Original Article

Autoimmune manifestations of visceral leishmaniasis in Chinese patients

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Background: Visceral leishmaniasis (VL) is a rare, parasitic infection with distinctive features that may mimic autoimmune diseases. In this study, we report on the laboratory autoimmune manifestations of VL in Chinese patients.

Methods: Twenty-seven patients who were hospitalized with VL were included in this retrospective study. Routine blood and biochemical tests were conducted, and a variety of autoimmune antibodies and complement fractions were detected. Continuous variables are expressed as means ± standard deviations, and categorical data are expressed as a number (percentage). Missing data were not included for statistical analysis. Data were analyzed with SPSS v. 13.0 statistical software.

Results: All patients had cytopenia (82% with pancytopenia) and hepatosplenomegaly, and 25 (93%) patients also suffered from fever. The prevalence of autoantibodies (number of patients with antibody detected/total number of patients tested for the antibody) for each antibody tested was as follows: antinuclear antibodies (ANA; 18/22, 82%), anti-neutrophil cytoplasmic antibodies (ANCA; 4/5, 80%), anti-mitochondrial M2 antibodies (AMA-M2; 1/6, 17%), anti-liver cytosol specific type 1 antibodies (anti-LC1; 1/6, 17%), anti-liver/kidney microsomal type 1 antibodies (anti-LKM1; 1/6, 17%), anti-centromere protein-B antibodies (anti-CENP-B; 4/21, 19%), anti-Sjögren's syndrome type A antibodies (anti-SSA; 2/21, 10%), anti-Sjögren's syndrome type B antibodies (anti-SSB; 1/21, 5%), anti-Jo-1 antibodies (1/21, 5%), anti-double-stranded DNA antibodies (anti-dsDNA; 1/25, 4%), direct antiglobulin test (direct Coombs; 6/6, 100%), and rheumatoid factor (RF; 3/11, 27%). Increased serum C-reactive protein (CRP) was found in 14 (100%) patients. Of the 19 patients tested for serum IgG, 17 patients (89%) were found with increased IgG levels, while complement 3 protein (C3) and complement 4 protein (C4) levels were not decreased in any of the 19 patients. Of note, in one patient followed up 1 month after therapy, only ANA was still present, and all the other laboratory autoimmune manifestations had disappeared.

Conclusions: VL infection associated with laboratory autoimmune manifestations is common. This may lead to patients with VL being misdiagnosed as having an autoimmune disorder. An obligatory differential diagnosis that considers VL should be undertaken for patients diagnosed with systemic lupus erythematosus (SLE), especially in endemic areas, is necessary.

Keywords: Visceral leishmaniasis (VL); systemic lupus erythematosus (SLE); autoantibodies

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Introduction

Visceral leishmaniasis (VL) is an infectious disease caused by the protozoan Leishmania species, mainly *Leishmania donovani*. It may present as an acute or chronic form and may include systemic involvement. Leishmania species are obligate intracellular parasites. They are carried in the sand fly gut as promastigotes and transmitted to humans by the bite of an infected sandfly (1,2). In tropical and subtropical countries, VL has become a major public health burden. In China, VL has been found in six provinces, including Sichuan.

VL is often asymptomatic. However, in certain situations, it may have a life-threatening course, with patients experiencing fever, weight loss, hepatosplenomegaly, and pancytopenia. Without treatment, VL can lead to a high fatality rate (2). Some laboratory features of VL, including cytopenia, hypergammaglobulinemia, and the presence of antinuclear antibodies (ANA), can resemble the laboratory features of some autoimmune diseases, especially systemic lupus erythematosus (SLE) (3-8). Although the exact immunological mechanisms related to VL is still not fully understood, the crosstalk between innate and adaptive immune systems and the type of the cell-mediated responses elicited play an important role in the disease progression (9-11). Once the infected sandflies get introduced into the skin dermis, the infective metacyclic promastigotes of Leishmania are engulfed by a variety of immune cells, such as macrophages, resident dermal dendritic cells and infiltrating neutrophils (12-14). The insertion of the sandfly's proboscis into the skin could induce inflammation driven by neutrophils (15,16), and subsequently tissue damage. The saliva of sandfly also has chemotactic activity for neutrophils and macrophages (16,17). Degranulation of neutrophils could recruit monocytes and the release of chemokines and proinflammatory cytokines further argument this inflammation process (18-20). Final resolution of infection requires a finely tuned interaction between innate and adaptive immune systems, culminating with the activation of microbicidal and parasite clearance functions within host cells.

Although there have been some reports published on the autoimmune manifestations of VL, there is no similar report of VL in the Chinese population. Considering that there may be differences among different ethics, for the first time, we analyzed 27 Chinese patients diagnosed with VL and focused on the findings that may help clinicians to differentiate VL from SLE.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3409).

