Alveolar Echinococcosis in a Belgian Urban Dweller

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Abstract

Human alveolar echinococcosis is a rare parasitic disease caused by larvae of the tapeworm E. multilocularis that colonizes the intestines of foxes. The disease predominantly affects the liver and mimics slow growing liver cancer. With a mere 13 reports coming mostly from southern rural regions Belgium has so far been spared from the disease. However alveolar echinococcosis appears to be slowly spreading to non-endemic European countries like Belgium and to urban centres. We report the first autochthonous case involving a patient having lived exclusively in downtown Brussels.

Heightened awareness by the medical community is necessary to detect this lethal disease at an early curable stage. In patients with an undetermined focal liver lesion – especially if calcified – and no firm evidence of malignancy, serological screening should be performed to exclude alveolar echinococcosis. (Acta gastroenterol. belg., **2013**, 76, **317-321**).

Key words : alveolar echinococcosis, Echinococcosus multilocularis, liver, liver parasitosis, diagnosis, treatment, surgery, benzimidazoles, albendazole.

Introduction

Human alveolar echinococcosis (AE) is a rare disease caused by larvae of a tapeworm found mainly in foxes and occasionally in domestic animals such as dogs and cats. The clinical evolution and radiological aspects of AE mimic malignancy and, as with malignancy, the prognosis is sombre if left untreated. Echinococcus multilocularis is endemic in the Northern hemisphere and in Europe it concentrates principally in an area encompassing the common borders between France, Germany, Switzerland and Austria. In contrast with E. granulosus that is responsible for cystic echionococcosis, E. multilocularis is not found in the southern hemisphere. Thirteen cases of alveolar echinococcosis have been reported in Belgium to date, mostly in southern rural regions. The present report is the first autochthonous case involving an urban dweller having lived exclusively in downtown Brussels.

Case

A 72 year-old man with no history of hepatitis or alcohol abuse complained of chest pain. Abdominal ultrasonography incidentally revealed a heterogenous 8.5 cm segment IV and V liver mass with irregular contours, containing small cysts and scattered punctuate calcifications, with segmental dilatation of bile ducts to segments V and VIII. The gallbladder appeared to be normal. Liver enzymes and liver function tests, carcinoembryonic antigen and α fetoprotein were normal. CA 19.9 was slightly elevated. Hepatitis B and C serologies were negative. Unenhanced computerized tomography showed a hypodense focal liver lesion with irregular contours containing scattered punctuate calcifications and upstream dilatation of segment V and VIII bile ducts (Fig. 1). There was no contrast enhancement except for a thin peripheral rim that enhanced during the arterial phase. There was moderate irregular uptake by the lesion on fluorodesoxy glucose positron emission tomography scan (FDG-PET). No primary tumor was found at colonoscopy and gastroscopy. Laparoscopy showed a polylobulated white lesion of hard consistency suggestive of malignancy. Wedge biopsy showed no malignancy or granuloma, just hyalin fibrosis and scattered lymphocytes.

An undetermined benign lesion, gallbladder cancer or peripheral cholangiocarcinoma were suspected. Localisation of the mass in the gallbladder bed was the sole argument in favour of gallbladder carcinoma. A normal appearing gallbladder without stones or a thickened wall, calcifications within the lesion, only mild uptake on FDG-PET scan, a negative surgical biopsy, and most notably the patient's excellent health status argued strongly against this diagnosis. The central position of the lesion in proximity to the hilum, an elevated CA 19.9 marker and intrahepatic bile duct dilatation were evocative of hilar cholangiocarcinoma but the absence of jaundice, the lack of progressive and prolonged contrast enhancement at CT scan and the good health status went against this hypothesis. Finally a benign lesion was postulated : segmental liver dystrophy associating congenital liver fibrosis and segmental biliary dilatation are features of Caroli's disease. The absence of symptoms, excellent health status and negative biopsy definitely pleaded in favour of benign disease. However in Caroli's disease the cysts are larger, often contain pigment stones and always communicate with the biliary tree. Furthermore congenital hepatic fibrosis is usually only present in diffuse forms of Caroli's disease.

