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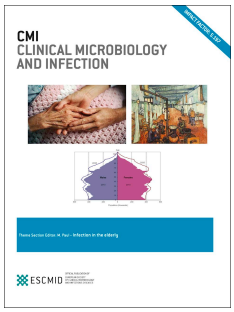

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Narrative review

Alveolar echinococcosis in immunocompromised hosts

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ABSTRACT

Background. Alveolar echinococcosis (AE) results of an infection with the larval stage of *Echinococcus multilocularis*. It has been increasingly described in individuals with impaired immune responsiveness.

Objectives. This narrative review aims at describing the presentation of AE according to the type of immune impairment, based on retrospective cohorts and case reports. Implications for patient management and future research are proposed accordingly.

Sources. Targeted search was conducted in PubMed using ((alveolar echinococcosis) OR (multilocularis)) AND ((immunosuppressive) OR (immunodeficiency) OR (AIDS) OR (solid organ transplant) OR (autoimmunity) OR (immune deficiency)). Only publications in English were considered.

Content. Seventeen publications were found, including 13 reports of 55 AE in immunocompromised patients (AE/IS) and 4 retrospective studies of 755 AE immunocompetent patients (AE/IC) and 115 AE/IS (13%). The cohorts included 9 (1%) solid organ transplantation (SOT) recipients, 2 (0.2%) HIV patients, 41 (4.7%) with chronic inflammatory/autoimmune diseases (I/AID) and 72 (8.3%) with malignancies. SOT, I/AID and malignancies, but not HIV infection, were significantly associated with AE (odds ratios of 10.8, 1.6, 5.9 and 1.3, respectively). Compared to AE/IC, AE/IS was associated with earlier diagnosis (PNM stages I-II: 49/85 (58%) vs 137/348 (39%), $p<0.001$), higher rate of atypical imaging (24/50 (48%) vs 106/375 (28%), $p<0.01$) and lower sensitivity of serology (19/77 (25%) vs 265/329 (81%), $p<0.001$). Unusually extensive or disseminated infections were described in SOT and I/AID patients.

Implications. Patients who live in endemic areas should benefit from serology before onset of a long-term immunosuppressive therapy, even if the cost-benefit ratio has to be evaluated. Physicians should explain AE to immunocompromised patients and think about AE when finding a liver lesion.

Further research should address gaps in knowledge of AE/IS. Especially, extensive and accurate records of AE cases have to be collected by multinational registries.

KEYWORDS

Echinococcus multilocularis, alveolar echinococcosis, immunosuppressive therapy, transplantation, HIV, cancer, malignant haemopathy, primary immune deficiency

INTRODUCTION

Alveolar echinococcosis (AE) is a parasitic disease due to the development of the larval stage of *Echinococcus multilocularis*, a tapeworm of canids (especially foxes) [1]. Only a few proportion of infected humans will actually develop viable parasitic lesions and there is cumulative evidence that host innate and acquired immune response is important in the clinical outcome [2]. After a short description of the immunological events involved in the antiparasitic response, this review will analyse clinical cases reported in each category of immune suppression backgrounds, and discuss implications for the management of these patients and perspectives for research.

PATHOPHYSIOLOGY OF ALVEOLAR ECHINOCOCCOSIS

Human infection occurs after accidental ingestion of eggs, which release an oncosphere that accedes to the blood circulation, then establishes in any vascularized organ, with a preferential location in the liver. There, it develops into the larval stage, also called metacestode (Fig 1) [3]. In accidental hosts, such as humans, the metacestode is a heterogeneous multicystic or multivesiculated structure that actively proliferates at its periphery. The parasite is surrounded by a strong infiltration of immune cells associated with dense fibrotic tissue, neovessels and epithelioid cells, and containing central caseous necrosis and calcifications [4].

Host-parasite interactions in human tissues lead to various clinical presentations. In most infected individuals (detected upon species-specific serology), no parasitic lesion is observed, suggesting that the parasite has been killed early [2]. In about 20% of cases, the metacestode aborts spontaneously at a later stage, forming a calcified non-viable parasite lesion, etiologically diagnosed on the basis of a positive serology, or upon histology and PCR [5]. These are called aborted or died-out lesions [2,3]. Finally, the evolutive form of AE, consisting of a viable parasite which continuously develops until its host dies, affects only a small percentage of infected individuals [2].

