Clinical and Immunologic Evaluation of 31 Patients with Acute Schistosomiasis mansoni

Amelia Ribeiro de Jesus,1 Angela Silva,2 Luciana B. Santana,2 Andrea Magalhães,1 Adriana Almeida de Jesus,1 Roque Pacheco de Almeida,1 Marco A. V. Régo,1 Marcelo N. Burattini,3 Edward J. Pearce,2 and Edgar M. Carvalho1

1Serviço de Imunologia, Hospital Universitário Prof. Edgard Santos, Universidade Federal da Bahia, Bahia; 2Departamento de Doenças Infecciosas, Universidade Federal de Sergipe, Sergipe, and 3Serviço de Doenças Infecciosas, Universidade Federal de São Paulo, São Paulo, Brazil; 4Department of Microbiology, Immunology, and Parasitology, Cornell University College of Veterinary Medicine, Ithaca, New York

Thirty-one patients with acute schistosomiasis were evaluated clinically and immunologically. Cytokine levels were determined in peripheral blood mononuclear cell (PBMC) supernatants. Levels of total and antigen-specific IgE, tumor necrosis factor (TNF)–α, and immune complexes were measured in serum samples. Clinical findings included general symptoms, liver damage, pulmonary involvement, and pericarditis. All patients had eosinophilia. Immune complexes were detected in 55% of the patients (mean ± SD, 7.8 ± 7.6 μg Eq/mL) and were associated with cough, dyspnea, and abnormal chest radiographic findings. Levels (mean ± SD) of TNF-α (1549.3 ± 767.6 pg/mL), interleukin (IL)–1 (2683 ± 1270 pg/mL), and IL-6 (382 ± 52.3 pg/mL) were elevated in PBMC. Serum TNF-α levels were elevated in 87% of the patients and were associated with abdominal pain. Higher interferon-γ levels were detected in PBMC of patients with acute disease than in those of patients with chronic schistosomiasis; IL-5 levels were higher in those with chronic disease. Low IL-5 levels were associated with weight loss. Proinflammatory cytokines and immune complexes with low Th2 responses might explain the immunopathogenesis of acute schistosomiasis.

Schistosoma mansoni produces 4 clinical conditions: acute disease and 3 chronic forms (intestinal, hepatointestinal, and hepatosplenic) [1, 2]. Although the chronic disease is the main cause of morbidity in endemic regions, the acute disease is more severe, and death has occurred in China in patients with acute S. japonicum infection [3–7]. Acute schistosomiasis due to S. mansoni infection is less severe and has been described as a toxemic syndrome that occurs 6–8 weeks after initial infection, manifested by unspecific symptoms, respiratory distress, and eosinophilia [8–13].

The pathogenesis of acute schistosomiasis has not been established. The co-occurrence of eosinophilia and respiratory distress suggests the presence of an immediate hypersensitivity reaction [3, 12, 13]. Lawley et al. [14] detected immune complexes in 14 (93%) of 15 persons with acute S. mansoni infection, but no associations with clinical symptoms were detected. Hiatt et al. [15] found a correlation between severity of illness and intensity of infection and a correlation between immune complex levels and disease severity and intensity of infection [16].

The immune responses to pathogens have been defined better since the TH1-TH2 model of CD4 T helper cell differentiation has been understood. TH1 cells secrete interferon (IFN)–γ and interleukin (IL)–2 and promote cell-mediated immunity, whereas TH2 cells secrete IL-4, -5, -10, and -13 and provide B cells with help for antibody production [17, 18]. The immune responses to schistosome antigens in chronically infected mice and in humans with intestinal and hepatointestinal diseases are characterized by high IL-4 and IL-5 and low IFN-γ production, which indicates a predominant TH2-type immune response, although some investigators have found a preferential TH1-type immune response in patients with hepatosplenic disease (high TNF-α levels and low IL-5 levels in peripheral blood mononuclear cell [PBMC] supernatants) [19–23]. In acute schistosomiasis, a TH1-type response, recognized by production of IL-2 and IFN-γ, occurs in the first 5 weeks after infection in mice, before the adult worm releases eggs [24, 25].

