

Echinococcosis and Allergy

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Abstract

The larval stages of *Echinococcus granulosus* and *E. multilocularis* are involved in parasitic diseases in humans: cystic echinococcosis (CE) ("hydatid disease") and alveolar echinococcosis (AE), respectively. Both diseases and parasites have tight links with allergy because of the immunological characteristics that contribute to maintain the larvae in their human host as well as their potential in inducing clinical anaphylactic reactions in some patients. Clinical observations in patients and data obtained from mass screenings in various countries have identified both forms of echinococcosis as "polar diseases," i.e., diseases where immunological background of the patients was related to the clinical presentation and course. In particular, abortive cases (i.e., spontaneous cures) have been found in many subjects in endemic areas. On the other hand, immune suppression was associated with severe disease. AE especially might be considered as an opportunistic infection. Experimental and clinical studies have shown that Th1-related immune response was associated with protection and Th2-related response was associated with parasite growth. Genetic characteristics of the host are related to both occurrence and severity of AE and are associated with the extent of IL-10 secretion, which is a major feature of chronic progressing echinococcosis.

Anaphylactic reactions, including urticaria, edema, respiratory symptoms, and anaphylactic shock due to spontaneous or provoked rupture of the parasitic cyst, are well known in CE. Anaphylactic reactions in AE are far less frequent, and have been observed in rare cases at time of metastatic dissemination of the parasitic lesions. *Echinococcus*-specific IgE is present in most of the patients and associated with severity. Specific histamine release by circulating basophils stimulated with *E. granulosus* antigens is present in all patients with CE and AE. *Echinococcus* allergens include (1) AgB 12-kDa subunit, a protease inhibitor and a potent Th2 inducer; (2) Ag5, a serine protease; (3) EA 21, a specific cyclophilin, with a homology with other types of cyclophilins; (4) Eg EF-1 β/δ , an elongation factor, with a homology with *Strongyloides stercoralis* EF that shares the same IgE epitope. A clinical cross-reaction with Thiomucase®, a mucopolysaccharidase used in arthritis treatment, has recently been published. However, despite the potential risk of allergic reactions, the dogma "never puncture a hydatid cyst" is no longer valid. International experience of the therapeutic technique of "puncture, aspiration, injection, re-aspiration" of hydatid cysts developed at the beginning of the 1980s has proved to be successful in a variety of selected indications that have been reviewed by WHO recommendations.

A better understanding of the immunological background of echinococcosis in humans has led to new therapeutic developments, such as immunomodulation using interferon alpha. Th2-driven immunological response and IL-10-related tolerance state are common characteristics of atopic allergy and echinococcosis. The example of echinococcosis stresses the ambiguous links that exist between parasitic and allergic diseases, and show the usefulness of comparing these diseases to better understand how immune deviation may lead to pathological events and to find new therapeutic and/or preventive agents.

Index Entries

Echinococcosis; hydatid disease; *Echinococcus granulosus*; *Echinococcus multilocularis*; allergy; anaphylaxis; immune deviation; tolerance; Th1; Th2; interleukin-10; immunogenetics.

Introduction

The larval stages of *Echinococcus granulosus* and *E. multilocularis* are involved in parasitic diseases in humans: cystic echinococcosis (CE) ("hydatid disease") and alveolar echinococcosis (AE), respectively (1). Contamination of humans occurs by the ingestion of the parasite (cestode) eggs, either after touching carnivores that are the final hosts of the worms, or after eating food contaminated by carnivore feces. CE behaves as a benign tumor/cyst, usually located in the liver and/or the lung (hydatid cyst), and is most often curable. Severe cases may be observed, however, owing to the dissemination of the cysts, either spontaneously or after surgery. The usual intermediate hosts are sheep, goats, cattle, or camels. AE behaves as a malignant tumor, initially located in the liver, then able to spread to any organ through metastases, and is lethal in the absence of appropriate therapeutic management. For this disease, the usual intermediate hosts are wild rodents, especially voles, or small lagomorphs.

Both diseases and parasites have tight links with allergy because of the immunological characteristics that contribute to maintaining the larva in its human host, as well as their potential in inducing clinical anaphylactic reactions in some patients. The infection of the intermediate hosts by the metacestode stage of *Echinococcus* species, and especially *E. multilocularis*, appears to be a very good model to unveil some of the mechanisms of the host-parasite interplay and a very good example of the ambiguity of the immune effector mechanisms on the host's health and survival (2). The combination of an epidemiological approach to AE and of immunological studies in humans and in experimentally infected murine inter-

mediate hosts has allowed a rather comprehensive picture to emerge during the last decade, and may apply to other situations of parasite infection or to other types of host-pathogen interactions, such as allergy.

