 patients with active disease (or in the 5 wedge hepatic resections performed for inactive disease).

DISCUSSION

The extensive spread of *E. multilocularis* in the contiguous United States and Canada since 1964 and its recent introduction and possible establishment in states along the Eastern seaboard are of concern. In 1924, when this parasite was introduced into Rebun Island, Japan, a small area with a high population density, a serious outbreak of AHD followed.[40] The first clinical case was reported in 1937, and by 1985, 131 cases of AHD had been identified, with 73 confirmed deaths. The cestode later became established on the island of Hokkaido. By April 1993, 323 proven cases of AHD had been found there and, in addition, nearly 500 other patients with positive serology were identified (M. Kamiya, personal communication, May 1993).

Role of Chemotherapy

The role of chemotherapy in the management of AHD is at an early stage of development, but is becoming increasingly important. The results of our 17-year experi-

Table 1. MAJOR SURGICAL PROCEDURES FOR ACTIVE ALVEOLAR HYDATID DISEASE 1950 TO 1992

Case No/ Age	Date of Surgery	Surgical Procedure	Vital Status	Survival Post-Diagnosis (yrs)	Results Clinical Assessment	Serology (last)	Clinical Notes
A. Resection for cure							
32/58	1953	Local Resection	D	26	Cured	–	Large mass aspirated 1951; diagnosis, sterile abscess; resection "in toto" 1953; died 7/79 of cancer
27/47	5/60 and 5/79	Radical right lobectomy	A	33	Recurrence Cured	–	Radical resection 1960; rising serology titers; CT revealed 2 × 3-cm recurrence, resected 5/79; clinically well
28/12	6/61	Radical right lobectomy	A	32	Cured	–	Large right hepatic mass with extension into chest wall and diaphragm resected; clinically well; 0.7-cm calcification in area of resection; 25 years after resection
29/45	1947 and 1966	Local resection then left lateral segmentectomy	D	42	Recurrence Cured	–	Cystic lesion locally resected 1947; recurrent mass in surgical scar resected 1959; palpable symptomatic recurrent hepatic mass resected 1966; death unrelated to AHD
26/42	1971	Open wedge resection	A	21.7	Cured	–	Diagnosis by serosurvey; a 10 × 12-cm mass resected by open wedge; clinically well
30/30	03/73	Open wedge resection	D	12.3	Recurrence controlled with MBZ. Died of cancer	+	A 12-cm mass of both lobes resected; rising serologies led to diagnosis of nonresectable recurrence 1980. Treated with MBZ for 42 months; died of cancer 09/85; *in vivo* viability test indicated parasite was dead
31/27	03/73	Extended right lobectomy	A	20.3	Cured	–	Abdominal pain; hepatic mass on scan; radical resection; clinically well
39/51	5/85	Open wedge, right	A	6.8	Cured	–	Diagnosis by serosurvey; a 3-cm lesion resected after 3 courses of ALBZ therapy viability assays negative
60/53	5/91	Open wedge right	A	2.2	Cured	–	Diagnosis by field US and serology survey; after 3 courses of ALBZ therapy a 3-cm lesion resected
B. Resection—incomplete							
33/22	1960	Extended left lobectomy	D	3	Recurrence died of AHD	+	Extensive resection but portal vein not totally cleared; died from recurrent massive lesion with 14-cm abscess 3 yrs postoperatively
38/48	6/84	Segmentectomy left	D	2.3	Died of cancer	–	Admitted with painful mass 6/84; treated with MBZ for 2 years. A 5-cm primary and 1 satellite lesion resected; a second satellite lesion not found; died of oat cell cancer of lung; no change in satellite lesion at autopsy
C. Palliative resections and procedures							
22/51	1950	Drainage of abscess	D	4.5	Died of AHD	ND	Abdominal mass explored; identification of abscess; chronic fistula × 4 years
23/52	1947/58	Marsupialization	D	0.7	Died of AHD	+	Multiple palliative procedures, 1947/58; hepatic cavity marsupialized 3/58
24/54	1957	Marsupialization	D	1	Died of AHD	+	Staged marsupialization of 15-cm hepatic lesion; developed fistula to colon and brain metastases
25/30	1950	Partial resection	D	13	Died of AHD	ND	A 15 cm "cyst" partially resected; died from advanced AHD with massive gastrointestinal gi bleeding, fistula to colon 4/63
1/34	2/80	Tube drainage of abscess	D	17	Died of AHD		Hepatic abscess (20 × 25 cm) treated with MBZ for 9 yrs; tube drainage of abscess in 1980; died of late complications of AHD
4/43	11/86	Hepaticojejunostomy	A	18.7	Improved	+	Under MBZ, wall of large hepatic abscess became thin and smooth; hepaticojejunostomy to drain abscess and insertion of percutaneous biliary stent for relief of right hepatic bile duct stenosis, 11/86
35/56	11/86	Hepaticojejunostomy	D	9.5	Died of CVA	+	Diagnosis by serosurvey; CT scan revealed 7 × 5.2 cm central asymptomatic mass; MBZ therapy; biliary stent for increasing biliary duct stricture then hepatojejunostomy 11/86; died of CVA 4/80, not related to AHD
34/50	11/80	Tube drainage of abscess	D	4	Died of biliary obstruction	+	Growth of two central lesions arrested for 4 years with MBZ therapy; died of complications of biliary obstruction

