Veterinary Parasitology 213 (2015) 103–109

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Review

Susceptibility versus resistance in alveolar echinococcosis (larval infection with *Echinococcus multilocularis*)

Bruno Gottstein*, Junhua Wang, Ghalia Boubaker, Irina Marinova, Markus Spiliotis, Norbert Müller, Andrew Hemphill

Institute of Parasitology, Vetsuisse Faculty and Faculty of Medicine, University of Bern, Switzerland

ARTICLE INFO

Keywords:
Alveolar echinococcosis
Resistance
Susceptibility
Regulatory T cells
TGF-beta
FGL2
PET-CT
Em18-ELISA

ABSTRACT

Epidemiological studies have demonstrated that the majority of human individuals exposed to infection with *Echinococcus* spp. eggs exhibit resistance to disease as shown by either seroconversion to parasite—specific antigens, and/or the presence of 'dying out' or 'aborted' metacestodes, not including hereby those individuals who putatively got infected but did not seroconvert and who subsequently allowed no development of the pathogen. For those individuals where infection leads to disease, the developing parasite is partially controlled by host immunity. In infected humans, the type of immune response developed by the host accounts for the subsequent trichotomy concerning the parasite development: (i) seroconversion proving infection, but lack of any hepatic lesion indicating the failure of the parasite to establish and further develop within the liver; or resistance as shown by the presence of fully calcified lesions; (ii) controlled susceptibility as found in the "conventional" alveolar echinococcosis (AE) patients who experience clinical signs and symptoms approximately 5–15 years after infection, and (iii) uncontrolled hyperproliferation of the metacestode due to an impaired immune response (AIDS or other immunodeficiencies). Immunomodulation of host immunity toward anergy seems to be triggered by parasite metabolites. Beside immunomodulating IL-10, TGFβ-driven regulatory T cells have been shown to play a crucial role in the parasite-modulated progressive course of AE. A novel CD4+CD25+ Treg effector molecule FGL2 recently yielded new insight into the tolerance process in *Echinococcus multilocularis* infection.

Contents

1. Introduction

Alveolar echinococcosis (AE) is one of the most severe helminthic diseases, caused by infection with the metacestode or larval stage of the fox tapeworm *Echinococcus multilocularis*. Human AE first affects the liver (Stojkovic et al., 2014), with a parasite tissue continuously proliferating and infiltrating, thus forming a growing hepatic lesion that consists of a large conglomerate of parasite vesicles, which are intermingled with mainly host connective tissue and immune cells. Inflammation and immunopathology is scarce, indicating that the parasite actively modulates the host innate and immune reaction. Similar to malignant tumors, metastasis formation into other organs can take place at a later stage of infection (Vuitton and Gottstein, 2010). Due to the malignant nature with infiltrative growth and metastatic spread characteristics, AE may

* Corresponding author at: Institute of Parasitology, Vetsuisse Faculty and Faculty of Medicine, University of Bern, Länggass-Strasse 122, CH-3001 Bern, Switzerland.
E-mail address: bruno.gottstein@vetsuisse.unibe.ch (B. Gottstein).