Host-Parasite Interplay in Echinococcosis: A Mitigated Th1 and Th2 Response

What Have We Learned From Follow-Up of Patients and From Mass Screenings?

In both cystic and alveolar echinococcosis in humans a wide spectrum of clinical presentations of the diseases do occur, from latent and spontaneously cured cysts/lesions to very aggressive forms of the disease, with fast growth of the parasite larvae in the primarily infected organ, invasion of neighboring organs/tissues, and distant locations (metastases) (1). Both *Echinococcus* sp. infections clearly belong to "polar diseases" as was described in leprosy, tuberculosis, or leishmaniasis. In addition, in AE, until the beginning of the 1980s, every exposure to *E. multilocularis* oncospheres was believed to be followed by larval development and by occurrence of the disease described as "alveolar echinococcosis." The implementation of mass screenings in endemic areas has revealed that the number of established infections in humans was far lower than the number of exposures to parasitic eggs (3–5). In fact, positive serological results in individuals living in endemic areas (i.e., subjects with specific antibodies against *E. multilocularis*) have been shown to account for at least four different situations: (1) "patent," overt disease with symptoms; (2) "latent," nonapparent disease; (3) calcified dead lesions in the liver; and (4) no apparent lesions (4,5). Surgical and pathological assessments of calcified lesions have demonstrated the parasitic nature of these lesions (3), and the clustering of subjects with specific antibodies in those areas where the number of "patent" cases was highest strongly suggests that these subjects actually had contacts with

the parasite in the previous years (4). Abortive cases of AE, i.e., spontaneously healed lesions after *E. multilocularis* infection, seem the rule in humans, and progressive, active AE appears now as the exception, accounting for only 10% of exposures (6,7). The conceptual consequences of these findings are the following: besides potential nonimmunological factors that can kill the oncospheres before their penetration through the intestinal barrier, natural mechanisms of defense are at work in the majority of human hosts. These natural defense mechanisms are able to stop the larval growth either after the beginning of its development in the liver (as exemplified by the "aborted" calcified liver lesions found in some subjects), or at the very first stages, during or after the parasite penetration of the intestinal mucosa.

What Do We Learn From Clinical, Biological, and Pathological Features of Echinococcosis?

Allergic reactions and anaphylaxis are well-known features of CE (1). Elevated total IgE as well as occurrence of specific IgE against *Echinococcus* antigens in the serum of patients with CE are also key biological features of the disease (8–10). IgE-dependent immune reactions were long neglected in AE: obviously, anaphylactic reactions are far less frequent than in CE (1,11). However, specific IgE antibodies against *E. multilocularis* antigens may be found in patients with AE (12,13), and histamine release from circulating basophils stimulated with *Echinococcus* antigens is a constant immunological feature of patients with AE (12). These observations clearly show that Th2-related immune response is operating in echinococcosis, and this apparently makes it similar to other helminth diseases (14).

When the hydatid cyst is established, cell infiltrate or granuloma is no longer visible around the cyst, which appears to be clearly separated from the adjacent liver or lung parenchyma (1). Conversely, the pathological features of the lesions induced by infection

with *E. multilocularis* larvae are very suggestive of a cellular immune response. The periparasitic granuloma is made up of T lymphocytes, macrophages (epithelioid cells and giant cells) that surround the parasitic vesicles and lead to the development of an irreversible fibrosis composed of highly cross-linked collagens in humans (11,15–18) as well as in rodent intermediate hosts (19). The relative ratio of T lymphocyte subsets in the liver affects the efficiency of the granuloma and thus the outcome of infection. A relatively high number of CD4⁺ T cells within the granuloma was associated with aborted or slow progression of the larva, while CD8⁺ T cells were predominant in inefficient granulomas in severe cases (20). In humans, too, a strong lymphocyte proliferation can be elicited following stimulation of peripheral mononuclear cells (PBMC) with *E. multilocularis* antigens, especially in patients with aborted lesions (21,22). Single T cells do react specifically with nonfractionated protein from *E. multilocularis* (23); and increased plasma level of IL-2 receptor α chain/CD25 is correlated with the volume of the lesions (24). Necrosis that is, with fibrosis, the second hallmark of the pathological findings and a source of clinical complications seems to be due both to the direct cytolytic effect of the larva or larval products and to a cytotoxic component of the cellular immune response, especially through TNF- α synthesis (25).