Embolization of the right branch of the portal vein followed by extended right hepatectomy would have been

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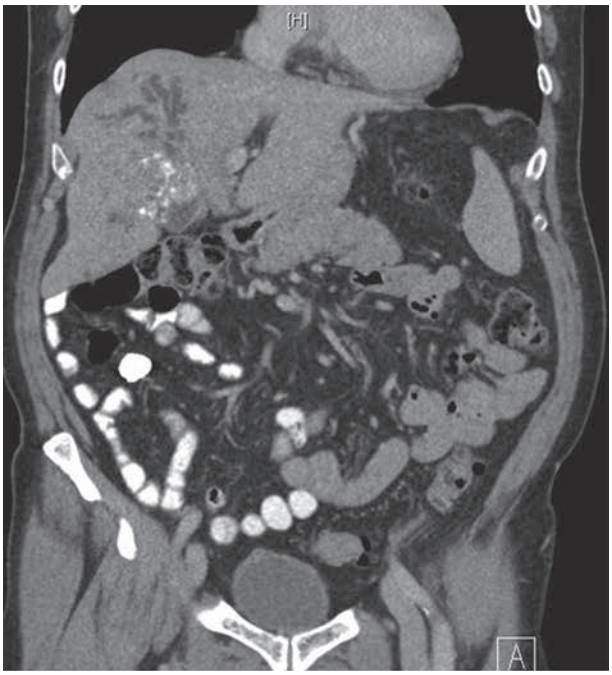

Fig. 1. — Coronal plane computerized tomography showing punctuate calcifications at the liver hilum and dilated peripheral segmental bile ducts.

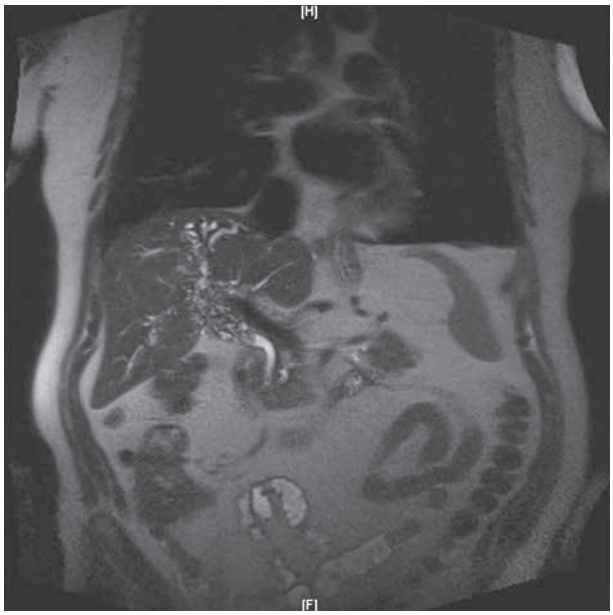

Fig. 2. — Coronal plane T2-weighted magnetic resonance showing numerous clustered small cysts (metacestodal vesicles) invading the liver hilum and hepatic pedicle.

necessary to achieve complete resection but because of the poor prognosis if the lesion were malignant and the possibility that the lesion might be of benign nature, a 'wait and see' attitude was adopted. The patient was not seen until three years later at which time the patient remained in excellent health but was slightly jaundiced. Computerized tomography and magnetic resonance (Fig. 2) showed diffusely dilated intrahepatic bile ducts, right lobe atrophy, thrombosis of the right hepatic artery and compensatory hypertrophy of the left lobe. The liver lesion abutted on the liver hilum and extended caudally along the hepatic pedicle. ERCP showed a 4 cm stenosis of the upper third of the common bile duct and temporary stents were placed. Immunodiffusion screening for Echinococcus multilocularis was positive. Specific tests for alveolar echinococcosis including ELISA Em2 and Western blot confirmed the diagnosis. Chest and brain computed tomography did not reveal parastic metastases. The patient was placed under lifelong albendazole chemotherapy. Anamnesis revealed that the patient had always lived in downtown Brussels and had owned two dogs 30 years previously. As a young adult he had worked in his parent's butchery shop plucking wild fowl.

