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Letters to the Editor

Autoimmunity in Dengue: Literature Review☆

Autoinmunidad en dengue: revisión bibliográfica

To the Editor,

We are writing the present letter in reference to the article published by Morel and Ramirez,[1] which reported the clinical signs and symptoms of 3 pediatric patients with dengue virus (DV) infection in Paraguay, a country in which this virus is endemic. The first case involved an 8-year-old boy in whom the disease was self-limiting. He required no treatment after a 14-day period during which the disease presented as fever, hepatosplenomegaly, tachycardia and bilateral pleural effusion, with positive DV serology. Serological tests for lupus anticoagulant, anticardiolipin, antinuclear and anti-DNA antibodies were all negative, and complement levels were normal. However, the clinical signs and symptoms in the other 2 cases were consistent with a macrophage activation syndrome (MAS). These cases involved a 3-year-old preschool boy and a 3-month-old male infant who had similar clinical signs and symptoms, characterized by fever and hepatosplenomegaly, in addition to anemia, leukopenia and neutropenia, and both responded favorably to glucocorticoids.[1] The MAS presents clinically with cytopenia, organ dysfunction and coagulopathies due to the inappropriate inactivation of the macrophages. It has been related to autoimmune disorders in different diseases, mainly systemic juvenile idiopathic arthritis, and has been linked to other autoimmune processes, as well.[2] Moreover, another case of MAS associated with dengue infection has been reported by Lai et al. The patient was a 55-year-old woman with neutropenia and lymphopenia, in addition to a myelogram showing evidence of hemophagocytosis. During her hospital stay, she was diagnosed as having nephrotic syndrome, and dengue infection was confirmed by a positive test for NS1 antigen and positive IgG and IgM serology, which demonstrated DV reinfection.[3]

Other cases of an association between autoimmune manifestations and DV infection have also been reported. Talib et al. described a case of systemic lupus erythematosus (SLE) and lupus nephritis triggered by DV, in which the serological test for NS1 antigen was positive. The diagnosis of SLE with lupus nephritis was confirmed because the patient met 4 of 11 diagnostic criteria of the American College of Rheumatology, among them, presence of antinuclear antibodies with a homogeneous pattern and positive test for anti-dsDNA.[4] We found few reports on the interrelationship of DV with lupus nephritis and SLE. However, the case of Talib et al. could be related to a kidney disease associated with a positive test for perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) or it may have developed as a lupus flare or *de novo* disease. Another report, from China, found an association between DV and ocular manifestations observed in young women, in whom DV infection provoked antibody production and immune complex deposition, with the subsequent development of retinal vasculitis.[5]

Antibody production played an important role in the pathogenesis of dengue. Several studies in animals and in hospitalized patients have shown that the generation of autoantibodies against platelets, endothelial cells and coagulation factors was correlated with disease severity and the development of hemorrhagic fever.[6,7] In particular, the titers of antibodies to endothelial cells, analyzed by flow cytometry, peaked during the acute phase, and subsequently decreased; even so, in contrast to findings in other chronic infections, they remained detectable for several months. The autoantibody levels were higher in patients who had dengue hemorrhagic fever or dengue shock syndrome when compared to those with DV infection; moreover, these autoantibody levels were similar among serotypes DENV-2, 3 and 4.[7] Another study reported the persistence of clinical symptoms 2 years after acute infection, associated with persistently high IgG levels and expression of the FcγRIIa gene polymorphism, together with the presence of immune complexes, positive test for antinuclear antibodies or rheumatoid factor, or high C-reactive protein levels.[8]

In countries with zones in which DV is endemic, this infection should be included in the differential diagnosis of any systemic disease, especially in the pediatric population, as the literature reviewed showed an increase in the incidence of atypical symptoms. Manifestations reported in clinically atypical cases in countries in which DV is endemic are related to systemic presentations, including hepatic disorders (27%), acalculous cholecystitis (9%), pancreatitis (9%), pulmonary conditions (9%) and cardiovascular problems (7%).[9]

In conclusion, we consider the report by Morel and Ramírez,[1] to be an important contribution. These authors have also conducted previous studies on the association between clinically evident autoimmunity and DV infection described above. Therefore, larger studies should be performed in populations in which this disease is endemic to better characterize the possible consequences of exacerbation of autoimmunity that can occur in these individuals over time.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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Differential Diagnosis of Acute Bilateral Uveitis in the Rheumatologist's Office☆

Diagnóstico diferencial de uveítis bilateral aguda en la consulta del reumatólogo

To the Editor,

Given the multiorgan involvement in systemic diseases, there is a growing trend toward the establishment of multidisciplinary services for outpatient care. In recent years, we are witnessing the creation of units shared with dermatologists, pulmonologists or nephrologists and, recently, ophthalmologists. Uveitis is an isolated condition in 50% of the cases; however, a detailed interview, thorough physical examination and general laboratory tests with an immunological study reveal an underlying rheumatic disease in the remaining 50%.[1] There are conditions, like the spondyloarthropathies and sarcoidosis, with which uveitis is frequently associated; however, there are less common diseases that we should not overlook.