Relationship Between Resistance/Susceptibility and Host Immunity

Comparison between susceptible and partially resistant strains of mice has shown that the immune response developed against *E. multilocularis* differs in these strains. Cellular immune response against parasitic antigens is stronger in infected resistant mice, tested either using specific delayed-type hypersensitivity reactions in vivo (26) or specific proliferation of lymphocytes in vitro (27). Resistance is increased by stimulation of cellular immune response: BCG administration in mice (28) and

Isoprinosine® treatment in humans (2). Impairment of cellular immunity is followed by an increase in susceptibility to *E. multilocularis* in experimental animals and by a more rapid and severe course of the disease in humans. This was shown as early as in the 1970s in immunosuppressed mice by Baron and Tanner (29), and further demonstrated later on using SCID mice, which were shown to be highly susceptible compared to the wild strain and to reconstituted mice (30), as well as in mice treated with cyclosporin (31). Liver transplantation, which has been proposed in very severe cases of AE since 1986, was a nearly experimental way of demonstrating the same increase in susceptibility in humans. Rapid increase in size of lung metastases, development of brain metastases, late reinvasion of the transplanted liver by parasitic cell remnants, and even early reinvasion of the transplanted liver within 3 wk from a spleen metastasis have been related to the therapeutic immunosuppression after liver transplantation (32–34). One case of co-infection by *E. multilocularis* and human immunodeficiency virus (HIV) has been reported, with a rapid and irreversible growth of *E. multilocularis* larvae in a young patient (35). Other cases have been observed in several European countries since then (EurEchinoReg network, personal communication). Echinococcosis thus appears to be another example of “opportunistic infection.”

Progressive Forms of Echinococcosis Associated With Th2 Cytokine Profile

As expected, and in agreement with the marked IgE humoral immune response and allergic reactions to hydatid fluid, cytokines found either in the supernatant of PBMC stimulated by specific echinococcal antigens or in the serum of patients with CE were mainly of the Th2 type, including IL-4 and IL-5 (36,37). High levels of IL-4 were especially found in patients with complicated or severely progressing disease (37,38). Unexpectedly, however, studies of cytokine secretion by PBMC

have shown that, in patients with AE, despite the pathological observations that suggest involvement of cellular immunity, in addition to a relatively low level of secretion of IFN- γ , IL-5 was also induced by parasitic antigens (39,40) and was very specifically produced by CD4 T lymphocytes (40). In mice experimentally infected with *E. multilocularis*, three stages of cytokine secretion could be identified: (1) a first stage of Th1 cytokine secretion including IL-2 and IFN- γ , associated with a slow parasite growth; (2) a second stage characterized by a mixed secretion of Th1 and Th2 cytokines, especially IL-5 and IL-10, associated with a rapid parasite growth; and finally (3) a last stage of immune suppression with a nearly complete inhibition of lymphocyte proliferation and of cytokine secretion following specific or nonspecific stimulation (41).

Tolerance State Associated With IL-10 Secretion in Echinococcosis

Spontaneous secretion of IL-10 by the PBMC is the immunological hallmark of patients with progressive forms of AE (40); conversely, IL-10 is significantly lower in patients with abortive lesions (42). Similarly, in CE, serum IL-10 decreased in all patients who responded to albendazole treatment and increased in patients who did not (37). A variety of cell types are involved in the secretion of IL-10 by resting and stimulated PBMC in patients with AE, especially CD4 and CD8 T cells, but also non-T non-B cells (40). “Suppressor” CD8 T cells, induced by parasitic products, were reported to be involved in tolerance to *E. multilocularis* (43); the relationship between the capacity of these cells to secrete IL-10 and their “suppressor” activity is unknown. The anti-inflammatory properties of IL-10 are well-known, especially through the inhibition of macrophage activation and cytotoxic functions (44). The crucial role of macrophages in the effector phase of the immune responses toward *E. multilocularis* has been reported, and their stimulation results in enhanced parasite killing