Discussion

Alveolar echinococcosis is a zoonosis due to liver infestation by larvae of the tapeworm echinococcus multilocularis. The tapeworm colonizes the intestines of wild carnivores like the red or arctic fox but also those of domestic animals such as dogs and cats. Eggs are released in the faeces and can then be ingested by intermediate hosts, usually small rodents, or aberrant hosts such as humans, who become infected by direct contact or through contamination by food or water. The eggs cross the intestinal barrier and are transported via the portal vein to the liver where they develop.

E. multilocularis is endemic in the Northern Hemisphere including Canada, Alaska, China, Japan and former Soviet Union. In Europe most of the 559 cases reported in the European Echinococcus Registry (1982-2000) were diagnosed in an area encompassing the common borders between France, Germany, Switzerland and Austria (1) (Fig. 3). In endemic regions the annual incidence of AE ranges from 0.03-1.2/100000. So far Belgium has been spared from the spread of AE with only 13 cases having been reported, most coming from the southern rural region (2,3,4). The National Reference Laboratory on Echinococcus multilocularis in humans (Laboratory of Parasitology – ULB Faculty of Medicine) recorded 8 autochthonous cases until 2003. In 2006 and 2007 two new cases were confirmed in patients 64 and 82 years old. In 2008 and 2009 no new cases were recorded. In 2010 and 2011 there were 1 and 2 new cases reported. Although the annual incidence seems stable – roughly 1 case per year – reports like the present one seem to indicate that the disease may be spreading northward and to urban centers. The recent increase in fox populations in cities like Brussels and cohabitation with humans are factors that could be expected to increase the likelihood of transmission to humans. However the

Fig. 3. — Regional distribution of autochthonous alveolar echinococcosis in Europe from 532 diagnoses ascertained from 1982 to 2000. Source: European Echinococcosis Registry, Ulm, Besançon, 2001. Reproduced with permission.

habitats of small rodents that constitute the reservoir of the disease are disappearing because of urban development. Urban foxes behave like scavengers, tending to feed on readily available food picked from garbage rather than hunt for food. This could explain the low prevalence of E. multilocularis in autopsy studies on foxes in Brussels where none of the 160 individuals were infected, compared to 50% in some parts of Wallonia and 1.7% in Flanders (5). In comparison major European cities in endemic zones such as Stuttgart and Zurich have fox infestation rates of 20% and 48% respectively (1). Although the relationship is not well established human activities such as farming, gardening, forestry, hunting, wild berry picking and cat or dog ownership could constitute risk factors (6,7). This is supported by the fact that only 7.1% of patients in the European registry did not farm, garden or own pets.

Contrary to the related species E. granulosus, E. multilocularis does not develop in the form of large parasitic liver cysts but rather develops an alveolar honey comb structure made up of numerous small vesicles ranging from < 1 mm to 15-20 cm in diameter. The wall structure of the vesicles are similar to those of E granulosus with a germinal and a laminated layer. The vesicles are surrounded by large granulomas comprising a thin layer of acidophilic necrosis bordered by a palisade of epithelioïd histiocytes, itself bordered by a polymorphic infiltrate composed of neutrophils, eosinophils, giant cells and histiocytes. This peripheral zone is also characterized by dense fibrosis (6). Granuloma formation and fibrosis represent an attempt by the host to contain the parasite. There are wide variations in host immune responses to the parasite which are dependent on genetic factors and determine the clinical course of the disease. In European populations it has been shown that the major histocompatibility complex allele HLA DR11 protects against the disease whereas HLA DPB1*0401 is associated with increased susceptibility and that HLA DR3/DQ2 phenotypes are associated with a severe infection (8). Mass screening with liver ultrasound and serology in endemic regions of Switzerland and the French Jura revealed a significant number of seropositive individuals with liver calcifications but no radiological signs of active disease, an indication that aborted infections may be common (9). In fact epidemiological studies estimate that only 10% of contaminations lead to overt infections (10). The role of cellular immunity and immune modulators such as Th1 and Th2 cytokines, interleukins and γ interferon are well established (6). In patients with overt AE it is as if all the actors of cellular immunity converging to contain the infection were at least partially neutralized by immune modulators, principally IL-10, resulting in immune tolerance and preventing the parasite from being destroyed but sufficient to induce severe fibrosis and cytotoxicity (6). The drawback of this dampened immunological response is the encasement of the liver vasculature and biliary tree by progressive fibrosis leading to life threatening complications such as cholangitis, liver ischemia, venous outflow obstruction, secondary biliary cirrhosis and portal hypertension.