Methods

Twenty-seven consecutively hospitalized VL patients were included in this retrospective study, drawing on data from 2006 to 2019 when the patients attended Sichuan Provincial People's Hospital. The diagnostic criteria of VL includes the detection of high titers of anti-leishmania antibodies, and these were detected by indirect immunofluorescence (IIF) assay, indirect hemagglutination antibodies, and the presence of intracellular parasites in bone marrow smears. Concretely, a confirmed case was defined with pathogenic examination (smear from bone marrow, spleen or lymph nodes to check for Leishmania spp. or culture the punctures to check for pre-flagellate Leishmania (the pre-flagellar body of Leishmania) (21). All patients were tested to ensure they were negative for hepatitis B, hepatitis C and human immunodeficiency viral infections. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Sichuan Provincial People's Hospital (No. 2021-452). Individual consent for this retrospective analysis was waived.

Laboratory data were obtained by retrospective review of the patients' charts, with all of the tests previously conducted in the Clinical Laboratory Department of Sichuan Provincial People's Hospital. Briefly, ANA, anti-double stranded DNA (dsDNA), and anti-neutrophil cytoplasmic antibodies (ANCA) were detected using IIF (Euroimmun, Lübeck, Germany). Extractable nuclear antigen antibodies, including U1RNP antibodies, Smith antibodies (anti-Sm), anti-Sjögren's syndrome type A antibodies (anti-SSA), anti-Sjögren's syndrome type B antibodies (anti-SSB), liver/kidney microsomal type 1 antibodies (anti-LKM1), and anti-liver cytosol type 1 antibodies (anti-LC1) were detected using the enzyme-linked immunosorbent assay (ELISA) (Euroimmun, Lübeck, Germany). Anticardiolipin antibodies (aCL) were also detected using the ELISA (Eurimmun, German). Serum globulin levels, complement 3 protein (C3) and complement 4 protein (C4) fractions of complement and rheumatoid factor (RF) were quantitated using nephelometry (Siemens Healthcare Diagnostics, Erlangen, Germany). C-reactive protein (CRP) was examined by immunonephelometry, and values higher than 7.9 mg/L

Table 1 Clinical characteristics of VL patients

Characteristics	Patient numbers
Sex (female/male)	4/23
Age (years), median [range]	37 [9–59]
Duration (months), median [range]	1.00 [0.17–24.00]
Anti-leishmania antibody positive, n [%]	27 [100]
Microscopic visualization of parasite from bone marrow aspirates or biopsy (yes/no)	23/4
Fever (yes/no)	25/2
Hepatosplenomegaly (yes/no)	27/0
Weight loss (yes/no)	14/13

VL, visceral leishmaniasis.

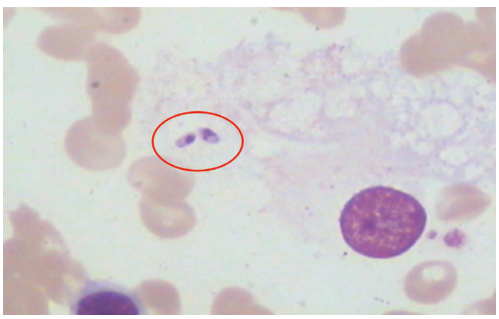

Figure 1 Leishmania parasites are demonstrated through a microscopic visualization on bone marrow smear (circle). Hematoxylin and eosin, ×400.

were considered positive. Serum ferritin was measured by ELISA using human anti-goat ferritin antibody (Meridian Life Science, Inc., Ohio, USA). D-dimer concentration was measured with a particle-enhanced, immunoturbidimetric assay in a calibrated SYSMEX7000 analyzer (Sysmex Corporation, Hyogo, Japan). The prothrombin time (PT) and the activated partial thromboplastin time (APTT) were also tested using the standard method.

Statistical analysis

The continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the distribution, and the categorical data were expressed as a number (percentage). Missing data were not included for statistical analysis. Data were analyzed with SPSS v. 13.0 statistical software.

Results

Twenty-seven patients (23 men and 4 women, aged from 9 to 59 years) were included in this study (*Table 1*). Twenty-two of the patients were diagnosed through the identification of Leishmania amastigotes in bone marrow smear (*Figure 1*). One patient was diagnosed by the identification of the parasite in a bone marrow biopsy instead of a smear. *Leishmania donovani* was not found in either the bone marrow smears or the biopsies of the other 3 patients; however, high titers of anti-leishmania antibodies were detected in these patients, and the effective treatment response to VL confirmed the diagnosis of VL in all three of them.

