Can cystic echinococcosis trigger autoimmunity?

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Cystic echinococcosis (CE) is a zoonosis and disseminated disease in worldwide caused by larval stage of Echinococcus granulosus. Little is known about parasitic molecules that behave like immunomodulatory antigens and the mechanisms that they use to evade the host’s immune response. Some authors suggested that immunomodulatory antigens of E. granulosus can directly inhibit the basic immune cell functions and stimulate the immune molecules for the development of CE. We aimed to evaluate the role of parasitic molecules of helmint E. granulosus and also evaluate the link between immunomodulatory effects of these molecules and autoimmunity etiopathogenesis of the host by serology. Twenty-eight non-operated patients with hydatid cysts (NOP) and 88 operated patients with hydatid cysts (OP) were included as study group and 54 healthy individuals with no known chronic diseases were included as control group in this study. The presence of ANA (Anti nuclear antibody), ASMA (Anti Smooth Muscle Antibody) and AMA/LKM (Anti Mitochondrial Antibody /Liver Kidney Microsomal Antibody) antibodies which were known as autoimmune parameters were investigated for all of the groups by using Indirect Fluorescent Antibody (IFA) kits (Euroimmune Labor Diagnostica, Germany). The ages of patients were between 16 - 83 years old and patient and control groups were matched for age and gender. Patients with positivity in at least one out of three tests were considered positive for autoimmunity. The antibodies were detected in 16(57,1%), 32(36,3%) and 12(23%) of NOP, OP and control groups, respectively It was detected a statistically higher significant difference between NOP and healthy controls (p < 0.01). No statistically significant difference was detected between OP and healthy controls (p > 0.05). No statistically significant difference was detected between OP and control groups, but we detected a moderately higher positivity in results of OP. It was detected a statistically significant difference between all of the patient groups (patients with NOP and OP) and control group (p < 0.05). As a result, detection of high autoantibodies in NOP regarding to our results suggested us, these chronic long-lasting disease process together with their immunoregulatory molecules may activate unknown autoimmune mechanisms of the host and lead to formation of autoimmunity. We also suggest that the decrease of autoantibodies in OP may be caused by the absence of antigenic stimulus originated from hydatid cysts.

Key words: Cystic echinococcosis; Echinococcus granulosus, ASMA; ANA; AMA/LKM, autoimmunity.

INTRODUCTION

Cystic echinococcosis (CE) is a widely zoonosis in worldwide caused by the larval stage of Echinococcus granulosus and affects humans and livestock species with economic burden. CE is also causes a major public health problem. There are many species in Echinococcus genus and E. granulosus and E. multilocularis are the most prevalent species as the causative agent of CE and alveolar echinococcosis, respectively (Eckert et al., 2000; Sadjjadi, 2006; Dalimi et al., 2002; Merdivenci, 1963; Unat et al., 1995). CE is transmitted through the gastroin-
This study was carried on with three different groups in Istanbul Cerrahpasa Faculty of Medicine and General Surgery Policlinics of Istanbul University, General Surgery and Microbiology Departments of Cerrahpasa Faculty of Medicine and General Surgery Policlinics of Istanbul Education and Research Hospital between October, 2008 - July, 2009. Twenty eight (18 females and 10 males) non-operated patients with hydatid cysts (NOP) and 88(50 females and 38 males) operated patients with hydatid cysts (OP) were included as study groups. 54 healthy individuals with no known chronic diseases were included as control group in this study.

We aimed to evaluate the role of parasitic molecules of helminth E. granulosus and also evaluate the link between immunomodulatory effects of these molecules and autoimmunity etiopathogenesis of the host by serology.

**MATERIAL AND METHODS**

This study was carried on with three different groups in Istanbul University, General Surgery and Microbiology Departments of Cerrahpasa Faculty of Medicine and General Surgery Policlinics of Istanbul Education and Research Hospital between October, 2008 - July, 2009. Twenty eight (18 females and 10 males) non-operated patients with hydatid cysts (NOP) and 88(50 females and 38 males) operated patients with hydatid cysts (OP) were included as study group and 54 healthy individuals with no known chronic diseases were included as control group in this study.