Being a very slow but relentless process, symptoms appear only after a latency period of 10-15 years. These include fatigue, weight loss, pain, hepatomegaly, jaundice, cholangitis, portal hypertension, Budd Chiari syndrome, liver abscess, secondary biliary cirrhosis and liver failure (11). In 97% of patients the parasite develops within the liver. The parasite can spread by contiguity to neighbouring organs such as the hepatic pedicle, retroperitoneum, diaphragm, vena cava, right atrium, pericardium, right lung and pleura, adrenal gland, kidney, stomach and peritoneum. The parasite can also give blood-borne metastases principally to the lungs (20% upon initial presentation) and brain (1%) – mostly in immunosuppressed patients (6).

Establishing the diagnosis through liver ultrasonography and serology can be straightforward when AE is suspected. Ultrasound shows a pseudotumoral inhomogenous liver mass with irregular limits and scattered calcifications. Large lesions may undergo central necrosis giving a pseudocystic appearance. Computerized tomography and magnetic resonance imaging show multiple irregular ill defined non-enhancing lesions displaying a typical 'geographical map' pattern. CT reveals calcifications in 90% of patients, presenting as multiple punctuate scattered calcifications, rim-like or a single large calcified mass. Early and persisting peripheral contrast enhancement reflects the presence of granulomas surrounding the central parasitic foci. On T2-weighted magnetic resonance multiple clustered small cysts – 'honey comb' or 'grape cluster' pattern – with a solid component or a larger cyst surrounded by a solid component are considered characteristic and highly specific for AE (12). By revealing the cystic component and calcifications respectively, T2-weighted MR and plain CT are complementary. The

main differential diagnosis is *hilar cholangiocarcinoma* (13). More than 50% of hilar masses are cholangiocarcinomas (14). Hilar infiltration is present in 50% of patients with AE (15). The local repercussions of AE on the surrounding liver are similar to those of cholangiocarcinoma : segmental biliary dilatation and liver atrophy, compensatory hypertrophy and capsular retraction. Dynamics of contrast enhancement at CT and MR will help to distinguish these two conditions. Typically AE shows no or little enhancement while cholangiocarcinoma exhibits slow progressive centripetal enhancement that becomes maximal in the late phase. Alveolar echinococcosis with extensive central necrosis resulting in a large cystic component may be confused with a *liver cystadenoma* or *cystadenocarcinoma*. Cystadenomas occur primarily in middle-aged women and can be unilocular or multilocular. Mural nodules, wall irregularities and coarse calcifications are suggestive of malignancy. Typically CT of cystadenoma will show a multilocular hypodense mass up to 30cm in size with a well defined wall that enhances little with contrast administration. Multifocal liver AE can mimic *fibrotic or necrotic liver metastases* that may enhance poorly with contrast medium. Finally the presence of multiple liver cysts may be evocative of a segmental form of *Caroli's disease*. However the absence of communication between the cysts and the biliary tree on MR-cholangiography will easily eliminate this diagnosis (16).

