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Informe de casos interesantes

Lupus and autoimmune shock: Use of intravenous gammaglobulin. Case report and proposal for a new designation

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RESUMEN

El estado de choque se caracteriza por hipotensión e hipoperfusión lo cual da lugar a disfunción celular, respuestas neuroendócrinas, liberación de mediadores inflamatorios y alteraciones de la microcirculación. La falla de perfusión se puede clasificar de manera simplista en: distributiva, como en el choque anafiláctico o séptico, y no distributiva como en el choque hipovolémico. Respecto al choque séptico existen grandes conocimientos: la interacción entre bacterias y los receptores Toll-like 2 y 4 (TLR-2, TLR-4) hace que se libere una tormenta de citocinas pro-inflamatorias, que favorecen la producción de óxido nítrico, además de perpetuar la hipotensión. El desequilibrio entre la liberación de citocinas pro y antiinflamatorias crea una falta de regulación inmunológica, que contribuye aún más con el síndrome de respuesta inflamatoria sistémica y desencadena el estado de choque, que recibió el nombre de *Disonancia Inmunológica* que le dio el Dr. Roger Bone. Desde nuestra perspectiva, éste término explica las alteraciones que mostraremos en un caso clínico, en donde el problema fundamental es el desajuste entre el sistema inmunológico del paciente y la instalación de un choque distributivo lo cual consideramos podría corresponder a un choque de origen autoinmune. Pensamos que la autoinmunidad es la plataforma que da lugar al estado de disonancia inmunológica responsable del choque. Por esta razón, en este caso en el que sospechamos un estado de choque basado en autoinmunidad, se administró gammaglobulina intravenosa así como pulsos de metilprednisolona en un intento por contrarrestar la disonancia inmunológica, con lo que se obtuvieron resultados satisfactorios.

Palabras clave: Lupus, autoinmunidad, gammaglobulina intravenosa, disonancia inmunológica.

ABSTRACT

Shock is a state of hypotension and hypoperfusion which in turn leads to cellular dysfunction, neuroendocrine responses, inflammatory mediator release, and alterations of the microcirculation. There are various ways of classifying tissue perfusion failure. A simple method is dividing them into a distributive category, such as septic or anaphylactic shock, and a non-distributive category such as hypovolemic shock. There is extensive knowledge on septic shock; the interaction between bacteria and the antigen presenting cell receptor (TRL-2, TRL-4) releases a proinflammatory cytokine storm, favoring the production of nitric oxide, thus perpetuating the hypotensive state. The imbalance between proinflammatory and anti-inflammatory cytokines creates an immunologic dysfunction, which favors the systemic inflammatory response syndrome and unleashes a shock state, a situation named *immunologic dissonance* by Dr. Roger Bone in 1996. From our perspective, this term explains the alterations presented in one particular case, where the cornerstone is the dysfunction of the patient's immune system and its culmination in a distributive form of shock, which from our hypothetical perspective is of autoimmune origin. We consider autoimmunity to be the platform leading to the state of immunologic dissonance responsible for autoimmune shock, which we believe merits a non-traditional approach. For this reason in a case in which we suspect shock based on autoimmunity, intravenous gammaglobulin was used in conjunction with a bolus of methylprednisolone in an attempt to counteract the immunologic dissonance; satisfactory results were obtained.

Key Words: Lupus, autoimmunity, intravenous immunoglobulin, immunologic dissonance.

Abbreviations: ANA, antinuclear antibodies; SLE, systemic lupus erythematosus; CSF, cerebrospinal fluid; CVP, central venous pressure; IVGG, intravenous gammaglobulin; BP, blood pressure; IL, interleukin; TNF, tumor necrosis factor; IFN-γ, interferon gamma; RANTES, Regulated-upon-Activation Normal T Expressed and Secreted; TLR, Toll-like receptor.