The presence of ANA (Anti nuclear antibody), ASMA (Anti Smooth Muscle Antibody) and AMA/LKM (Anti Mitochondrion Antibody/Liver Kidney Microsomal Antibody) antibodies which were known as autoimmune parameters were investigated for all of the groups by using Indirect Fluorescent Antibody (IFA) kits (Euroimmune Labor Diagnostica, Germany). The positivity criteria for ANA, ANA/LKM and ASMA are ANA ≥ 1/40, ANA/LKM ≥ 1/100 and ASMA ≥ 1/100. The ages of the patients and control group individuals were between 16-83 and patient and control groups were matched for ages and gender. Patients with positivity in at least one out of three tests were considered positive for autoimmunity.

**RESULTS**

Autoantibodies were detected in of 16 (57%), 32 (36.3%) and 12 (22.2%) of NOP, OP and control group individuals, respectively. It was found a statistically significant difference between NOP and control group (p < 0.01). We did not find a statistically significant difference between OP (p > 0.05) but the positivity in the operated patients was higher. A statistically significant difference was found for total cystic hydatid groups (active+inactive) against control group (Table 1).

### Table 1. Autoantibody distribution of NOP, OP and control group individuals.

<table>
<thead>
<tr>
<th>Patient and Control Groups (n=170)</th>
<th>ANA</th>
<th>ASMA</th>
<th>AMA/LKM</th>
<th>ANA + ASMA</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-operated patients (n = 28)</td>
<td>10</td>
<td>35.7</td>
<td>2</td>
<td>7.1</td>
<td>2</td>
</tr>
<tr>
<td>Operated patients (n = 88)</td>
<td>24</td>
<td>27.2</td>
<td>8</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>Control group (n = 54)</td>
<td>8</td>
<td>15.4</td>
<td>0</td>
<td>4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Non-operated Patients X Control Group: p < 0.01
Operated Patients X Control Group: p > 0.05
Non-operated Patients + Operated Patients X Control Group: p < 0.05.

**DISCUSSION**

The prolonged survival of E. granulosus within the human host indicates that some mechanism is operating to permit parasite evasion of the host immune response. Several publications have described autoimmune phenomena in patients infected with hydatid cysts (Colebrook and Lightowlers, 1995). The hydatid cyst secretes and exposes numerous immunomodulatory molecules to the host’s immune system. Chronic nature of E. granulosus infection involves the immunoregulatory molecules that directly suppress the function of certain immune cell subsets and stimulate other cell populations related to human CE disease. (Siracusano et al., 2008). Researchers, have identified and characterized a number of E. granulosus antigenic molecules including: antigen 5 (Capron et al., 1967), antigen B (AgB) (Williams et al., 1971), Eg95 (Lightowlers et al., 1996), EgA31 (Fu et al., 1999), elongation factor b/d (Margutti et al., 1999), cyclophilin (Ortona et al., 2002), EpC1 (Li et al., 2003), HSP70 (Ortona et al., 2003); EgTeg (Ortona et al., 2005) and TPx (Salinas et al., 1998).