We report the case of a 46-year-old woman with a history of hepatitis C virus, endometriosis and migraine who presented with red eye and a sharp pain in her left eye. She was diagnosed with anterior uveitis and, once infection had been ruled out as the cause, was treated with topical glucocorticoids. Over the following weeks, she developed anterior uveitis in her right eye and it appeared anew in the contralateral eye, neither of which resolved completely with the treatment. She had no accompanying clinical manifestations or signs or symptoms suggestive of autoimmune or infectious disease. Laboratory tests revealed acute renal failure, with a creatinine level of 2.15 mg/dL and proteinuria of 1 g in 24 h, with no microhematuria, glycosuria or sterile pyuria. Given the suspicion of an underlying systemic disease, the patient was referred for further evaluation. She underwent an immunological study that included rheumatoid factor, antineutrophil cytoplasmic antibodies (ANCA) and antinuclear antibodies (ANA), all of which were negative; her complement and immunoglobulin levels were normal, tests for HLA-B27 and HLA-B51 were both negative, and her angiotensin-converting enzyme level was normal. In view of the progressive deterioration of her glomerular filtration rate, renal biopsy was performed. The results of the histological study were consistent with acute tubulointerstitial nephritis. On the basis of the clinical, analytical and histological findings, she was diagnosed with tubulointerstitial nephritis with uveitis (TINU), and a regimen of oral glucocorticoids was begun at doses of 0.5 mg/kg/day, and tapered until they were discontinued after 8 months of treatment. The patient's renal function returned to normal, the proteinuria disappeared and, after 12 months of follow-up, she has had no new episodes of uveitis.

Acute tubulointerstitial nephritis with uveitis (TINU syndrome) is an uncommon disorder that is somewhat unknown to rheumatologists. It should be considered in the differential diagnosis of those patients with recurrent uveitis who are frequently to be found in our offices.[1] Depending on the pattern of presentation, the differential diagnosis of uveitides includes the diseases summarized in Table 1. The differential diagnosis of acute anterior uveitis should include spondyloarthropathies, cytomegalovirus infections, herpes simplex or herpes zoster, relapsing polychondritis, systemic lupus erythematosus, Behçet's disease and TINU syndrome. Bilateral involvement further limits the alternatives to spondyloarthropathies, Behçet's disease and TINU syndrome. Thus, it is very important that the study of these patients include the determination of renal function and urinalysis. This syndrome was first described in 1975 by Dobrin et al.[2] and, to date, some 250 cases have been reported,[3–5] the majority in the pediatric, ophthalmology and nephrology literature. The mean age at presentation is 15 years (range: 9–74 years), and there is female predominance. The risk factors reported for the development of acute tubulointerstitial nephritis include infections, drugs (anti-inflammatory agents, antibiotics) and autoimmune diseases.[1,4–6] The presenting clinical signs and symptoms of interstitial nephritis are generally nonspecific: fever, weight loss, fatigue and malaise. The usual

Table 1
Differential Diagnosis of Uveitides According to Their Most Common Pattern of Presentation.

Type of uveitis	Associated diseases
Acute anterior	
Unilateral	Spondyloarthropathies, cytomegalovirus, herpes simplex, herpes zoster, relapsing polychondritis, systemic lupus erythematosus, Kawasaki disease
Bilateral	TINU syndrome, spondyloarthropathies, Behçet's disease
Chronic anterior	Juvenile chronic arthritis, Sjögren's syndrome, sarcoidosis, tuberculosis
Intermediate	Multiple sclerosis, Lyme disease, Whipple's disease, sarcoidosis, TINU syndrome
Posterior	Toxoplasmosis, cytomegalovirus, tuberculosis, syphilis, Sjögren's syndrome, Vogt-Koyanagi-Harada syndrome, sarcoidosis, Behçet's disease
Panuveitis	Vogt-Koyanagi-Harada syndrome, sarcoidosis, Behçet's disease, juvenile chronic arthritis, tuberculosis
Retinal vasculitis	Behçet's disease, systemic lupus erythematosus, granulomatosis with polyangitis, syphilis

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