In humans with acute schistosomiasis, higher IFN-γ and lower IL-5 levels are found in supernatants from PBMC than those found in supernatants from PBMC of patients with chronic disease [26]. Chronically infected patients from areas in which
schistosomiasis is endemic do not present with the toxemic symptoms of acute schistosomiasis. The acute syndrome affects persons not previously exposed to the parasite antigens, which suggests an important modulatory effect of the immune system in controlling the toxemic disease [2, 3, 13, 26]. However, the role of immune response in the pathogenesis of human acute schistosomiasis remains unclear.

In this study, we evaluated the immune responses of 31 patients with acute schistosomiasis who were exposed to the same water source of infection and for a similar time period. We correlated these responses with the patients’ clinical abnormalities. We also compared the immune responses of persons with acute schistosomiasis with those of chronically infected persons in an area in which schistosomiasis is endemic.

Subjects and Methods

Study subjects and clinical evaluation. Patients with acute schistosomiasis (n = 35) were recruited from Aracaju, the capital of Sergipe State, Brazil, from March through May 1999. Active case finding was done by 2 infectious disease physicians after the detection of acute schistosomiasis in 7 members of a family exposed to water in the same lake in Abaí’s, 55 km south of Aracaju. All patients were exposed to the same lake water. Abaí’s is a tourism area heavily visited during holidays by people from Sergipe, other Brazilian states, and foreign countries. The study population had high socioeconomic and nutritional status. Inclusion criteria were history of recent water contact in the Abaí’s lake, symptoms indicating acute infectious disease, and initial *S. mansoni* egg–negative stool examination results that became positive during the follow-up period. Exclusion criteria were any past diagnosis of or treatment for schistosomiasis. On the basis of these criteria, 4 patients were excluded from the study.

The remaining 31 patients had complete clinical examinations that included clinical history and physical examination, followed by laboratory evaluation that included Kato-Katz stool examination (a quantitative method for detection of *S. mansoni* eggs in stool samples), total and differential blood cell counts, analysis of liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyltransferase [γ-GT], and alkaline phosphatase [AP]), and analysis of urea, creatinine, and urine (biochemical and cellular components). Echocardiography, chest radiography, and spirometry tests were also performed. Patients were initially evaluated at 33–60 days after water exposure and were followed up once a week with clinical examination and stool examination, until the parasitologic results became positive for schistosome eggs. During this weekly follow-up, all clinical support was given to the patients until their major symptoms improved. They were also followed up at 5 and 12 months after study enrollment with clinical and laboratory examinations. All patients with *S. mansoni* eggs in stool were treated with oxamnique (15–20 mg/kg of body weight).

Twenty-one ethnically similar patients with chronic schistosomiasis, who are part of a cohort study in the endemic area of Caatinga do Moura, Bahia, were selected for comparison of their immune responses with those of the patients with acute disease. The patients with chronic disease were selected on the basis of presence of hepatic fibrosis (degree I or II), determined by abdominal ultrasonography according to the 1992 World Health Organization criteria [27]. Selection criteria for the control patients included similar ages and egg counts by Kato-Katz stool examination. The control patients were compared with those with acute schistosomiasis in all immunologic evaluations except total IgE. For analysis of total IgE, we included 45 serum samples obtained from patients with chronic schistosomiasis who were tested for total IgE 6 months before the acute-stage serum was tested. The patients with chronic schistosomiasis from the endemic area are treated every 3 years with praziquantel (30–50 mg/kg/body weight) per guidelines of the National Foundation of Health of Brazil.

Parasitologic methods. Parasitologic examinations were done by the Kato-Katz method [28–31], in which 42 mg of stool sample is examined and the results are multiplied by 24 to give the number of eggs per gram of stool. Two stool samples were collected from each subject at the first evaluation (33–60 days after water exposure) and each week thereafter until *S. mansoni* eggs were detected. The parasitologic examinations were usually positive 60–120 days after water exposure.

Antigens. The antigens used were soluble extracts of adult parasites (SWAP) and of parasite eggs (SEA) [32, 33].

Immunologic procedures. The immunologic evaluation was performed while the stool examinations were still negative for eggs. Blood samples were obtained from 13 patients 33–45 days after water exposure and from 18 patients 45–60 days after exposure. Eighteen patients still had symptoms when the blood samples were collected. Serum samples were aliquoted and were stored at −20°C for later evaluation of total and *S. mansoni*–specific IgE, TNF-α, and immune complex levels. Specific IgE to SEA was measured by ELISA, as described elsewhere [32, 34]. Forty-five stored serum samples from chronically infected patients who had intestinal or hepatointestinal forms of disease were used as controls for total IgE measurement. For SEA- and SWAP-specific IgE, the chronically infected patients were the same as those used as control patients for the evaluation of cellular immune responses.