and protection of the host (45,46). On the other hand, an impairment of chemotactic and phagocytic properties of cells of the phagocytic system has been shown in *E. multilocularis* hosts (47–49); this suggests that anti-inflammatory effects, mediated by cytokines, are actually operative at the systemic level. A preliminary report has confirmed that locally, in the periparasitic granuloma, T cells secreted IL-10 and the data suggest that IL-10 production is highest closer to the parasitic vesicles (50). Contact inhibition of effector macrophages could be induced either through this anti-inflammatory cytokine secretion or, more directly, through the contact between the parasitic cells and/or the laminated layer. Analysis of the cell surface markers of the epithelioid macrophages lining the parasitic vesicles in humans has shown a very unusual expression of these markers, particularly a high expression of CD25, the inducible α chain of the IL-2 receptor, a chain usually expressed only by activated T cells (25). Such an abnormal expression of CD25 has been shown in other granulomatous diseases and could be related to a particular functional state of the macrophages.

Several experiments have suggested that *E. multilocularis*, either by cell–cell contact or by its products, could inhibit and/or modulate the immune response at the very early stage of antigen presentation to T cells. *E. multilocularis* was shown to modify the accessory cell function and interfere with antigen presentation through a parasite-derived macrophage modifying factor (51). Similar interference has been reported using various species of cestodes, including *E. granulosus* (51,52). It was shown that immature dendritic cells of human origin did not mature and had a reduced capacity to take up dextran via mannose receptors in the presence of crude nonfractionated *E. multilocularis* antigen; however, further maturation could be induced by proinflammatory cytokines. These mature dendritic cells, pulsed with *E. multilocularis* antigen, were slightly better inducers of T-cell proliferation than nonpulsed

dendritic cells (53). Finally, a particular role for the laminated layer—which is secreted by the metacestode at a very early stage of its development—and for its nonproteic carbohydrate components has been evoked (54). In addition to a “barrier” effect that could prevent immune recognition by the surrounding T cells, the carbohydrate components of the laminated layer could be involved in the modulation of antigen recognition, T-cell activation, and cytokine production locally and, thus, in the subsequent diversion of the immune response toward a tolerant stage mediated by Th2 cytokines and IL-10. Other noncarbohydrate parasitic products could also be involved. A differential capacity to modulate IL-10 secretion and other aspects of the immune response has been ascribed to various antigenic preparations from *E. multilocularis*, especially the alkaline phosphatase of the parasite (42).

Immunogenetic Correlates in Alveolar Echinococcosis

A European study of 150 AE patients has shown a significant association between HLA DR 11 and protection, HLA DPB1*0401 and susceptibility, and HLA DR3 and DQ2 and severe clinical evolution of the disease (55). The HLA B8, DR3, DQ2 haplotype is observed with an unusual frequency in patients with autoimmune diseases, characterized by an increased and inappropriate humoral immunity and a relatively inefficient cellular immune response (56,57). In fact, studies on cytokine secretion by PBMC from HLA DR3+, DQ2+ patients with AE, compared with patients without this HLA haplotype, have shown that the spontaneous secretion of IL-10 was much higher in HLA DR3+, DQ2+ patients (58). A limited number of family cases have been observed in endemic areas; preliminary data indicate that relatives with progressive forms of *E. multilocularis* infection shared both HLA haplotypes and the associated clinical presentation of the disease (59). Other genes within the MHC that are known to be related to the initiation and/or the

effector phase of the immune response could also be involved; some of them were studied, such as the TNF gene and the MHC class 1 transport-associated protein (TAP) gene. No significant correlation was observed between occurrence and/or severity of the disease and polymorphism in the TNF promoter gene. However, 63% of 94 patients with AE from the same European endemic area as mentioned above had the homozygote Thr-Thr form of the TAP2 665 codon site, vs 45% of controls (60). The association between TAP2 polymorphism and AE was particularly significant in patients with severe disease and was not related to a linkage disequilibrium with HLA DR3. Its immunological significance, if any, is unknown; it could be related to the unexpected and characteristic infiltration of the lesions by CD8 T cells (20,61) and to the possible role of these cells in immune suppression and in the maintenance of IL-10 secretion at the proximity of the lesions, and thus in the mechanisms of tolerance.

Modulation of Host's Immune Response to Prevent Echinococcosis and/or Its Complications?