Immunodiagnosis is mandatory to confirm the diagnosis but also to evaluate the effectiveness of treatment during followup (6). 95% of patients have a positive serology but most tests are unable to differentiate between cystic and alveolar echinococcosis. The Em2plus-ELISA test is highly sensitive and specific for AE but cannot differentiate between active and non-active lesions. Western blot is also specific for AE. As in other parasitic diseases 10% of patients with AE display eosinophilia and 80% have polyclonal hypergammaglobulinemia. High levels of IgG1 and IgG4 antibodies can also be observed. IgG4 antibodies disappear after successful eradication, making them a useful marker of recurrence.

Surgery and chemotherapy are the cornerstones of treatment for AE. International guidelines recommend a stage-specific multidisciplinary approach (17). Whenever feasible radical surgical resection of the parasitic mass offers the only chance of cure. In recent series this has been possible in 30% of patients owing to an earlier diagnosis and progress in liver resection techniques (6). Relapse rates of 11% and 24% have been reported after curative resections (18,19). Relapses can occur as long as 224 months after surgery. Two centimetre margins are recommended because of possible microscopic invasion of neighbouring liver tissue (18). A long term follow-up study of 113 patients treated in Zurich showed that curative liver resection was superior to chemotherapy and that liver resection with palliative intent (debulking) was not indicated because it offered no advantage compared to medical treatment (20). Other palliative surgical procedures such as bilioenteric anastomosis, liver abscess drainage and portocaval shunting have been replaced by less invasive percutaneous or endoscopic techniques (6). Liver transplantation is an exceptional indication in highly selected patients with unresectable forms of AE limited to the liver (21). Over a 20 year period 55 patients were transplanted in 19 centers worldwide (22). Five year actuarial and disease-free survival was 71% and 58% respectively. In a European multicenter study relapses occurred in 6/45 patients and were associated with undiagnosed extrahepatic disease, high dose immunosuppression and the absence of perioperative benzimidazole treatment (21). Indications for liver transplantation include liver failure due to secondary biliary cirrhosis or chronic Budd Chiari syndrome and refractory angiocholitis not amenable to other treatments.

Inoperable patients and those having palliative resections should receive lifelong benzimidazole (BMZ) chemotherapy. BMZ have significantly improved the prognosis of inoperable AE. The present 10 year survival is in the order of 80%, up from 6-25% in historical controls (11). Curative resections should be consolidated with a 2 year course of BMZ. BMZ treatment is advised prior to and following liver transplantation. Albendazole (Zentel®) and mebendazole (Vermox®) are the currently available drugs. Until recently BMZ were considered to be only parasitostatic but several studies now seem to indicate that in a minority of non-resected patients BMZ may be parasitocidal (23,24,25). However at present there are no reliable clinical, biological or morphological parameters attesting a parasitocidal effect. Recently FDG-PET has emerged as a reliable method for discriminating between active and inactive lesions, allowing the prospect of discontinuation of treatment in patients showing no signs of parasite activity (26,27). One study suggested that sterilization of AE correlated well with disappearance of specific antibodies as measured by Em2plus ELISA, calcifications occupying more than 50% of the lesion and a negative FDG-PET (24). Another study failed to show any reliable predictive value of parasite death for lesion size, regressive changes on imaging, calcifications, duration of BMZ treatment, kind of treatment and Em2plus serology (23). Studies seem to indicate that parasite death under BMZ treatment occurs only in a minority of patients and cannot at present be reliably predicted and ascertained. FDG-PET does seem valuable in the early detection of recurrences for patients in whom BMZ have been discontinued.

In conclusion AE appears to be spreading to previously non-endemic European countries like Belgium. In patients with an undetermined focal liver lesion, especially if calcified, and no firm evidence of malignancy, serological tests should be performed to exclude echinococcosis. Heightened awareness by the medical community in non-endemic regions including large cities is necessary in order to detect this lethal disease at an early curable stage.

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