Serum TNF-α levels were measured by using a commercial kit (R&D Systems) per the manufacturer’s instructions. The cutoff was 3 pg/mL (mean + 2 SD of the concentration obtained from a control group, selected from Brazilian *S. mansoni*–unexposed medical students and laboratory workers).

Circulating immune complex levels were determined with a Clq binding assay kit by following the manufacturer’s instructions (CIC-C1q; Buhlmann Laboratories). We expressed results in microgram equivalents per milliliter, based on a standard curve made with aggregated IgG. The cutoff was 3.2 μg Eq/mL.

The lymphoproliferative test was performed only in the patients with acute schistosomiasis, as described elsewhere [35]. In brief, PBMC were fractioned from total heparinized fresh blood by density gradient centrifugation (Histopaque 1077; Sigma Diagnostics). PBMC were collected from the interface and were washed 3 times with 0.9% saline. For lymphocyte proliferation, PBMC were adjusted to 10^6 mL in RPMI 1660 with glutamine and bicarbonate and were supplemented with 10% human AB serum. In all, 2 × 10^5 cells in 200-mL aliquots were incubated in 96-well flat-bottom plates, either without stimulus or stimulated with antigens SEA and...
SWAP (10 μg/mL) and mitogen pokeweed (1:100), and were cultured for 5 days at 37°C in a 5% CO₂ humid incubator. In the last 6 h, 1 μCi of [³H]thymidine was added to each well. Lymphocyte blastogenic data are shown as stimulation index (SI) = counts per minute of the stimulated culture divided by the counts per minute of the unstimulated culture.

The cytokine assay was performed as described elsewhere [32]. PBMC were adjusted to 3 × 10⁶ cells/mL in RPMI, and 1 mL was cultured in each well of 24-well plates, either without any stimulus or stimulated with SEA, SWAP, and mitogen phytohemagglutinin (10 μg/mL of each). Cultures were incubated for 24 h (IL-1 and IL-6) or for 72 h (IFN-γ, IL-5, IL-10, and TNF-α) at 37°C in a 5% CO₂ incubator. The supernatants from these cultures were used to measure the cytokine levels by sandwich ELISA, using commercial kits (IFN-γ and TNF-α, Genzyme Diagnostics; IL-5, Pharmingen; IL-1, -6, and -10, R&D Systems).

Statistical methods. IgE and cytokine levels of patients with acute schistosomiasis were compared with those of the patients with chronic infection, using the Mann-Whitney U test. Analyses between 2 continuous variables were made with the Spearman correlation test (InStat software). Associations between categorical clinical data with the immunologic parameters were analyzed by stratified statistical analysis (Fisher’s exact test; EpilInfo software). Results were considered significant if, at α < 5%, P < .05. All data are shown as mean ± SD unless noted.

Results

Characteristics and infection status of study subjects. We studied 31 patients with acute schistosomiasis: 11 male and 20 female patients. No significant differences were observed between patients with acute and chronic disease in age (21 ± 10.5 and 19.3 ± 9.2 years, respectively) or infection levels (172 ± 32.9 and 185 ± 74.5 eggs/g of stool, respectively; P = .42 and P = .09, respectively, Mann-Whitney U test).

Clinical manifestations of acute schistosomiasis. Clinical data are shown in figure 1. All but 1 of the 31 patients exhibited serious clinical symptoms. The first symptoms appeared 21–28 days after water exposure. Malaise and fever, present in 90% of the patients, were the first complaints in order of occurrence, followed by weight loss in 26 (83.9%), chills in 25 (80.6%), headache in 27 (87.1%), myalgia in 23 (74.2%), and facial and lower limb edema in 15 (48.4%). Diffuse abdominal pain occurred in 29 patients (93.5%), diarrhea in 25 (80.6%), and both symptoms in 23 patients (74.2%). Hepatosplenomegaly was observed in 11 patients (35.5%), and hepatic enzyme levels were high in 12 patients (38%). All hepatic enzyme levels (AST, ALT, AP, and γ-GT) were elevated in 3 patients, 3 had elevated levels of AP and γ-GT, 3 had only elevated AP levels, and 3 had only elevated γ-GT levels.