As it has been proposed in atopic diseases that share many characteristics with echinococcosis, immune modulation could be used in patients with echinococcosis in order to reverse the cytokine profile and thus make the immune response more effective. IFN- γ has been used in a limited number of patients with AE. Two reports have been published that show temporary stabilization of the lesions, with a satisfactory tolerance of the drug (62,63); prolonged administration of IFN- γ , however, was not able to reverse the abnormal Th2 profile in the treated patient (63). In one patient with AE whom we treated with IFN- α because of a concomitant HCV hepatitis, we observed a decrease in the size of the lesions and a shift in the cytokine profile toward Th1 (64). Very encouraging results have been obtained in mice treated with IFN- α 2a at the time of experi-

mental infection, with a total protection against parasitic growth in 5 of 12 infected mice, a marked reduction of larval lesions in 7 of 12 mice, and a significant modulation of cytokine secretion (significant decrease in IL-10 and IL-13 by peritoneal macrophages and spleen cells) and effector cell functions (significant increase in phagocytic and killing capacities of macrophages) (49). These results are opening new perspectives in the treatment of this very severe disease.

Echinococcosis, IgE, and Allergy

Clinical Allergy and Anaphylactic Reactions in Cystic Echinococcosis

Anaphylactic reactions have been reported in cystic echinococcosis for several decades (1) and are usually observed in case of overt or unapparent rupture of the parasitic cyst. Unusual locations or circumstances make that such events are still regularly published in the medical literature. A variety of allergic symptoms has been described in patients with CE. They include urticaria that may be only mild (65) or present as chronic and apparently "idiopathic" urticaria (66), or as giant urticaria associated with systemic signs and symptoms (67). Respiratory symptoms may also be observed: asthma may be the first manifestation of hepatic hydatidosis (68) and acute bronchospasm may occur when the cyst is manipulated at surgery (69). Anaphylactic shock is the most impressive and severe clinical presentation of IgE-dependent allergic reactions in CE. It may occur apparently spontaneously and precede any other symptoms (70–72). Recurrent life-threatening anaphylactic shocks, with or without laryngospasm, may be due to small, incomplete rupture of the cyst (73,74). In a series of 502 patients operated on in Bulgaria, 61 (12%) had a variety of clinical symptoms of allergy before surgery (75). Such unusual presentations of CE through allergic/anaphylactic reactions in otherwise asymptomatic patients, without known precipitating factors,

emphasize that, in endemic regions or if patients from endemic regions are concerned, physicians should keep a high suspicion for hydatid disease as a possible etiology for seemingly idiopathic anaphylactic reactions. Overt rupture of the cyst, however, is a much more frequent cause of anaphylaxis: it may be observed after trauma, even trivial, such as that from a sport (football) accident (76). The most usual circumstance is surgery, however (75), even in the immediate postoperative period (75,77), or laparoscopy (78). As for other etiologies of anaphylactic shock, tryptase measurement is of help for diagnosis (79). A combination of preoperative histamine H1 and H2 receptor blockers has been shown to lessen the hemodynamic changes that are usually observed in operations for hydatid cysts (80) but the usefulness of any preoperative treatment for the prevention of anaphylactic shock has never been demonstrated.

Cyst Puncture and Anaphylaxis in Cystic Echinococcosis

Anaphylactic reactions, and especially shock with fatal outcome, that might occur when cysts rupture and/or when they are surgically manipulated or opened have led to the prohibition of any puncture of hydatid cysts for decades. The dogma “never puncture a hydatid cyst” is, however, no longer valid (81). Since the first attempts in the middle of the 1980s (82,83), PAIR (i.e., **p**uncture, **a**spiration, **i**njection, **r**easpiration) procedure has become a validated alternative to surgical treatment of CE (1,81,84–87). It can be used in inoperable cases of CE, in patients who refuse surgery, in cases of relapse after surgery, or in failure to respond to chemotherapy; it is a simpler and safer procedure than surgery in developing countries, especially after mass screenings using ultrasound examination (88). Cysts must be carefully selected for PAIR treatment—i.e., liver cysts of types I and III, according to Gharbi classification (89), and CE1 and CE2 in the WHO-IWGE consensus classification (1,81)

without communication with the biliary tree. The procedure must be associated with benzimidazole treatment (1,81). Technical precautions are important. The critical point is the angle of puncture; normal liver parenchyma must be present between the puncture point and the surface of the cyst to avoid leakage of cyst fluid (prevention of anaphylactic reactions) and spillage of protoscoleces (prevention of recurrences). Direct puncture of a cyst close to the abdominal wall must be avoided and epinephrine, hydrocortisone, and basic resuscitation equipment have to be readily available when PAIR is performed (1,81). Allergic symptoms may indeed occur during this procedure and several instances of anaphylactic shock have been observed, with a few fatalities; they are, however, less frequent than during surgical operations. In a recent published series of 84 hepatic cysts punctured in 61 patients, 5 developed urticaria and 2 an anaphylactic reaction that was successfully treated (90).