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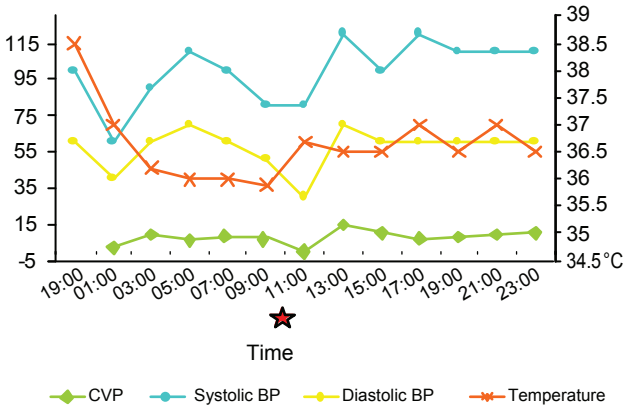
A 10 year-old male, resident of Hidalgo, México, who presented with muscle weakness which impeded walking, heliotrope erythema, Gottron papules in November 2004. Based on the myopathic pattern found on the electromyography, juvenile dermatomyositis was diagnosed. Treatment with prednisone and methotrexate was given. Due to lack of improvement, the patient was referred to our Instituto Nacional de Pediatría. He developed persistent thrombocytopenia <100,000 and lymphopenia <1500; he had epileptic seizures without apparent cause, positive ANA, and malar rash, all of which substantiated systemic lupus erythematosus (SLE) ACR criteria. Treatment was initiated with oral cyclophosphamide 3 mg/kg/day, and prednisone 1 mg/kg/day. On February 23, 2005 he presented with fever and suffered generalized tonic-clonic seizure. A complete work-up was done with the following findings: CBC: RBC, 4.25; Hb, 13.1 mg/dL; Hct, 40%; WBC, 4600 10^3/µl, NA 3500 10^3/µl, LA 1000 10^3/µl, Mon 1000 10^3/µl, Plat 52000/µl, Arterial gas PH 7.37 PO2 89.6 PCO2 27.6 HCO3 15.8 CO2T 16.6 Sat 96.7% Lactate 25, C3 91, C4 19.7, CRP 0.44, antiDNAds (-), ANCA (-), anti-B2 glicoprotein 1 (-), Anti-cardiolipin (-). A brain CAT scan was reported as normal, lumbar puncture with normal CSF and negative cultures. The patient presented with tachycardia, weak peripheral pulses, altered state of consciousness and hypotension four hours after the onset of symptoms, for which he received two IV Hartmann solution boluses. A central catheter was placed; a CVP of 2 mmH_2O, which required inotropic support with 10 mcg/kg/min of dopamine; this improved the peripheral pulses, blood pressure and spontaneous diuresis. Once cultures were obtained, a double antibiotic therapy was initiated with IV dicloxacillin and 1.5g ceftriaxone bid. Ten hours later the patient presented hemodynamic decompensation, and once more, altered state of consciousness, a CVP of 1 and a BP of 80/30 mmHg. A bolus of methylprednisolone 30 mg/kg/dose was administered, along with a dose of IV gammaglobulin 1 g/kg (IVGG), which resulted in clinical and hemodynamic improvement, with a BP of 110/70 mmHg and normal body temperature. The patient's hemodynamic course is depicted in figure 1. The patient is currently under treatment with cyclophosphamide OD and dexamethasone. He is in good clinical condition and without lupus reactivation.



Source:; Source: clinical chart
CVP: Expressed in cmH2O, Blood pressure expressed in mmHg
★ Gammaglobulin IV 1g/Kg and bolus of methylprednisolone 30mg/Kg

Figure 1. Evolution in time of the hemodynamic condition.

DISCUSSION

This case is an example of a patient with an autoimmune disease which is clearly active, with thrombocytopenia, lymphopenia, hypocomplementemia, epileptic seizures, and who presented a sudden onset of distributive shock. Treatment was initiated with IV fluids, antibiotics and vasopressors without clinical improvement. Due to the sluggish course and lack of evidence of an infection, IVG was given in addition to a bolus of methylprednisolone, which lead to a clinical recovery with rapidly progression to hemodynamic stability, not related to the effect of antimicrobials. This fact supports the theoretical concept of how the use of steroids, through their negative regulation via transcriptional effects on genes that encode cytokine expression, along with the use of IVG which regulates the idiotype-antiidiotype net, and the direct block of cytokine expression can be, and in fact is, useful in reverting the specific form of shock described.[9] We consider that the patient was not in a septic shock since C reactive protein was normal with negative cultures and because following the administration of IVG and methylprednisolone, improvement was remarkable. We propose that the autoimmune process unleashed the state of immunologic dissonance in our patient, leading to a distributive form of shock which responded satisfactorily to a non-traditional approach, such as the use of IVG and high dose steroids.

Autoimmune shock hypothesis

Autoimmunity is the result of the interaction of susceptible genes and environmental factors, which generates antibody and pathogenic immune-complex production. This process requires B and T cell hyperactivity, as well as failure of multiple immunoregulators circuits; it leads to the loss of immunologic tolerance, adopting the role of autoantigens and resulting in an autoimmune response. [18] This process is carried out by the innate immune response through antigen presenting cells which release growth factors, nitric oxide, prostaglandins, leukotrienes, metaloproteinases and proinflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, TNF-α, interferon-γ), the last of which increases the inflammatory response and activate the specific immunity. [4] Macrophage activation has a tendency to give rise to the production of proinflammatory cytokines such as IL-12. [15] This cytokine directly stimulates TH1 differentiation, perpetuating a proinflammatory state. [16] This is exacerbated by the diminished differentiation of CD4+ T lymphocytes towards Th17 regulating T lymphocytes due to the specific circulating cytokines. In specific immunity B and T cells become hyperactive due to the loss of immunologic tolerance. [18] Therefore, in cellular immunity there is an alteration causing an overexpression of Th1 T lymphocytes, which causes an excessive production of proinflammatory cytokines. Each cytokine has a specific biologic effect: IL-1 induces fever, activates the endothelium, and acts as an acute phase reactant. IL-2 favors T Lymphocytes (TL), NK and B Lymphocytes (BL) proliferation and activation. IL-6 participates in fever, endothelial cell activation, BL proliferation, and acts as an acute phase reactant. IL-12 promotes Th1 differentiation and increases IFN-γ synthesis. TNF-α has important effects on the pathogenesis of fever, activates endothelial cells, is an acute phase reactant, and participates in apoptosis. Its involvement in autoimmunity is important due to the fact that it promotes itself. [5] TNF-α is one of the most potent cytokines involved in the immunopathogenesis of shock. [17] IFN-γ activates NK cells. On the other hand, hypocomplementemia reflects the overstimulation of this system secondary to the consumption of factors, especially C3 which correlates it in an inversely proportional manner to the expression of antibodies against ds DNA, resulting in exacerbated cytotoxicity. All of these immunologic mechanisms create a domino effect which favors the proinflammatory state and cellular damage and reflect the consequential process of immunologic dissonance.