Respiratory problems were also evident as cough in 25 patients (80.6%), dyspnea in 16 (51.6%), chest pain in 12 (38.7%), and restrictive respiratory insufficiency in 9 (29%). Interstitial infiltrates were observed on chest radiographic films in 7 patients (23%). Echocardiography showed pericarditis in 6 patients (19%), and the chest radiographic films of these patients showed interstitial infiltrates. Four patients had abnormal echocardiography, chest radiography, and pulmonary function test results. Eosinophil count was high in 30 patients (540–7380 eosinophils/mL); this was the abnormality most frequently found by clinical examination. Leukocytosis was observed in 8 subjects (25.8%). One patient was admitted because of respiratory insufficiency, intense abdominal pain, ascites, and diarrhea with dehydration. He was treated with prednisone (1 mg/kg of body weight) for 4 days and with a single dose of oxamniquine.

![Figure 1](http://jid.oxfordjournals.org) Clinical and laboratory data for 31 patients with acute schistosomiasis. Bars show frequency (%) of symptoms, signs, and abnormal laboratory findings. *One patient did not undergo a blood cell count, but all patients (100%) had eosinophilia.
No abnormalities were observed at the 12-month follow-up. (9.7%) had abnormal spirometry and 4 (12.9%) had pericarditis. in 29 patients (93.5%) and malaise in 11 (35.5%). Three patients (20 mg/kg of body weight). The remaining patients were treated as outpatients but needed intense medical assistance for 3 weeks: 1 patient received corticosteroids for 5 days because of respiratory insufficiency. Work absenteeism was 100% for as long as 2 weeks. The 5-month follow-up showed a persistent eosinophilia in 29 patients (93.5%) and malaise in 11 (35.5%). Three patients (9.7%) had abnormal spirometry and 4 (12.9%) had pericarditis. No abnormalities were observed at the 12-month follow-up.

Immunologic findings of acute schistosomiasis. There was no significant difference in total IgE level between patients with acute and chronic schistosomiasis (724.8 ± 1038.31 vs. 978.8 ± 1325.21 IU/mL; figure 2A). SEA-specific IgE in patients with acute disease had an OD of 0–4.27 at 450 nm (0.59 ± 1.06); in patients with chronic disease, OD was 0–2.55 (1.16 ± 0.99; P = .07, Mann-Whitney U test; figure 2B). The OD at 450 nm for IgE specific to SWAP in patients with acute disease was 0–0.128 (0.06 ± 0.038) and did not differ significantly from that in patients with chronic disease (0–0.224; 0.06 ± 0.07); P = .16, Mann-Whitney U test (figure 2C). No correlation was observed between eosinophil counts in peripheral blood and total or SEA- or SWAP-specific IgE levels in patients with acute disease (P > .1, Spearman correlation test).

The most striking finding was that PBMC from most patients with acute disease spontaneously released high levels of the inflammatory triad TNF-α (1349.3 ± 767.6 pg/mL), IL-1 (2683.2 ± 1270.1 pg/mL), and IL-6 (381.8 ± 52.3 pg/mL; figure 3). In addition, detectable levels of IFN-γ (93.6 ± 115.66 pg/mL) were present in the supernatants of unstimulated PBMC from these patients (data not shown). In comparison, nonstimulated PBMC from chronically infected patients produced little TNF-α or IFN-γ spontaneously (24.7 ± 54.87 and 2.1 ± 6.92 pg/mL, respectively; P < .0001, Mann-Whitney U test; data not shown). Stimulation of PBMC of patients with acute disease with either SEA or SWAP did not result in increased production of TNF-α, IL-1, or IL-6, but higher levels of IFN-γ were detected in SEA-stimulated PBMC (see figure 4).

TNF-α levels were also elevated in serum samples of 26 (87%) of 30 patients with acute disease who were tested (range, 0–85; 13.4 ± 20.5 pg/mL). These levels were higher than those observed in healthy control subjects (1.7 ± 0.60 pg/mL; P = .0002) and in patients with chronic disease (6.9 ± 3.9 pg/mL), although the differences were not statistically significant (P = .82; figure 5). High levels of serum TNF-α were associated with abdominal pain (P = .02, Fisher’s exact test). There were no significant differences between the lymphoproliferative responses of PBMC stimulated with SEA (SI, 3.01 ± 3.71) and SWAP (2.4 ± 2.74; P = .81, Mann-Whitney U test) in patients with acute schistosomiasis (data not shown).