The initial pro-inflammatory Th1/Th17 immune response is considered to be putatively efficient against the parasite (Table 1) [6]. In susceptible hosts, the response progressively turns into a mixed

78 Th1/Th2 response, with contribution of regulatory T $CD4^+FoxP3^+$ lymphocytes (Treg) and IL-10
79 secretion, allowing parasite survival [6]. Humoral immunity, although present, appears as not
80 effective in the control of AE.

81 **Table 1. Summary of research findings about immunity in alveolar echinococcosis**

Factor	Associated with parasite control	Associated with parasite development	References
Cell populations	M1 macrophages, polymorphonuclear, NK, Th1 and Th17 cells	M2 macrophages, Th2 and Treg cells	[4,6–13]
Cytokines	IFN-α, IL-12, TNF-α, IFN-γ, IL-17	IL-4, IL-5, IL-9, IL-10, IL-13, TGF-β1, FGL-2	[4,6,10,14,15]
Drugs	Albendazole, mebendazole	Cyclosporine, methotrexate, steroids	[6,16]
Tissue response	Type IV hypersensitivity, fibrosis	Angiogenesis	[4,17]

82

83 **DIAGNOSIS**

84 Diagnosis relies on conventional imaging techniques (ultrasonography (US), Magnetic Resonance
85 Imaging (MRI), Computed Tomography (CT)) and detection of anti-*Echinococcus* antibodies [18,19].
86 Serological assays are of major interest, as most commercially available anti-*Echinococcus* ELISA (e.g.
87 using EgHF, EgP, Em2, Em2+ or EmVF antigens) and immunoblot assays have a high sensitivity for AE
88 diagnosis (80-98%) [18,20]. Specificity of these assays is excellent in the general population (>95%),
89 however cross-reactions are frequent in patients with cystic echinococcosis (CE) due to *Echinococcus*
90 *granulosus* (13-86%, depending on the technique used) [20]. Although CE and AE imaging are
91 different, it is recommended to use *E. multilocularis*-specific assays (anti-Em2, anti-Em2+) to avoid

cross-reactions. Furthermore, the anti-*Echinococcus* IgG immunoblot can display species-specific patterns, in favour of either *E. multilocularis*, *E. granulosus,* or *Echinococcus* sp. infection. In case of negative serology, diagnosis can rely on histology and/or PCR on biopsies.

Discrimination between evolutive and aborted lesions in humans is often difficult. Currently, the best marker to assess viability of the parasite is the detection of anti-recEm18 antibodies, which can be detected by ELISA (commercially available), with 45-80% sensitivity and 99-100% specificity for evolutive AE [18,20,21], and/or PET-scan [19].

Advanced imaging techniques allow staging of the disease using the PNM classification proposed in 2006 [22]. This system is based on three parameters similarly to the TNM system for tumours: P for the location and extension of the parasite within the liver (P0 to P4), N for the involvement of neighbouring organs (N0 or N1), and M for the metastasis (M0 or M1). Depending on the PNM classification, AE cases are then staged from I to IV, i.e. the less and the most severe, respectively.

OVERALL FINDINGS REGARDING IMMUNOCOMPROMISED PATIENTS

A total of 170 AE patients with immunosuppressive conditions (AE/IS) were mentioned in the literature, including 57 SOT recipients, 4 HIV-positive patients, 45 patients with inflammatory or auto-immune disorder (I/AID), 72 with cancer and 2 with a primary immune disorder (PID) (Table 2). Of note, 8 patients had both cancer and I/AID, and 1 SOT recipient had an haematological malignancy. Four retrospective cohort studies were published, one from France (1982-2012) [23], two others from Switzerland (late 90's-2020) [24,25], and one from Canada (2013-2020). Altogether, these studies described 115 AE/IS cases with previously mentioned backgrounds vs 755 AE cases in immunocompetent individuals (AE/IC). An increasing number of AE/IS cases was highlighted (6/166 AE cases (3.6%) in 1992-2002, vs 42/229 AE cases (18.3%) in 2002-2012 in the French cohort, $p<0.01$) [23]. By comparing the prevalence of each immunosuppressive condition between AE patients and the general population, SOT, I/AID and malignancies, but not HIV infection, were overrepresented among AE patients (odds ratios of 10.8, 1.6, 5.9 and 1.3, respectively) (Table 3).