A disease characterized by these alterations is SLE, which is the underlying disease in the patient presented. Multiple cytokine-mediated alterations have been demonstrated in patients with SLE. [15,16] For example, IFN-γ produced by TL and NK is a potent inductor of chemokines which favors the expression and activation of inflammatory cells. [11] IL-2 is a classic Th1 cytokine of great importance in patients with SLE since IL-2 receptors are directly associated with disease activity. [12] An increase in IL-12, IL-18 and IL-8 has also been observed in patients with active lupus [13,15,16]; all of these interleukins are mainly proinflammatory, they promote the expression of Th1 and participate in chemotaxis of the cells involved in the inflammation cascade. [16] The elevated TNF-α and IL-10 levels observed in these patients reflects the hyperactivation of the cells responsible for the excessive autoantibody production. The cytokines activate the endothelium, which in turn produces unwarranted amounts of nitric oxide. [17] TNF-α and IL-1 activate the neutrophils which damage the endothelium and release molecules which favor vascular permeability. All of these mechanisms induce hypotension and decreased tissue perfusion, causing a state of shock.

At present we can refer to a state of immunologic dissonance as it was conceived by Dr. Roger Bone: "The proinflammatory and anti-inflammatory forces may ultimately reinforce each other, creating a state of increasingly destructive immunologic dissonance" [1], which contributes to a distributive shock, but not caused by an infectious, neurogenic, or allergic etiology. For this reason we propose a new term: Autoimmune Shock. This shock is different from an infectious entity in that the initial stimulus does not depend on peptidoglycans, polysaccharides, or superantigens, [2,3,8], but on the multiple dysregulation mechanisms resulting in the release of proinflammatory cytokines. Autoimmune shock occurs as in this case, in patients with an underlying autoimmune disease in which all other etiologies responsible for shock have been ruled out. As previously mentioned, all immunologic interactions which take place in patients with active autoimmune disorders generate a state of stress in the strict sense of the word, such as Dr. Hans Selye pointed out, possibly being so significant as to unleash a state of shock [19].

Within our proposal we suggest that in the presence of this entity, i.e., an autoimmune shock, it is necessary to change the traditional approach to shock. For this reason we propose the use of intravenous gammaglo-

bulin, which is capable of blocking proinflammatory cytokines such as IL-1, IL-6 and TNF-α through natural antibodies directed against the afore mentioned cytokines. Clinical and experimental evidence suggests the benefit of intravenous gammaglobulin in autoimmune diseases mediated by autoantibodies or self-aggressive T cells, as well as inflammatory disorders associated with a imbalance in the cytokine network through a complex mechanism which includes expression and function modulation of Fc receptors, interference with complement and cytokine activation, idiotype-antiidiotype network blockade, inhibition of dendritic cell maturation, and modulation of B and T cell activation. It has been observed that gammaglobulin balances the Th1:Th2 relationship which is of vital importance to the reestablishment of lost homeostasis in autoimmunity. We also propose the attainment of synergy with methylprednisolone in order to effectively modulate the immunologic dissonance. As an effective glucocorticoid with transcriptional effects on NFκβ and AP1 genes which encode cytokine expression, methylprednisolone blocks the following cytokines: IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-12, FNT, IFN-γ, RANTES y GM-CSF[14], thus acting as antiinflammatory. Other effects include decreased nitric oxide synthesis, neutrophil and monocyte chemotaxis inhibition, eicosanoid synthesis inhibition via downregulation of phospholipase A2 and COX-2, and diminished activation of degradation enzymes such as colagenases. [14] All of these antiinflammatory effects are increased exponentially with intravenous gammaglobulin in order to correct the immunologic dissonance causing the state of shock occurring in patients with underlying autoimmune disorders.

This single case report should make us think and look intentionally for similarities in order to contribute with new cases to facilitate recognition and more importantly appropriate and timely treatment.

CONCLUSION

We present an atypical case of autoimmune shock which responded to a non-traditional treatment. We postulate from an etiologic point of view a new possible perspective of shock, the Autoimmune Shock, based on the clinical features, presentation, course, treatment, and resolution.

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