Routine blood and biochemical tests, immunoglobulin tests, and bone marrow examination were performed in all of the patients after hospital admission. ANA were examined in 22 patients. Laboratory tests revealed the existence of a broad spectrum of autoantibodies and hematological abnormality in VL patients (*Table 2*).

All patients were cured after treatment with sodium antimony gluconate. One patient was followed up and re-evaluated 1 month after therapy. Before treatment, the patient's ANA titer was 1:320, and the patient tested positive for many autoimmune antibodies, including anti-dsDNA, anti-histone antibody, anti-Jo-1 antibody, and P-ANCA. Serum levels of CRP, ferritin and IgG were elevated to 48.8 mg/L, 1,556.82 ng/mL, and 22 g/L, respectively. One month after treatment, the patient's ANA titer remained positive (1:320), while all the other autoimmune antibodies returned a negative result on testing. Serum levels of CRP, ferritin, and IgG returned to normal.

Discussion

The hallmarks of VL may mimic symptoms of autoimmune diseases, especially of SLE. The presenting autoimmune symptoms of VL patients generally include pancytopenia, hypergammaglobulinemia, and the production of autoantibodies, such as ANA, and others. Polyclonal activation of B cells is considered to be the main reason of immunoglobulin and autoantibody formation (22,23). Extensive cross-linking of membrane immunoglobulins by microbial antigens or cytokines produced by other cells can stimulate the polyclonal activation of B cells (24). In addition, Leishmania parasites, themselves, may cause tissue destruction, thus releasing self-antigens, which act as B-cell mitogens (23).

Table 2 Hematological and immunological laboratory findings in VL patients

Item (reference range)	Prevalence (number of patients with antibody or protein detected/total number of patients tested)	Value, mean ± SD
Anemia (<115 g/L)	96% (26/27)	91.7±14.7
Leucopenia (<3.5×10^9/L)	85% (23/27)	2.2±1.0
Thrombocytopenia (<101×10^9/L)	74% (20/27)	72.0±26.3
Extended APTT (>36.5 s)	57% (12/21)	39.0±8.2
Extended PT (>12.6 s)	57% (12/21)	13.2±1.9
Elevated D-dimer	33% (1/5)	19.7±38.5
Positive ANA	82% (18/22)	–
1:100	47.8% (11/22)	–
1:320	30.4 (7/22)	–
Anti-dsDNA	4% (1/25)	–
Anti-SSA	10% (2/21)	–
Ant-SSB	5% (1/21)	–
Anti-CENP-B	19% (4/21)	–
Anti-Jo-1	5% (1/21)	–
Anti-Sm	0 (0/21)	–
Anti-AMA-M2	17% (1/6)	–
Anti-LKM1	17% (1/6)	–
Anti-LC1	17% (1/6)	–
ANCA	80% (4/5)	–
RF (>20 IU/mL)	27% (3/11)	19.4±19.4
Direct Coombs' test	100 (6/6)	–
Indirect Coombs' test	0 (0/6)	–
Elevated IgG level (>16.00 g/L)	89% (17/19)	29.8±15.1
Decreased C3 level (<0.900 g/L)	0 (0/19)	1.2±0.3
Decreased C4 level (<0.100 g/L)	0 (0/19)	0.2±0.1
Elevated CRP level (>3 mg/L)	100% (14/14)	49.7±27.6
Elevated ferritin level (male >274.66 ng/mL, female >204.00 ng/mL)	75% (6/8)	829.3±648.5

SD, standard deviation; APTT, activated partial thromboplastin time; PT, prothrombin time; ANA, antinuclear antibodies; dsDNA, double-stranded DNA; SSA, Sjögren's syndrome type A; SSB, Sjögren's syndrome type B; CENP-B, centromere protein-B; Jo-1, histidyl-tRNA synthetase; Sm, Smith; AMA-M2, mitochondrial M2; LKM1, liver/kidney microsomal type 1; LC1, liver cytosol specific type 1; ANCA, anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor; IgG, immunoglobulin G; C3, complement 3 protein; C4, complement 4 protein; CRP, C-reactive protein.

Some small case series have reported the presence of immunocomplexes, complement consumption, and elevated antibodies in VL patients (5,24,25). Most of these studies have involved Caucasian patients, and there has been scant research of VL in Asian patients. Out study is the first known study to report the autoimmune manifestations of VL patients in China. Since several factors relating to hosts, vectors, and parasites have been implicated as

determinants of VL (26), there may be some differences in the autoimmune manifestations between Chinese VL patients and VL patients from other continents.