Calreticulin (CRT) causes persistent infections and was expressed from cyst germinal layer and protoscoleces and it was suggested that CRT has some effects on the protoscolex infectivity. Calreticulin (CRT) is a well-conserved and highly pleiotropic protein, present in every cell of higher organisms, except erythrocytes. CRT is associated with lectin-like chaperoning, calcium storage and signaling, gene expression, phagocytosis of apoptotic cells, autoimmunity, antiangiogenesis and inhibition of tumoral growth, lytic activity of perforins from T and NK cells, and inhibition of C1q-dependent complement activity in vitro (Cabezón et al., 2008; Johnson et al., 2001; Michalak et al., 1999).
We suggest that humoral and cellular immunity mechanisms may be affected from the synthesis of proteins like CRT. These proteins may have responsibility for the modulation of immune response and infectivity of *E. granulosus* in non-operated cases having capability of producing protoscoleces and fertile *E. granulosus*. Thus, we detected autoimmune markers (ANA-ASMA) as statistically significant higher in NOP than control group. Because these proteins may modulate both innate and adaptive host immune responses, AgB plays a prominent role in the immunomodulatory mechanisms that *E. granulosus* uses to develop progress and cause chronic disease (Siracusano et al., 2008b). To survive in host tissues the parasite must be able to adapt metabolically to the host microenvironment and plentiful AgB in hydatid cyst fluid probably guarantees parasite survival. (Zhang et al., 2003; Siracusano et al., 2008a). 12 kDal sub-unite of AgB has similarities to the serine protease inhibitors and inhibits neutrophile chemotaxis with a strong chemo-attractant activity (Shepherd et al., 1991). Cyst fluid extracting during immune response may activate neutrophiles and help releasing of protoscoleces and cause the development of secondary cysts (Rigano et al., 2001). Rigona et al. (2004) reported that AgB significantly inhibited polymorphonuclear cell (PMN) recruitment but left their random migration and oxidative metabolism unchanged. They also produced significantly lower IFN-γ concentrations. Patients’ peripheral blood mononuclear cells (PBMC) stimulated with AgB produced IL-4 and IL-13 but did not produce IL-12. These findings confirm that AgB plays a role in the escape from early immunity by inhibiting PMN chemotaxis. They also add new information on the host-parasite relationship, suggesting that AgB exploits the activation of T helper cells by eliciting a nonprotective Th2 cell response in patients with progressive disease. Kanan and Chain (2006) reported that the monocyte precursors were not differentiated when purified AgB and crude hydatid cyst fluids were contacted with dendritic cells (DC) of host and Ag B has a critical role in the interactions of DC subsets with *E. granulosus*.

Rigano et al. (2007) suggested that *E. granulosus* AgB interferes with host DC functions through two strategies. First, it impairs monocyte precursor differentiation into iDCs (immature dendritic cells), rendering them unable to mature when they are stimulated with LPS. Even though suppressing monocyte differentiation alone might be sufficient to prevent or impair the host immune response, AgB also modulates sentinel DC maturation, priming DCs to polarize lymphocytes into Th2 cells that benefit the parasite. Their another distinct finding for AgB was that it reduced LPS induced production of IL-12p70 but not LPS-induced production of IL-6, providing further evidence that this *E. granulosus* antigen actively modulates DC responsiveness in a manner favoring a Th2 outcome. These findings strengthen the hypothesis that AgB has direct anti-inflammatory effects on the innate immune response.

Kaufmann (1994) suggested that hsp 70 proteins of *E. granulosus* has epitope similarity with the host heat shock protein hsp 70 and may play a role in triggering of autoimmunity based on this antigenic mimicry. Even, Colebrook and Lightowlers (1995) did not detect a relationship between autoimmunity and cyst hydatid disease in a serological study, in some of the other studies, researchers detected that *E. granulosus* related immunomodulatory proteins like CRT, Ag B and hsp 70 have immunomodulatory effects for antigen-presenting cells like B and T lymphocytes, neutrophils and dendritic cells. A serious immunopathogenesis may be resulted from this immunomodulatory effects and other mechanisms like antigenic similarity and escaping from host immune system. We also detected significantly higher seropositivity for autoimmune markers in active NOP against control but this higher seropositivity was not found in OP against control However, we detected higher seropositivity for autoimmune markers in OP and a significantly higher seropositivity was detected for total cystic hydatid groups (active-inactive groups) against control group.

As a result, detection of high autoantibodies in NOP regarding to our results suggested us, these chronic long-lasting disease process together with their immunoregulatory molecules may activate unknown autoimmune mechanisms of the host and lead to formation of autoimmunity. We also suggest that the decrease of autoantibodies in OP may be caused by the absence of antigenic stimulus originated from hydatid cysts.

**SUMMARY**

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REFERENCES