Note: ND = not done.

ence with chemotherapy trials have been summarized in detail.[33] We believe that in some patients, chemotherapy should be considered an alternative to surgical management. For example, in one of our patients (case 51), a 67-year-old woman with a 4.5-cm lesion, surgery has been deferred largely because the location of the lesion would require a relatively high-risk procedure for a person of her age. This patient received only 3.5 courses of ALBZ because she developed a severe skin rash. She has been observed for follow-up for 6 years and remains asymptomatic. In another young, healthy patient (case 53), surgery for a readily resectable 2 × 4-cm lesion initially was

recommended, but was declined by the patient. He received seven courses of ALBZ therapy. After being observed for 5 years, surgery is no longer advised. All follow-up CT scans on these two cases have revealed no increase in lesion-size; areas of low attenuation have been greatly reduced, and calcifications have become more confluent and dense.

The therapeutic dose and duration of therapy for the benzimidazole drugs has not been established. An urgent need exists to gain more knowledge about the efficacy of chemotherapy from each new case of AHD. An investigation by Eckert and Jacquier in Switzerland (J. Eckert, unpublished data, January 1993) showed that treatments with MBZ averaging 19 months proved to be inadequate in 12 patients, and in 1 of our patients, (case 60) treated with three courses, ALBZ also failed to kill the larval cestode.[33] We favor the use of ALBZ *versus* MBZ because it provides much higher serum levels of the drug and because effective therapy appears to be obtained in a much shorter period of time. Additionally, in one controlled study with cystic hydatid disease, ALBZ appeared to be more efficacious than MBZ.[31] Therefore, we recommend that, whenever possible, four to six cycles of ALBZ be given preoperatively, followed by viability studies on resected tissue. We believe that this regimen would provide some protection against intraoperative spread or postoperative recurrence for the patient and important additional data regarding the appropriate dose and duration of therapy with ALBZ would become available to clinical investigators. The risks of adverse reaction to these drugs, including hepatotoxicity, leukopenia, and dermatitis with possible Stevens Johnson syndrome, must be understood clearly, and careful monitoring of liver function tests and complete blood counts are essential.[8,11,16,17,33]

A recent, favorable report from China by Liu et al.[41] presents results of a study of 11 patients with unresectable AHD lesions who were treated with long-term (13 to 60 months), high-dose (10 mg/km q 12 hrs), continuous therapy. Analysis of CT findings of the lesions were used to assess the efficacy of therapy with ALBZ. In seven cases (64%), "the lesions were almost completely calcified and cured," whereas 3 cases (27%) were improved with "incomplete calcification of the peripheral margins."[41] No serious toxic effects were observed. This report suggests that ALBZ therapy should be administered over a longer period of time and at a higher dose than has been recommended and raises the question of whether interruption of therapy really is indicated.