Clinical Allergy and Anaphylactic Reactions in Alveolar Echinococcosis

In AE, the low rate of anaphylactic symptoms (11,12) could be related to a more “masked” form of *Echinococcus* antigens in patients with AE than in those with CE: the extremely fibrotic lesions of AE cannot rupture, and the echinococcal fluid may never be in contact with mast cell-bound IgE. In fact in rare patients with allergic symptoms in AE, anaphylactic manifestations occurred while parasitic cells were migrating to other organs than the liver and were eventually leading to metastases, especially through pulmonary embolism (12).

Echinococcosis and IgE Antibodies

Depending on the location of the cyst (lung versus liver) and/or the technique, *E. granulosus*-specific IgE is present in 25% to 75% of patients with CE; using appropriate techniques, specific IgE against AgB, Ag5, or recombinant antigens is present in more than

three fourths of patients (1,91,92). Total IgE and specific IgE against *E. granulosus* antigens are more elevated when cysts are multiple, when they are located in the central part of the liver, and when they contain daughter cysts (93). IgE and IgG4 levels significantly correlate with IL-5 production (94); however, in the same study, high eosinophil count did not correlate with high IL-5 levels. A positive correlation was found between IgE levels and severity of the disease and/or progression/regression after treatment (9,10,93). The decrease of specific IgE after complete surgical removal of the cyst(s) is slow: measurable serum-specific IgE is found in 55% of patients 1 yr after surgery (8). Specific histamine release by circulating basophils stimulated with *E. granulosus* antigens is present in 100% of patients (95).

In AE, despite the rare occurrence of allergic symptoms, total and specific serum IgE (using a RAST technique with *E. granulosus* antigen) are elevated in 50% of the patients and specific IgE-dependent stimulation of peripheral basophils by *E. multilocularis* antigens in vitro may be found in all patients (12). Using the Pharmacia CAP technique with *E. multilocularis* antigen, serum-specific IgE may be demonstrated in two thirds of patients with AE (13). Total IgE and specific IgE and IgG4 against *E. multilocularis* antigens are highly elevated in those patients with the most aggressive disease (9). Disappearance of IgE and decline of IgG4-specific antibodies have been shown to be significantly associated with regression of the lesions in patients treated with antiparasitic drugs, and both Th2-related antibody isotypes are the first to disappear after surgical cure (96,97); this represents indirect evidence of the prominent stimulation of Th2 cytokines by the viable parasite.

Characterization of *Echinococcus* sp. Allergens

Echinococcus allergens, i.e., those specific antigens from *Echinococcus* that are able to induce IgE secretion, have especially been

studied for *E. granulosus*. They may be found among the main *E. granulosus* well-known antigens used for diagnosis (AgB and Ag 5) as well as among less-studied antigens; however, they all share common characteristics with environmental allergens: they are well-conserved proteins all along the evolution of species, with major enzymatic or transport properties. AgB is a 12-kDa subunit with protease inhibitor properties and a potent Th2 inducer. Patients' PBMC stimulated with AgB produce IL-4 and IL-13 but do not produce IL-12; AgB especially skews the Th1/Th2 ratio toward a preferentially immunopathology-associated Th2 polarization in patients with progressive diseases (98). Serine protease properties have been assigned to Ag 5, which also induces IgE production (99). By immunological screening of a cDNA library derived from protoscoleces of *E. granulosus* using IgE from patients with CE and allergic manifestations, Ortona et al. (100) have isolated a protein, EA 21, with close homology with *Malassezia furfur* cyclophilin allergen (Mal f 6), with human cyclophilin, and also with cyclophilin of *Schistosoma japonicum* (101). Amino acid sequence homology between cyclophilin and a cDNA-cloned antigen of *E. granulosus* had already been disclosed in 1989, but the immune properties of the parasite cyclophilin was not studied at that time (102). Immunoblotting analyses showed that serum IgE-binding reactivity of EA 21 differed significantly in patients with and without allergic reactions (80% vs 27% respectively); conversely, 20% of patients with allergic manifestations, and 63% who did not, had specific IgG4 and total IgG to EA21 (100). EA 21 induced a proliferative response in 80% of patients' PBMC regardless of the allergic manifestations, but, unexpectedly, it induced no IL-4 production. In this study, the IgE-positive reaction to EA21 in 2 atopic subjects who had polyspecific allergic reactions, including skin-prick test reactions to birch pollen, suggest the presence of crossreactive epitopes between *E. granulosus* cyclophilin and birch cyclophilin (Bet v 7). This possible cross-reaction needs to be confirmed