In clinical practice, VL patients often present with increased levels of serum immunoglobulins and increased production of autoantibodies, which could easily lead to a misdiagnosis as SLE. Recently, Santana *et al.* reviewed original studies of cases of VL-infected patients, in order to identify the clinical and laboratory manifestations of VL mimicking SLE (7). The literature review identified 18 cases of VL mimicking SLE. The most common manifestations in VL patients were reported as intermittent fever, pancytopenia, visceromegaly, and increased acute phase reactants. The most common laboratory results were positive ANA (17 cases, 94%), positive RF (10 cases, 56%), and positive direct Coombs' (9 cases, 50%) tests. Even for tests generally considered highly specific for SLE, such as the anti-dsDNA test, the prevalence of a positive result in VL patients was 16% (25,27). Other autoimmune antibodies, such as RF, an-dsDNA, anti-Sm and ANCA, were detected in 24.4–63%, 4.5%, 6%, and 25% of VL patients, respectively. The results of direct and indirect Coombs' tests were positive in 13% and 6% of VL patients, respectively, and some studies showed decreased C3 and C4 levels in VL patients (25). In this current study, all the patients had cytopenia (82% with pancytopenia) and hepatosplenomegaly, and most of them (93%) presented with fever. In the patients who underwent laboratory tests, increased serum levels of CRP, IgG, and ANA were generally noted. This was consistent with most results previously reported. Of note, the prevalence of ANCA (80%) and the prevalence of direct Coombs' (100%) in this current study were higher than those of other studies; although in this study, these were not tested in every patient. The prevalence of anti-dsDNA was low (5%) in this study, and another highly specific antibody of SLE, anti-Sm, was absent. Levels of C3 and C4, APTT, and PT were normal in VL patients. APTT and PT are typically normal in VL patients, and the same was observed in the current study.

In this study, clinical and laboratory manifestations mimicking SLE in Chinese VL patients were identified, as has been reported in other countries. The prevalence of autoantibodies and other laboratory parameters differed significantly from other studies, which should prompt further investigation to explore the genetic and racial characteristics of VL as well as the differences between the leishmaniasis strains.

VL commonly resembles SLE, yet the distinction between the two illnesses is sometimes difficult to tell. Here, the clinical and laboratory findings of VL are presented which may help medical practitioners to differentiate these two entities. The hematological abnormalities of SLE include hemolytic anemia, leucopenia or lymphopenia, and thrombocytopenia, due to the presence of autoantibodies directed against erythrocytes, leucocytes, and platelets (28). Splenomegaly is not commonly seen in SLE patients, unless lymphoma or other concurrent infection is combined. However, splenomegaly is quite common in VL, due to the proliferation of parasites, and so cytopenia in VL patients is mainly due to splenomegaly and hypersplenism. In addition, the highly elevated CRP commonly seen in VL is not usually seen in SLE, unless symmetrical polyarthritis, pleurisy, or concurrent infection occurs. Hypergammaglobulinemia, while common in SLE patients, is much more common in VL patients. In this study, the IgG level of one VL patient was 61 g/L. However, in SLE patients, highly elevated IgG is rare. Furthermore, the failure of steroid treatment and the normal levels of C3 and C4 suggested a possible infectious origin. In this study, VL was more prevalent in male patients; SLE, in contrast, tends to be more prevalent in females. However, considering the relatively small number of patients in this study, further studies with an expanded sample size are needed to confirm the real incidence of VL among specific populations.

On the other hand, underlying factors, such as malnutrition, HIV coinfection, or treatment with corticosteroids or immunosuppressive drugs are contributory factors in disease reactivation, hence VL may also occur in SLE patients as an opportunistic infection and mimic SLE flare-up, as previously reported (29). Therefore, VL must be ruled out diligently before starting immunosuppressive therapy in patients with immunological abnormalities, especially in endemic areas. Moreover, VL should be considered in patients with autoimmune disorders who do not respond to steroid and immunosuppressive treatment. For those suspected cases in high-risk endemic areas, high titers of anti-leishmania antibodies are helpful for VL diagnosis, but it does not serve as the unique diagnostic criterion owing to diversified test methods and lack of uniform standards. Once diagnosed, specific treatment should be initiated. Antimonials are considered as the most effective choice for VL, and Liposomal amphotericin B is also thought to be an effective and safe choice in most cases. In our study, all patients were cured after treatment with antimonials.

It has to be noted that the sample sizes included in all the current studies exploring the autoimmune features of VL are relatively small, which may due to the relatively low incidence of VL and low detection of autoimmune abnormalities. However, if the autoimmune features of VL are ignored, it is an easily misdiagnosed disease. More studies with larger samples need to be conducted in the future for better illustration of the problem.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Sichuan Provincial People's Hospital (No. 2021-452). Individual consent for this retrospective analysis was waived.

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