Late Complications

The hepatic lesions caused by the larval stage of *E. multilocularis* enlarge because of proliferation of membranes and destructive invasion, rather than by displacement. The central sterile abscess that may develop is fed by numerous biliary ducts, which accounts for high output drainage. In case 1, this measured 500 to 800 mL daily for 31 months.[8] Outflow channels to the common duct were demonstrated by contrast studies in three such cases, but they are subject to blockage by biliary stones and necrotic debris.[8,16] Large lesions that occupy the major part of the organ invariably surround or encroach on important bile ducts and vessels. The intense scarring and fibrosis that is associated with these lesions inevitably result in stricture or obstruction of some of these structures. Under chemotherapy, proliferation may be arrested, yet biliary obstruction eventually may occur, often years after chemotherapy was started. Internal drainage was established in two patients by means of hepaticojejunostomies, using a Roux-en-y loop, to manage persistent intrahepatic strictures of the common duct and a large, somewhat symptomatic hepatic abscess.[33] The anastomosis eventually stenosed in each case, and percutaneous biliary stents were required. Those complications occurred 6 and 12 years after therapy with MBZ was initiated. Such late complications have been observed in five patients who received long-term MBZ therapy, and they contributed to the death of four. *In vivo* vole viability tests demonstrated nonviability in each of these cases.[33] We believe that such late complications are not the result of continued growth of the parasite, but represent the effects of gradual constriction of scar tissue, which may occur even after the death of the larval cestode. Consequently, patients with biliary strictures associated with AHD may have long-term survival. The use of stents in these cases is complicated by problems of sludging or blockage of the stent with encrustations, requiring frequent changing of the tube. One of the patients undergoing hepatojejunostomy died of a vascular stroke after being managed 3.4 years with a stent. A second patient (case 4), now surviving 6.6 years with a stent, also developed a stenosis of the portal vein with resulting portal hypertension and associated upper gastrointestinal bleeding from esophageal varices. The stricture recently was dilated by balloon venoplasty, and a percutaneous intrahepatic porto-caval shunt was inserted (Department of Hepatology, University of Washington, Seattle, WA) with good initial results. In this case, a recent trial with ursodiol (ursodeoxycholic acid) to reduce sludging has been encouraging, with intervals between tube changes increasing from 2.3 months to 5 months. The use of a U-drainage tube may have advantages over a straight catheter in such cases.

Incomplete Resections

After resection, known or suspected residual tissue of the larval cestode may be left, or a satellite lesion that

either was inaccessible or could not be identified may exist. Advances in surgical techniques currently offer such solutions as replacement of the inferior vena cava or even organ transplantation.[42] Case 3, described earlier, illustrates the potential danger of untreated postoperative residual lesions. However, in contrast to this case, an unidentified satellite lesion in case 38 (Table 1) was managed expectantly under chemotherapy, apparently with excellent results. Our Alaskan experience has led us to support a very conservative approach to such problems, for the following reasons.

Not infrequently, the natural host defenses appear to control and eventually, may kill the larval cestode in such residual tissue. That may be attributable in part to the very high serum antibodies produced when the lesion reaches a large size or as might occur in association with surgical procedures. We believe that this was the sequence of events in case 27, in which a 2 × 3-cm recurrent lesion was resected 17 years after the patient's initial surgery.[11] The limited growth over many years, negative viability studies, and histopathologic studies of the resected lesion have led us to conclude retrospectively that the recurrent lesion was nonviable when it was resected (Fig 2). In another patient (case 28), a routine CT follow-up study made 25 years after resection revealed a 0.7-cm, totally calcified lesion at the resection site, representing, we believe, a small postoperative residuum of larval cestode that had been killed by host defenses. Such occurrences may not be uncommon. Ammann et al.[23] described five similar cases in which residual calcifications, or areas of low attenuation on CT which progressed to calcification under chemotherapy, were found at the site of hepatic lesions thought to have been completely resected. The frequent occurrence of spontaneous destruction of the larval cestode in our Eskimo patients, and other factors, indicate that host defenses in humans can be effective under certain circumstances.[37]

Technical Considerations

Resection of the AHD lesion should be undertaken with a 1 to 2-cm wide margin. Computed tomography studies are helpful in determining the extent of resection, which in some cases, may require a trisegmentectomy. However, it is important to conserve as much hepatic tissue as possible. In practice, the majority of resectable lesions can be managed well by an open-wedge, nonanatomic resection, even in some cases in which single or multiple foci involve both lobes. We frequently have performed direct and percutaneous needle aspirations and believe there is no associated risk of dissemination. At surgery, large hepatic lesions should be palpated for deep fluctuation. Diagnostic needle aspiration may produce a heavy "pea soup-like" fluid that is characteristic of a central abscess. The reticence associated with needle aspiration of *E. granulosus* cysts recently has been challenged[43,44,45] and should not, in our view, be applied to AHD. The finding of small, readily seen fragments of translucent laminated membrane in aspirated fluid is pathognomonic of infection by *E. multilocularis.* These membranes originate, in all likelihood, from central areas of the lesion that have undergone necrosis liquefaction, and are believed to be nonviable.[46]

Proliferation of the larval cestode is most active in the peripheral part of hepatic lesions, whereas deeper portions may be undergoing necrosis with areas of calcification. Biopsies should be taken from the outer, superficial portion of the lesion and should be very generous, especially if the tissue is to be submitted for *in vivo* viability studies. A deep biopsy also runs the risk of entering a central cavity. In Figure 3, a good surgical biopsy is shown, illustrating appropriate size with an ample number of microcysts, essential in obtaining sufficient laminated membranes for intraperitoneal animal inoculations.