Table 2. Summary of published cases and cohorts of alveolar echinococcosis in immunocompromised patients

Population	Number of case reports	Number of cases in cohort studies	Progressive AE[1]	References
SOT recipients	48[2]	9[3]	Yes	[23–32]
HIV/AIDS	2	2	Yes	[23,24,33,34]
Chronic I/AID	3[4]	41[4]	Yes	[23–25,32,35–37]
Malignancies	0	72[5]	No	[23–25,32]
Primary immune disorder	2	0	Yes	[38,39]

SOT Solid organ transplant, I/AID Inflammatory and Autoimmune disorder

[1] Progressive AE: unusually fast-growing or extensive AE

[2] Including 45 patients who had liver transplantation for incurable AE, and 2 and 1 patients who had kidney and lung transplantation, respectively, for another indication

[3] Transplanted organs: 4 kidneys, 2 hearts, 1 liver, 2 not specified

[4] Including 12 patients with rheumatoid arthritis, 9 with non-rheumatoid arthritis, 2 with vasculitis, 4 with another chronic inflammatory disease (inflammatory bowel disease, sarcoidosis, collagenosis, Still disease), 3 with another autoimmune disease (systemic lupus, Sjögren's syndrome, autoimmune encephalitis) and 14 not specified

[5] Includes 44 solid cancers, 12 haematological malignant diseases and 16 "malignancies" (not specified)

Table 3. Prevalence of immunosuppressive conditions in alveolar echinococcosis patients and general population

	Prevalence among AE patients: n/N (%)	Estimation of prevalence in the general population	Odds ratios and significance[4]
SOT recipients	9/870 (1.0%)	97/100.000[1]	10.8, p<0.001
HIV/AIDS	2/870 (0.2%)	180/100.000[2]	1.3, p=0.955
Chronic I/AID	41/870 (4.7%)	3.000/100.000[3]	1.6, p<0.01
Malignancies	72/870 (8.3%)	1.500/100.000[2]	5.9, p<0.001
Total	115/870 (13.2%)	4.777/100.000	3.0, p<0.001

SOT Solid organ transplant, I/AID Inflammatory and Autoimmune disorder

[1] Estimation based on the whole number of living SOT recipients in France in 2021, from the public "Agence de la Biomédecine" database (https://rams.agence-biomedecine.fr/bibliotheque-de-donnees).

[2] Estimation based on (i) the whole number of individuals living with HIV in France and Switzerland, and (ii) the prevalence of cancer in France in 2000 and 2008, from the public WHO database (https://gateway.euro.who.int/en/).

[3] Estimation from Cooper et al. 2003 [40].

[4] Statistical test: Fisher's exact test

Compared to AE/IC, AE/IS cases were diagnosed more often incidentally (66/86 (77%) in AE/IS vs 144/341 (42%) in AE/IC, p<0.001) and, consequently, earlier in the parasite development (PNM stages I-II: 49/85 (58%) in AE/IS vs 137/348 (39%) in AE/IC, p<0.01). Clinical presentation of the symptomatic cases was not compared between AE/IS and AE/IC. Importantly, AE/IS was significantly associated with false negative serology compared to AE/IC patients (58/77 (75%) in AE/IS vs 64/329 (19%) in AE/IS, p<0.001), but this could be also related to earlier diagnosis [19]. A high frequency of atypical liver ultrasound and CT imaging findings were described in the French cohort (48%, 24/50), suggesting cancer metastasis (36%, 18/50), liver abscess (8%, 4/50), haemangioma (2%, 1/50) or