Figure 4 shows the cytokine profile in SEA-stimulated PBMC supernatants. High levels of TNF-α (1016 ± 742.04 pg/mL) and IFN-γ (330.9 ± 502.7 pg/mL) production were detected in 30 (96.8%) and 22 (71%) of the patients with acute schistosomiasis, respectively (figure 4A). These responses were significantly higher than those of patients with chronic disease (TNF-α, 55 ± 100.7 pg/mL; IFN-γ, 98.5 ± 363.13 pg/mL; P < .0006 for both, Mann-Whitney U test; figure 4B). The levels of IL-5 (154.5 ± 277.6 pg/mL) and IL-10 (75.6 ± 95.1 pg/mL) pro-
Reduced by SEA-stimulated PBMC from patients with acute disease were similar to those of patients with chronic disease (IL-5, 87.7 ± 23.1 pg/mL; IL-10, 90.5 ± 66.6 pg/mL; P > .10 for both, Mann-Whitney U test). In patients with acute disease, a direct correlation was observed between IL-10 levels in SEA-stimulated PBMC and duration of infection (r = .44, P = .02, Spearman correlation test). In addition, low levels of IL-5 in SEA-stimulated PBMC were associated with weight loss (P = .04, Fisher’s exact test). Low levels of IL-5 in PBMC supernatants and high serum levels of TNF-α were associated with abdominal pain (P < .002, Fisher’s exact test). The levels of IL-5 produced in response to SWAP were significantly higher for patients with chronic than for patients with acute schistosomiasis (987.4 ± 229.5 pg/mL; P = .01, Mann-Whitney U test; figure 6).

Immune complexes were detected in 17 (55%) of the patients with acute schistosomiasis (7.8 ± 7.6 µg Eq/mL) but in none of 12 patients with chronic schistosomiasis (0.8 ± 0.6 µg Eq/mL) or in 5 healthy subjects (1.7 ± 1.6 µg Eq/mL; figure 7). An association was observed between high levels of serum immune complexes and cough, dyspnea, and abnormal chest radiographic findings (P = .05 for each, Fisher’s exact test). Although no significant association was found between pericarditis and detection of immune complexes in serum (P = .09), 5 of the 6 patients who had pericarditis had high levels of immune complexes (range, 7.1–24.9 µg Eq/mL; 15 ± 8.1 µg Eq/mL).

In 10 patients who were reevaluated 5 months after treatment, serum TNF-α levels had decreased to the levels of control subjects (before treatment, 7.2 ± 4.9 pg/mL; after treatment, 1.7 ± 1.00 pg/mL; P = .0021, Mann-Whitney U test). Spontaneous production of proinflammatory cytokines in PBMC supernatants was still seen 5 months after treatment but at lower levels than before treatment (table 1).

**Discussion**

Acute schistosomiasis is a severe disease, and the mechanism involved in its clinical manifestations is not completely understood. In the present study, we clinically and immunologically evaluated 31 patients exposed to the same body of contaminated water. They were evaluated during the prepatent period, 33–60 days after exposure. The patients had symptoms that included malaise, headache, myalgia, edema, and abdominal pain as well as major organ involvement, such as liver and spleen enlargement, elevated liver enzymes, pericarditis, and restrictive respiratory insufficiency.

Because eosinophilia is an important feature of acute schistosomiasis, some of the clinical findings (e.g., respiratory distress) were attributed earlier to an immediate hypersensitivity mechanism [3, 12, 13]. However, the patients with acute schistosomiasis in this study presented with respiratory insufficiency, but with a restrictive rather than an obstructive pattern, suggesting an interstitial pulmonary involvement. In addition, total and
parasite-specific IgE levels were not associated with respiratory symptoms. Similar IgE levels were found in persons with both acute and chronic schistosomiasis, but respiratory distress is not a feature of the chronic disease. Because immune complexes were associated with cough, dyspnea, abnormal chest radiographic findings, and pericarditis, it is likely that respiratory distress and pericarditis in acute schistosomiasis could be mediated by immune complex deposition in these tissues. In fact, pulmonary vasculitis and pericarditis are features of systemic lupus erythematosus, an immune complex–mediated disease [36].