Superimposed bacterial infection of the central abscess associated with acute symptoms of fever, malaise, and toxicity is a complication of advanced AHD and was observed in two cases. These infections apparently were the result of ascending, biliary tract infections. However, none of the patients in the 42 cases in this experience had sepsis.

There only is a limited role for palliative surgery in the management of advanced AHD. We have placed greater reliance on long-term chemotherapy in such cases. Patients with very large symptomatic central abscesses and those who develop bacterial infections should have internal drainage through a procedure such as a Roux-en-y jejunal loop.

Until more is learned about the therapeutic dose of MBZ and ALBZ, chemotherapy should, in our view, be continued postoperatively, in addition to any preoperative treatment. We have elected to complete at least a total of 12 cycles of ALBZ or 4 years of MBZ. Follow-up CT and serology studies should be obtained every 6 to 12 months for many years. When the lesion is completely removed surgically, the serology can be expected to revert promptly to negative. Where the lesion is retained, as in patients with unresectable disease or after an incomplete resection, seroconversion usually is not observed for many years, even when the lesion is treated successfully by chemotherapy.

Among populations at increased risk for infection by *E. multilocularis,* programs for early detection by means of ultrasound and seroscreening are most important. By such measures, we have seen an increase in the resectability rate among the five active cases diagnosed since 1985, from 20% to 80%. The four resectable cases in this

group are believed to be well, two following resection of small lesions and two as the result of chemotherapy.

Summary of Diagnosis and Management

The following steps for diagnosis and management are suggestions that may be helpful to physicians, especially to the surgeon who may unexpectedly encounter this disease at exploratory laparotomy.

Diagnosis: a firm, infiltrating, white-to-yellowish, hepatic mass with the gross appearance of cancer. Extension into adjacent structures or metastasis to the omentum or regional lymph nodes may be encountered. Diagnosis is confirmed by frozen section, using the periodic acid Schiff method. Needle aspiration for characteristic "pea soup" fluid is suggested if the mass is fluctuant or large.

Management: assess the extent of disease and whether there is invasion of the inferior vena cava or porta hepatis. Resect if accessible and localized. If the lesion is resected initially, postoperative chemotherapy is recommended. If resection is to be postponed for further evaluation or diagnosis, obtain baseline CT and ultrasound studies and serology for echinococcosis (EM-ELIZA, Gottstein). Start ALBZ, 400 mg or 600 mg, twice daily by mouth, with meals. Obtain complete blood counts and liver function tests every other day for at least 6 weeks, then weekly. After 1 or 2 weeks of chemotherapy, draw blood 4 hours after A.M. dose for serum ALBZ-sulfoxide levels. Complete four to six cycles of ALBZ (1 cycle = 28 days of ALBZ followed by a 14-day drug-free interval). The importance of the 2-week drug-free interval is not clear and may be omitted. Schedule surgery about 1 week after the last dose of ALBZ (so residual tissue-ALBZ will not give false-negative viability result). Submit a 2 to 4-g biopsy in saline from a superficial part of the lesion or a large portion of the resected specimen to a proper facility, such as that of Dr. Robert Rausch, University of Washington, Seattle, Washington, for *in vivo* viability assay. Keep tissue under refrigeration, but prevent freezing. (Contact facility for shipping instructions). Resume ALBZ postoperatively to complete a total of at least 12 cycles and up to 36 cycles (months), depending on the severity of the clinical problem. Adjust the dose to acquire serum levels of about 1000 ng/mL. Report the results of your case in the literature.

For lesions requiring extensive or high-risk surgery, especially in poor-risk patients, chemotherapy as an alternative to surgery should be considered. For very large, central abscesses or problems of biliary obstruction, internal drainage or diversionary procedures may be useful. In patients with very difficult problems or poor long-term outlook, consider following ALBZ with MBZ therapy indefinitely. Inactive, burned-out infections suspected in small, heavily calcified lesions may require no treatment, although resectional biopsy may be appropriate if the lesion is found at surgery. Postoperative surveillance is important, with CT and serology every 6 months × 4, then annually. A rising serologic titer after "complete" resection strongly suggests a recurrence.[47]

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