hematoma (2%, 1/50) instead of typical imaging (heterogeneous mass with calcifications and/or clustered microcysts) (Fig 2) [23]. This proportion was significantly higher compared to German and Turkish reports in the whole AE population, showing only 28% (106/375) of atypical imaging findings ($p<0.01$) [41,42]. Interestingly, the French retrospective study also reported a better treatment efficacy in AE/IS patients compared to AE/IC ((21/41 (51%) vs 50/187 (27%) of lesion regression after 1 year of treatment, $p<0.01$)). However, the authors also emphasized the high frequency of side effects (40%), possibly associated with high concentrations of albendazole sulfoxide in plasma, thus encouraging pharmacological monitoring in these patients. However, this proportion was not significantly different from the 20% (7/35) observed in a previous German cohort of AE patients [43]. Mortality was significantly higher in AE/IS compared to AE/IC patients (16/80 (20%) vs 13/313 (4%), $p<0.001$), but was not clearly imputed to AE. The main conclusions of these studies are summarized in Table 4.

Table 4. Main facts regarding alveolar echinococcosis and immune suppression

Item	AE/IS	AE/IC	Significance (Fisher's exact test)	Interpretation for AE/IS compared to AE/IC	References
PNM stage I-II of disease at diagnosis	49/85 (58%)	137/348 (39%)	p<0.001	Diagnosed earlier, due to systematic check-up[1]	[23,24,32]
Misleading US and CT imaging (cancer metastasis, abscess, haemangioma or hematoma)	24/50 (48%)	106/375 (28%)[2]	p=0.008	Higher rate of atypical imaging	[23,41,42]

Sensitivity of serology	19/77 (25%)	265/329 (81%)	p<0.001	Lower sensitivity of serology	[23,24,32]
Regression at 1 year under benzimidazole treatment	21/41 (51%)	50/187 (27%)	p<0.01	Higher efficacy of benzimidazole	[23]
Benzimidazole side effects	19/48 (40%)	7/35 (20%)	p=0.093	Slightly higher frequency of side effects	[23,43]
Mortality imputable to AE	0/50 (0%)	3/187 (2%)	p=1.0	Not significantly different	[23]

US, ultrasound; CT, computed tomography

[1] This observation was described in European countries, benefiting from advanced health care procedures, but can vary according to health policies

[2] Data obtained from two retrospective studies of AE imaging. The populations were not strictly composed of AE/IC cases, as AE/IS were not excluded.

ALVEOLAR ECHINOCOCCOSIS AND SOLID ORGAN TRANSPLANT RECIPIENTS

Due to their mechanisms of action on cellular immunity, immunosuppressive agents used for the prevention of graft rejection (cyclosporin, tacrolimus, mycophenolate) theoretically facilitate AE progression. Indeed, solid organ transplant (SOT) recipients were the first patients described with rapidly extensive AE. In 1990, two patients who had liver transplantation for AE salvage and pre-existing pulmonary lesions, were reported as having rapidly growing lung lesions [26], and between 1990 and 1992, recurrence of AE was observed in the transplanted liver [26,27]. In 2003, Koch et al. reported a 10-year survival of 45%, in a retrospective cohort of 45 patients, managed by liver transplantation for otherwise untreatable AE between 1985 and 1998 [28]. Among the twenty deaths observed during follow-up, 5 (25%) were due to relapse, and 9 (45%) were perioperative deaths.

They highlighted the detection of new parasitic lesions (mostly in brain and lungs) in 16% (6/45), and graft invasion in another 16% (6/45). Similar clinical presentations were also reported in kidney and lung transplant recipients [29–32]. These data suggest that SOT recipients can present unusually rapidly progressive AE, with an increased risk of dissemination.