in the future, using a larger panel of polyspecific or monospecific sera from allergic subjects.

Another major cross-reacting allergen found in protoscoleces and hydatid fluid of *E. granulosus* is an elongation factor 244 residues long with a predicted molecular mass of 31 kDa: Eg EF-1 β/δ (103). Serum IgE-binding reactivity to Eg EF-1 β/δ differs significantly in patients with and without allergic reactions since 90% of sera from patients with a history of allergic reactions bind Eg EF, whereas only 52% of sera from patients without such a history do not (104). Eg EF-1 β/δ induces PBMC proliferation in a majority of patients with CE, irrespective of the allergic manifestations, and skews Th1/Th2 cytokine activation toward a preferentially Th2 polarization (104). Eg EF-1 β/δ has a strong homology with a *Strongyloides stercoralis* EF: epitope mapping has identified an immunodominant epitope of 18 residues with 78% identity and 89% similarities between *E. granulosus* and *S. stercoralis* IgE-immunoreactive antigens. Cross-reactivity between allergens from various species and even genera or families among parasites has often been stressed. Like elongation factors, paramyosins could also be cross-reacting allergens with epitopes specific for platyhelminthes. It has been shown that the target molecule of SJ18 ϵ 1, a monoclonal IgE antibody to *Schistosoma japonicum* that induces significant protection toward a challenge infection, was a paramyosin and that the target epitope was common among paramyosins of *S. mansoni*, *Taenia solium*, and *E. granulosus* (105). Cross-reactivity with more distant molecules is suggested by the recent clinical observation of IgE-mediated anaphylaxis to Thiomucase®, a mucopolysaccharidase of sheep origin, used in the treatment of joint disorders (106). In this patient treated with Thiomucase, positive prick tests and specific IgE were found using BSA, cat, and sheep allergens, but also *E. granulosus* extracts. Cross-reactivity was demonstrated by a positive inhibition (54%) of an *E. granulosus* CAP assay by Thiomucase. Although the molecular basis of such a cross-reaction is unknown, this

observation suggests that *Echinococcus* sp. may share epitopes with enzymes of nonrelated origin and that such cross-reactions might have clinical significance.

Conclusion

Besides such anecdotal reports, partial identities of *Echinococcus* allergens with a variety of molecules well known to promote a Th2 cytokine profile, to induce IgE synthesis, and, in appropriate situations, to trigger clinical allergic reactions raises the question of the intrinsic nature of allergens, of the common features of helminthic and allergic diseases, and of the significance of IgE production in such diseases. In several helminthic diseases, IgE has been shown to be involved in the protection of the host against the parasitic agent. This is particularly true in intestinal nematodes, has been convincingly demonstrated in schistosomiasis, and can be suspected in cestode infection at the adult stage (14,107). In larval cestodosis, however, protective function has never been evidenced for IgE, either clinically or experimentally. Conversely, the Th2 cytokine profile specifically promoted by parasitic components and/or by the particular environment of parasitic antigen presentation at the very early stage of the larval development appears to be essential in protecting the parasitic larva against the killing effects of the Th1-related effectors of the host's immune response, and thus in the development of a disease state (2). IgE secretion and IgE/mast cell effector functions might well thus be regarded as a "side effect" of the imbalanced Th2 cytokine secretion; this situation is quite similar to that observed in allergic diseases. Finally, several reports suggest a negative correlation between parasitic and allergic/atopic diseases in the population (108). Association of allergic/atopic diseases with either CE or AE has received very little attention and could be fruitfully studied to confirm the hypothesis of the intervention of a robust anti-inflammatory net-

work by persistent immune challenge, with IL-10 as a key factor, to prevent the occurrence of allergic reactions in patients with parasitic infections (108).

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