Constitutional symptoms were present in most patients with acute schistosomiasis. Thus, mechanisms other than the immune complex might be implicated in these symptoms. The high production of the proinflammatory cytokines IL-1, IL-6, and TNF-α found in cultures of unstimulated PBMC from patients with acute schistosomiasis and the detection of TNF-α in the serum of 87% of these patients could explain all constitutional symptoms and some of the organ involvement. Active secretion of proinflammatory cytokines by PBMC ex vivo might indicate that those persons were in the process of mounting an aggressive immune response when samples were obtained. Alternatively, the parasite antigens could drive a direct activation of the innate immunity. Production of these proinflammatory mediators occurred in the absence of appreciable levels of the anti-inflammatory cytokine IL-10. In fact, in IL-4 and IL-10 knockout mice infected with *S. mansoni*, the high mortality rate was related to inflammatory mediators [19, 37–39]. The ability of proinflammatory cytokines to mediate tissue damage has been described in bacterial toxemic shock, meningitis, cerebral malaria, leishmaniasis, and hanseniasis [40–45].

People residing where schistosomiasis is endemic usually do not present with acute disease, suggesting that the adaptive immune response protects them from developing the acute toxemic condition [2, 3, 13, 26, 46–48]. Patients with chronic intestinal and hepatointestinal schistosomiasis present with a Th2-type immune response, with low or no IFN-γ production in response to parasite antigens [20–22], although Mwatha et al. [23] reported a higher production of IFN-γ and TNF-α in hepatosplenic schistosomiasis. Montenegro et al. [27] found a dominant Th1 response in patients with acute schistosomiasis; however, the patients had been infected for 120 days, had positive parasitologic results, and had very high IL-10 levels in PBMC supernatants.

The present study clearly shows higher levels of IFN-γ production in patients with acute schistosomiasis than in persons with chronic schistosomiasis. However, fewer patients with acute disease produced IL-10 in response to SEA, when compared with the patients with chronic disease. We also found a positive correlation between IL-10 levels in SEA-stimulated PBMC and time after water exposure. Because Montenegro et al. [27] detected higher levels of this cytokine in later stages of disease (120 days), we hypothesize that, after egg secretion, IL-10 might be one of the cytokines involved in down-regulating the Th1 response, which dominates the early acute phase of disease. In the present study, low IL-5 levels were detected in patients with acute schistosomiasis, but persons with chronic disease exhibited a high IL-5 response to SWAP. In addition, low IL-5 levels in SEA-stimulated PBMC from the patients with acute disease were associated with weight loss. These data suggest that the Th2-type response seen in patients with chronic schistosomiasis may serve as an anti-inflammatory modulator of the toxemic symptoms of acute schistosomiasis. In fact, the role of the Th2-type response in preventing tissue damage and preventing the development of a severe inflammatory disease during acute schistosomiasis has been documented in knockout mice for IL-4 and IL-10 genes [37–39].

Although morbidity due to chronic schistosomiasis has decreased because of the availability of effective drugs, such as oxamniquine and praziquantel, acute schistosomiasis continues to be a serious health problem because it is potentially fatal,
especially schistosomiasis due to *S. japonicum* infection. Diseases usually result from parasite products in tissue and from the chemical compounds produced by innate and adaptive immune responses of the host. Adaptive mechanisms of the host interact with infectious organisms to control their growth and neutralize their products and usually mount a balanced immune response and do not cause excessive tissue damage. The results of our study suggest that the severe toxic syndrome and major organ involvement observed in acute schistosomiasis are mediated by proinflammatory cytokines and immune complexes and that an absence of a Th2-type response, which could exert an anti-inflammatory response, contributes to maintaining the toxic symptoms. Our data shed light on the immunopathogenesis of acute disease due to *S. mansoni* infection. Similar mechanisms might operate in acute *S. japonicum*, an even more severe condition, and should be studied. Corticosteroids are usually needed for treatment of patients with severe cases of acute schistosomiasis [10, 11, 13], but this drug produces a generalized immune suppression. Understanding the pathogenesis of this severe disease will enable development of other therapeutic measures based on immune modulators.

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### References