ALVEOLAR ECHINOCOCCOSIS AND HIV/AIDS

While HIV and *E. multilocularis* co-infection is often taken as an example of the opportunistic behaviour of the parasite, only few cases have been reported to date. The first was published in 1997, and was diagnosed in a six-year-old girl with AIDS [33]. The clinical presentation displayed multiple unusual features: the young age of the patient, the extensive parasite growth and the negative serological testing. Furthermore, the girl had a dramatically low $CD4^+$ T cell count ($12/mm^3$) and a negative lymphoproliferative assay with *E. multilocularis* antigen. A second case was published 7 years later, in a 40 year-old male [34]. Although the patient was immunocompromised over nearly a decade ($CD4^+$ T cells between 27 and $150/mm^3$), the parasite had an usual growth rate, as the lesion was retrospectively observed on a CT scan performed 8 years before AE diagnosis. Only 2/870 (0.2%) HIV patients were mentioned in retrospective studies [23,24]. Altogether, these reports showed that HIV is an uncommon condition for accelerated AE development. Only a dramatically low $CD4^+$ T cell count appears to favour the parasite growth (< 20-50/mm^3).

ALVEOLAR ECHINOCOCCOSIS AND CHRONIC INFLAMMATORY DISEASES OR AUTO-IMMUNE DISORDERS

As for SOT, I/AID are theoretically adequate backgrounds for rapidly progressive AE. Indeed, most of these disorders are treated with long-term immunosuppressive therapies, which often have broad-spectrum effects on immune effectors (e.g. steroids, methotrexate...) or an anti-Th1 biological activity (e.g. TNF-α inhibitors, anakinra (IL-1 receptor antagonist)…). Such cases were actually reported in patients affected with auto-immune encephalitis and rheumatoid arthritis [35–37]. Among the retrospective cohorts of AE/IS, 40/115 patients (35%) had I/AID, and at least 14/115

(12%) and 6/115 (5%) were treated with methotrexate and TNF-α inhibitors, respectively [23–25,32]. Of note, at least 27/115 (23%) were treated with steroids, without specification concerning the indication (SOT, malignancy, I/AID or other) nor the dosage. Although it seems probable that all immunosuppressive regimens do not equally favour AE, fundamental and clinical data suggest that long-term administration of steroids or TNF-α inhibitors could accelerate AE progression. Other immunosuppressive therapies were observed in patients with accelerated AE, such as rituximab (anti-CD20) [23,30,37], however they are mostly associated with steroids or TNF-α inhibitors, which prevent to reliably conclude on their imputability.

ALVEOLAR ECHINOCOCCOSIS AND MALIGNANCIES

The few reports of AE concomitant to malignancy were compiled in retrospective cohorts. Out of the 115 AE/IS detailed cases, 44 (38%) had solid cancer (15 of the digestive tract, 9 of the respiratory tract, 15 urogenital or breast, 1 of the skin and 3 others), 12 (10%) had haematological malignancies (4 myeloproliferative syndrome, 6 lymphoproliferative syndrome, 1 Fanconi anaemia) and 16 (14%) had unspecified malignancy [23–25,32]. The median time between onset of immunosuppressive condition (IS) and AE diagnosis was shorter for solid cancers than for other conditions, probably because AE was often diagnosed incidentally during extensive workup (83%) [23]. Despite the high number of AE diagnosed in patients with malignancies, no clear evidence of aggressive AE has been reported. On the contrary, these cases often benefited from an earlier management due to incidental diagnosis [23].

PRIMARY IMMUNE DEFICIENCIES

Only two cases of AE were described in patients with PID, both were young patients (14 and 17 yo) with Hyper-IgE Syndrome (HIES) [38,39]. This rare PID is characterized by recurrent infections, eosinophilia and elevated IgE serum levels. The syndrome is associated with a defect of the Th17 response, leading to bacterial and fungal opportunistic infections [44]. The fact that these two young patients presented with disseminated AE is highly unusual, as the mean AE incubation time is

between 5 and 15 years [2]. Even if more evidence needs to be collected, these observations suggest that Th17 defects, including *Card9-Syk* deficiencies, could favour AE development [45]. Unlike most of PIDs, such deficiency can be diagnosed in apparently healthy children or adults [46,47]. The part of such defects in unusually extensive AE is currently not known. Further studies (extensive analysis of immune cell populations, complete workup for autoimmunity, whole-genome sequencing) are needed to ensure that rare and yet undiagnosed PIDs are not hidden beyond those atypical cases, particularly when they occur in children. Indeed, taken together, 21 paediatric case reports have been described in the literature, including 24% under 10 years and 24% with disseminated lesions [33,39,48–57]. In almost all cases, assessment of immune status was unreported or limited to T $CD4^+$ and T $CD8^+$ cell counts and HIV serology. However, it should be kept in mind that atypical presentations may be not only related to immune disorders, but can be associated with vascular abnormalities [56,58–60].