http://dx.doi.org/10.1016/j.vetpar.2015.07.029
0304-4017/

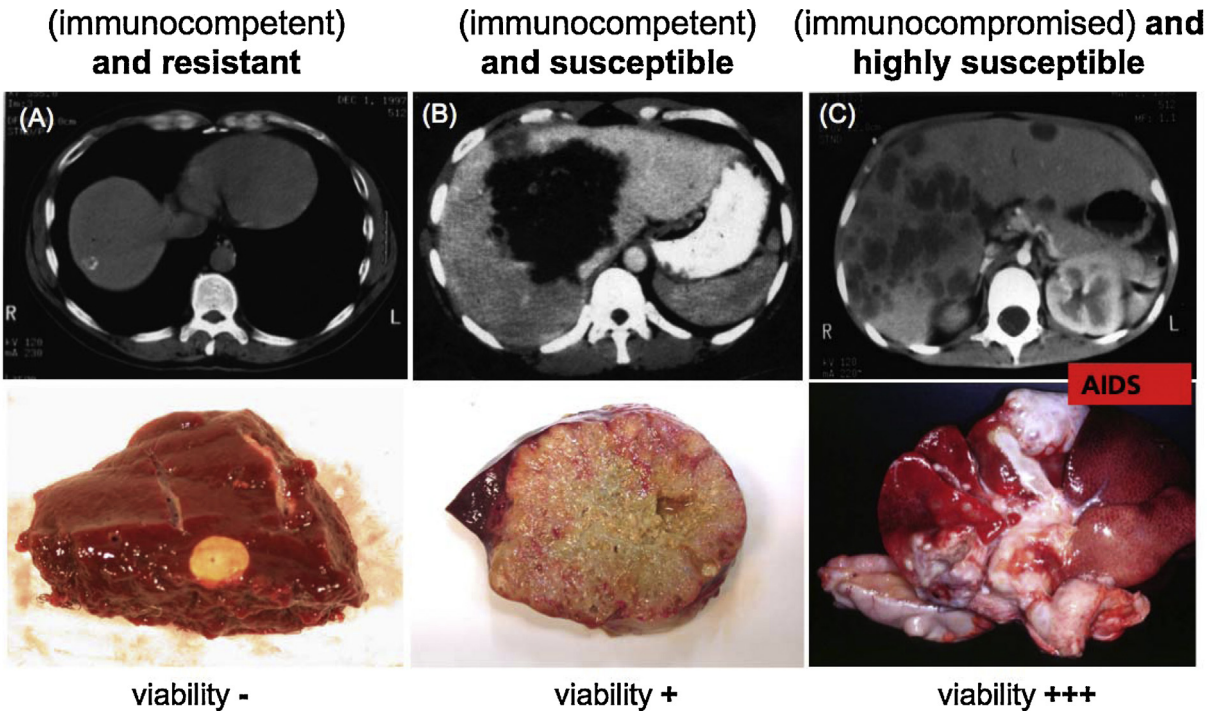

Fig. 1. Hepatic lesions formed upon *E. multilocularis* infection can be classified into the following three presentations: (A) "resistant" AE as shown by the presence of 'dying out' or 'aborted' metacestodes; (B) controlled susceptibility as shown by a slowly growing metacestode tissue — this group refers to immunocompetent AE patients, and (C) uncontrolled hyperproliferation of the metacestode due to an impaired immune response, including AIDS or other immunodeficiencies, e.g. following orthotropic liver transplantation. Upper picture line presents typical CT features of the three classes; lower picture line shows typical native liver lesions as presenting after surgery.

cause premature death in advanced stages. However, in Europe, thanks to life-long administration of the benzimidazoles albendazole and/or mebendazole in those patients who cannot benefit from radical surgical resection of the lesions, i.e. two third of patients, it has become a chronic disease, with significant impairment of quality of life. Numerous complications occur in these patients, including biliary obstruction with jaundice, septicaemia due to repeated cholangitis and bacterial super-infection of necrotic cavities in the lesion, portal hypertension, chronic Budd-Chiari disease, secondary biliary cirrhosis, as well as stroke, pulmonary complications, and a variety of diseased conditions related to distant metastases (Stojkovic et al., 2014).

Radical surgical removal of hepatic lesions is the optimal treatment option, but is feasible in only about 30% of the patients (Stojkovic et al., 2014). In advanced stages of AE, surgery is often incomplete due to the diffuse infiltration of metacestode tissue into non-resectable structures or sites. The currently available chemotherapy, based on the benzimidazole derivatives albendazole and mebendazole, has clearly increased the life expectancy of affected patients, and was shown to be effective in 55–97% of AE cases (Torgerson et al., 2010; Piarroux et al., 2011; Stojkovic et al., 2014).

Epidemiological studies have demonstrated that the majority of human individuals exposed to infection with *E. multilocularis* eggs exhibit resistance to disease as shown by either seroconversion to parasite-specific antigens and maintenance of a seropositive status, and/or the presence of 'dying out' or 'aborted' metacestodes (Rausch et al., 1987; Bresson-Hadni et al., 1994; Romig et al., 1999; Gottstein et al., 2001). For those individuals where infection leads to disease, the developing parasite is partially controlled by host immunity: in the case of immunocompetence, a slowly growing metacestode is observed, referring to that form of AE where first clinical signs appear years after infection. In the case of impaired immunity, caused by AIDS, other immunodeficiencies or immunosuppressing therapies such as following organ transplantation, cancer chemotherapy, or chronic inflammatory diseases, an uncontrolled proliferation of the metacestode is observed, leading to a more rapidly progressing disease status (Chauchet et al., 2014).

One of the frequently encountered questions raised by clinicians is, how many people infected with *E. multilocularis* eggs will effectively develop disease (AE) (→ see Fig. 1b), and how many exhibit resistance to disease; and among the infected "resistant" individuals, how many present early abortion of infection (i.e. no lesion detectable at all) and how many present spontaneous late abortion (i.e. fully calcified lesions still detectable by imaging procedures) (→ see Fig. 1a). So far, only a very rough approach to answer these questions can be attempted, i.e. based on the following reflections:

In the study of Gottstein et al. (2001) carried out with healthy Swiss blood donors living in a hyperendemic area of Switzerland, a rounded seroprevalence of 0.2% was found (Table 1), using a highly specific serological test (Em2-ELISA: 99% specificity in Gottstein et al., 1993; 100% specificity in Gottstein, 1989). In Switzerland, for the same time period, the annual incidence was 0.2 AE cases per 100,000 inhabitants, which equals 0.0002% in percent of the population. As AE-experts repeatedly stated that the time interval between infection (=plus/minus time-point of seroconversion) and diagnosis of symptomatic disease ranges between 5 and 15 years (mean 10 years), we can correct the annual case incidence by a factor of 10, so as to merge both serological and clinical baselines.Based on this theoretical approach (serological prevalence of 0.2%, corrected clinical prevalence of 0.002%), one can conclude that from 100 AE-seropositive people, only one person will develop disease, and the other 99 will appear as "resistant" to disease. The subsequent question on how many seropositive resistant individuals will present hepatic "died-out" lesions, and how many will remain "negative" in any imaging aspects, one can again use the work of Gottstein et al. (2001) to perform a rough estimation: In this