IMPLICATIONS

Populations exposed to long-term immunosuppressive therapy such as cyclosporin, TNF-α inhibitors or steroids are at risk of progressive AE. While data are scarce regarding other treatments, physicians should be aware that the use of such drugs could accelerate progression and dissemination of AE. Considering the occurrence of rapidly extensive AE in SOT and I/AID patients, serological screening and abdominal imaging (if not previously done) could be proposed to these patients before onset of the immunosuppressive therapy, even if the benefit of such recommendation should be evaluated. Whether cancer is actually a risk factor is not clear, as it can be associated with AE diagnosis due to extensive check-up [23]. Conversely, it could be even hypothesized that AE is a risk factor for cancer, as it induces chronic immunosuppression by itself [4]. Finally, HIV infection does not seem to be a risk factor, nor a significant cause of progressive AE.

LIMITATIONS

Our review has some limitations as it relies on retrospective cohorts and case reports, which made it at risk of declaration bias. Also, we decided to restrain our analysis to well-defined immunocompromised backgrounds, i.e. SOT, I/AID, HIV infection, malignancy and PID. However, other backgrounds can be associated with opportunistic infections, such as cirrhosis, pregnancy, asthma or diabetes. Of note, both retrospective cohort studies from Switzerland included such patients, without detailing if their characteristics were different from other backgrounds.

PERSPECTIVES

The details of the causative relationship between immunosuppressive conditions and AE evolution remains unclear (Table 5). This is mostly due to the low number of AE cases, which makes difficult to build consistent cohorts. The next step toward filling this gap in knowledge of AE is to improve and harmonize data collection in endemic countries. Complementarily, fundamental research is of paramount importance to understand the effect of immunosuppressive therapies on AE development. Especially, clinical studies cannot discriminate if immunosuppressive therapies impact invasion through the intestinal barrier, early establishment of the larvae or late stage of AE. Also, more immunological and genetic studies are needed to assess if rare PIDs are responsible for some of the cases of unusually extensive AE.

To date, there is no data supporting modified medical treatment or follow up in AE/IS. Even if albendazole seems to be more effective in AE/IS, possibly due to the reduced fibrosis or the earlier diagnosis, it is not clear whether these patients are at risk of late relapse, or if it would be beneficial to extend the duration of treatment and/or follow-up.

In areas endemic for AE, physicians who manage patients under long-term immunosuppressive therapies should deliver health education, by explaining what AE is and the ways to avoid infection. Overall, the probably most important suggestion to these physicians would be to think about AE when finding a liver lesion.

Table 5. Unanswered questions about alveolar echinococcosis and immunocompromised hosts

Topic	Questions
Management of patients	Would it be reasonable to perform systematic anti-*E. multilocularis* serology and abdomen imaging before onset of an immunosuppressive regimen[1] for people living in endemic areas? Should patients with unusually extensive lesions and children with AE benefit from extensive immunological check-up? Should treatment and/or follow up duration be extended for these patients?
Epidemiology	Which immunosuppressive drugs, and what treatment duration, are associated with an increased risk of AE? Is cancer favouring AE, or conversely AE favouring cancer? Are there other backgrounds favouring AE?
Pathophysiology	Do immunosuppressive regimens favour parasite establishment, development, or both?

[1] Especially SOT recipients regimen, TNF-α inhibitors and steroids

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CONFLICT OF INTERESTS

None of the authors declares any conflicts of interest.

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CONTRIBUTION

Conceptualization: F.R.-G. Investigation: B.A. Writing-first draft: B.A. Writing-review and editing: all authors contributed equally.

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472